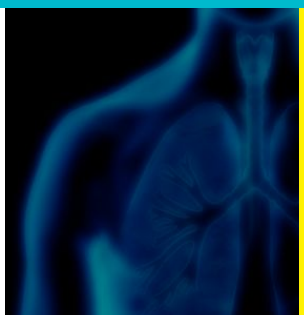


From selection of patients with non-small-cell lung cancer to the cost of treatment in Portugal:



EVALUATION OF SECOND AND THIRD LINES TREATMENT

ANTÓNIO MANUEL FERREIRA ARAÚJO

TESE DE CANDIDATURA AO GRAU DE DOUTOR EM CIÊNCIAS MÉDICAS
SUBMETIDA AO INSTITUTO DE CIÊNCIAS BIOMÉDICAS DE ABEL SALAZAR
DA UNIVERSIDADE DO PORTO

PORTO 2010

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PORTO 2010

To my wife, Ana Coelho

To my daughters, Ana Cláudia e Inês Filipa

To my parents and my brother

To my patients

“To get the right patient for the right treatment at the right time”

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To the **Lung Cancer Patients**, for whom I hope the results of these studies will bring benefits.

List of Publications

According the art. 8 of the Decree-Law nº 388/70 the present Thesis has already produced the following publications in scientific peer-reviewed journals:

1. **Araújo A**, Ribeiro R, Azevedo I, Coelho A, Soares M, Sousa B, Pinto D, Lopes C, Medeiros R, Scagliotti G: **Genetic polymorphisms of the epidermal growth factor and related receptor in non-small cell lung cancer**. *Oncologist* 2007;12:201-210.
2. Parente B, Queiroga H, Teixeira E, Sotto-Mayor R, Barata F, Sousa A, Melo MJ, João F, Neveda R, Cunha J, Fernandes A, Manuel M, Cardoso T, Ferreira L, Nogueira F, Duarte J, Semedo E, Brito U, Pimentel F, Barros S, Costa F, Almodôvar T, **Araújo A: Epidemiological study of lung cancer in Portugal (2000/2002)**. *Rev Port Pneumol* 2007;13:255-265.
3. **Araújo A**, Barata F, Parente B, Rego S, Teixeira E, Melo M, Queiroga H, Cunha J, Duarte J, Coelho A: **Pemetrexed in second line treatment of non-small cell lung cancer – The Portuguese experience**. *Rev Port Pneumol* 2008;14 (supp 2):S9-S20.
4. **Araújo A**, Parente B, Sotto-Mayor R, Teixeira E, Almodovar T, Barata F, Queiroga H, Pereira C, Pereira H, Negreiro F, Silva C: **An economic analysis of erlotinib, docetaxel, pemetrexed and best supportive care as second or third line treatment of non-small cell lung cancer**. *Rev Port Pneumol* 2008;14:803-827.
5. **Araújo A: Reply to the Editor - An economic analysis of erlotinib, docetaxel, pemetrexed and best supportive care as second or third line treatment of non-small cell lung cancer**. *Rev Port Pneumol* 2009;15:560-566.
6. **Araújo A**, Barata F, Barroso S, Cortes P, Damasceno M, Parreira A, Espírito Santo J, Teixeira E, Pereira R. **Cost of cancer care in Portugal**. *Acta Med Port* 2009;22:525-536.

7. Araújo A: Pemetrexed plus Bevacizumab for second-line therapy of non-small-cell lung cancer: The importance of patient selection. J Clin Oncol 2010;28: e131.

I, hereby declare that I have actively participated actively in the gathering and study of the material included in each of the publications presented and had written the manuscripts in collaboration with the other authors.

Summary

Worldwide, in 2008, there were 12.4 million incident cases of cancer, 7.6 million deaths from cancer and 28 million persons alive with cancer within five years from initial diagnosis. Globally, lung cancer was the commonest incident cancer and the most frequent cause of cancer-related mortality in men. Portugal is the second European country with the lowest incidence of lung cancer, sharing about 7.8% of cancer incidence and ranked in fourth place.

Tobacco is the leading cause of preventable death and trends of cigarette smoking consumption in each country nicely predict the respective lung cancer incidence, with a gap of nearly 20 years between the two curves. Comparing with the rest of Europe, Portugal has one of the lowest rates of cigarette consumption which justify the compared lower rate of lung cancer.

Non-small-cell lung cancer (NSCLC) accounts for 75%-85% of all histotypes of lung cancer. Despite extensive research, the overall prognosis for patients with NSCLC remains poor, with a 5-year survival rate of only 14%. For advanced or metastatic NSCLC double-agent platinum-based therapy remained the backbone of treatment. But in virtually all patients with advanced disease initial therapy will ultimately fail and second-line therapy will often be necessary. For second-line treatment, three agents have been approved so far: two cytotoxic drugs, docetaxel and pemetrexed, and one targeted therapy, erlotinib.

Prognostic and predictive factors are relevant for the patient and for the physician, because they can give an accurate prognosis (in terms of disease recurrence or progression and patient survival), helping to establish the best treatment choice, design the right clinical trials and interpreting the results. Classic prognostic factors include a tobacco consumption history, performance status and co-morbidities of the patient. Nowadays, there are also molecular markers as prognostic factors, such as the epidermal growth factor receptor (*EGFR*), the excision repair cross-complementing 1 (*ERCC1*), the ribonucleotide reductase subunit M1 (*RRM1*) and the breast cancer susceptibility gene1 (*BRCA1*). These, with *KRAS* mutation and histology are the ones considered potential predictive factors. Actually, the goal is to identify in advance the subpopulation of patients most likely to respond to a particular therapy that would not only increase the likelihood of response, but would also avoid needlessly treating those patients who have little probability of benefiting from treatment.

In Portugal cancer was considered one of the priorities on the Health National Plan for 2004-2010, with important end-points such as the reduction of mortality rates, promotion and expansion of therapeutic rationality, promotion of equitable access to drugs and facilitation of patients' access to innovative medicines. The national gross domestic product (GDP) and the GDP *per capita* are well below the mean of the European Union, and the bulk of the health system is a public model. But the situation regarding the quality of the provision of health services involves: sparse culture of quality; organizational deficit of health services; lack of performance indicators and for decision support; insufficient structured support to areas of diagnostic and therapeutic decision. Nevertheless, in the Portuguese Great Options for the Plan 2010-2013, health is not a priority.

Portugal does not have a reliable cancer registry and because of that it is very difficult to know the Portuguese reality about cancer care. The last Portuguese National Cancer Registry is from 2001 and is known by everyone that this registry has many flaws on the registration process, and the registry of death certificates also presents many faults. These facts create great difficulties to estimate the true rate of incidence of the NSCLC and consequently the current clinical practice in terms of its treatment. The Oncologic Pulmonology Committee of the Portuguese Society of Pulmonology tried to know a little more about the Portuguese reality by launching a hospital based registry. Between 2000 and 2002, the 22 participants' hospital registered 4396 new lung cancer cases. Adenocarcinoma was the most frequent histologic sub-type, and 76,9% of cases were advanced or metastatic lung cancer. For this reason 20,3% of the patients only had best supportive care and 43,7% have received chemotherapy alone.

The Portuguese population with advanced or metastatic NSCLC responds similarly to the European population to second and third-line treatments, in terms of efficacy and safety.

With the appearance of the EGFR-TKIs, like gefitinib and erlotinib, for of chemotherapy-refractory locally advanced or metastatic NSCLC treatment, *EGFR* took a major importance. A positive *EGFR* mutation status could predict better response to EGFR-TKIs. Patients carrying different functional polymorphic alleles from *EGFR* and *EGF* genes may potentially respond differently to EGFR-TKIs, although this question remains unanswered. Furthermore, there is scant information regarding the influence of genetic polymorphisms on EGFR and EGF expression levels in peripheral blood and tumor tissue. Therefore, further research to understand the roles of *EGF* and its receptor remains a priority.

NSCLC is associated with high economic costs. Before introducing a new drug on the market, this should prove its added therapeutic value and then its cost-

effectiveness ratio should be calculated. The new drugs are expensive and generally effective for a relatively small subset of treated patients. This is the reason that, for a society to consider spending its money in these new drugs for a group of patients, they must be effective for a certain patient and cost-effective for the society.

Because erlotinib was the last new drug introduced in Portugal for second and third-line treatments of advanced or metastatic NSCLC, a cost-minimization and cost-utility analysis was performed, to compare the costs and clinical benefits of erlotinib for this indication with those of the three possible clinical care alternatives - docetaxel, pemetrexed and best supportive care. The model shows that for second or third line treatment of NSCLC, erlotinib could add a benefit in terms of QALY when compared with docetaxel, pemetrexed or best supportive care, and a lower cost than that for the active treatments. It was also concluded for the need of a prospective randomized phase III trial, comparing all the active treatments in terms of efficacy, utility, toxicity and use of healthcare resources.

A crucial study evaluating the costs of cancer treatment in Portugal was performed, so that decision makers can take informed and reasoned decisions regarding the allocation of funds from the national health budget for the area of oncology. In the present days, the percentage spent with cancer from the total of the health budget is a little more than half, and *per capita* value is below half of the mean on EU. A comparison between the total spent with cardio-vascular diseases and cancer in Portugal, shows that the amount allocated to the first is more than twice.

Personalized cancer medicine has the potential to save costs to the insurance companies and to governments. The ability to use genomic information to exclude large numbers of patients from treatment consideration with particular agents to which they are unlikely to derive benefit not only spares patients from needless treatment, but also could have a substantial impact on the reimbursement costs associated with these relatively expensive therapies. On the other hand, formal pharmacoeconomic analyses will provide greater insights into the true value of treatments. Studies which permit this evaluation are a very important tool for decision makers, especially when it comes to defining decisions over diseases such as lung cancer and drug policies, allowing a rational utilization of available resources to obtain an optimal cost/benefit ratio.

Resumo

No mundo, em 2008, foram registados 12.4 milhões de novos casos de cancro, 7.6 milhões de mortes por cancro e 28 milhões de pessoas a viver com cancro com mais de 5 anos após o diagnóstico. Globalmente, o cancro do pulmão é o tipo de cancro com maior incidência e é a causa mais frequente de mortalidade relacionada com o cancro no homem. Portugal é o segundo país europeu com a mais baixa taxa de incidência de cancro do pulmão, correspondendo a cerca de 7.8% da incidência total de cancro e classificando-o em quarto lugar.

O tabaco é a principal causa de morte evitável e as curvas de consumo de cigarros em cada país fazem prever com exactidão a respectiva incidência de cancro do pulmão, com um hiato de cerca de 20 anos entre as duas curvas. Comparando com o resto da Europa, Portugal tem uma das mais baixas taxas de consumo de cigarros o que justifica a baixa taxa de cancro do pulmão.

O cancro do pulmão de não pequenas células (CPNPC) corresponde a 75%-85% de todos os tipos histológicos de cancro do pulmão. Apesar da intensa pesquisa, o prognóstico global para os doentes com CPNPC mantém-se desanimador, com uma taxa de sobrevivência aos 5 anos de apenas 14%. Para o CPNPC avançado ou metastático a terapia de duplete baseado na platina é a base do tratamento. Mas, virtualmente todos os doentes com doença avançada irão desenvolver falência à terapêutica inicial e será necessária uma segunda linha de tratamento. Para o tratamento de segunda linha, existem três fármacos aprovados: duas drogas citotóxicas, docetaxel e pemetrexedo, e uma terapia dirigida a alvo, erlotinib.

Os factores de prognóstico e preditivos são importantes para o doente e para o médico, porque podem fornecer um prognóstico preciso (em termos de recorrência ou progressão da doença e sobrevivência), ajudam a estabelecer o melhor tratamento, a desenhar os ensaios clínicos mais correctos e a interpretar os seus resultados. Factores de prognóstico clássicos incluem a história de consumo de tabaco, o estado geral e as co-morbilidades do doente. Actualmente, existem também marcadores moleculares que se tornaram factores de prognóstico, tais como o receptor do factor de crescimento epidérmico (*EGFR*), o “excision repair cross-complementing 1” (*ERCC1*), o ribonucleotídeo reductase subunidade M1 (*RRM1*) e o gene de susceptibilidade para o cancro da mama 1 (*BRCA1*). Estes, juntamente com a mutação do *KRAS* e a histologia são considerados potenciais factores preditivos. Identificar precocemente a subpopulação de doentes que mais provavelmente

responderá a uma terapia particular e que não só aumente a probabilidade de resposta mas evite tratamentos desnecessários àqueles doentes que têm poucas hipóteses de beneficiar com o tratamento, é presentemente o objectivo principal do tratamento oncológico.

Em Portugal, o cancro foi considerado uma das prioridades do Plano Nacional de Saúde para 2004-2010, com os objectivos de reduzir as taxas de mortalidade, promover a expansão da terapêutica racional, promover a equidade no acesso aos medicamentos e facilitar o acesso aos medicamentos inovadores. O produto interno bruto (PIB) nacional e o PIB *per capita* estão muito abaixo da média da União Europeia e o fulcro do sistema de saúde português é um modelo público. Mas a situação, no que concerne à qualidade de fornecimento dos nossos serviços de saúde, envolve: uma cultura de qualidade escassa; uma organização deficiente dos serviços de saúde; uma falta de indicadores de desempenho e de apoio à decisão; insuficiente apoio estruturado para as áreas de diagnóstico e terapêutica. No entanto, nas Grandes Opções do Plano 2010-2013 de Portugal, a saúde não é uma prioridade.

Portugal não possui um registo de cancro fiável e, por esse motivo, é muito difícil conhecer a realidade portuguesa sobre os cuidados oncológicos, a real taxa de incidência do CPNPC e, conseqüentemente, a prática clínica corrente no que diz respeito ao seu tratamento. O último Registo Oncológico Nacional data de 2001 e apresenta muitas falhas. O registo dos certificados de óbito é também muito deficiente. No Comité de Pneumologia Oncológica da Sociedade Portuguesa de Pneumologia tentou-se conhecer um pouco melhor a realidade portuguesa, tendo-se lançado um registo baseado nos hospitais. Entre 2000 e 2002, os 22 hospitais participantes registaram 4396 novos casos de cancro do pulmão, o adenocarcinoma foi o sub-tipo histológico mais frequente e 76,9% eram carcinomas do pulmão em estágio avançado ou metastático. Por esta razão 20,3% dos doentes realizaram apenas os melhores cuidados de suporte e 43,7% submeteram-se apenas a quimioterapia.

A população portuguesa com CPNPC avançado ou metastático responde aos tratamentos de segunda e terceira linha, em termos de eficácia e segurança, de modo semelhante à população europeia.

Com o aparecimento dos inibidores da tirosina cínase do EGFR (EGFR-TKIs), tais como o gefitinib e o erlotinib, para o tratamento do CPNPC avançado ou metastático refractário à quimioterapia, o *EGFR* ganhou uma grande importância. A existência de mutação do *EGFR* pode prever uma melhor resposta aos EGFR-TKIs. Doentes portadores de diferentes alelos polimórficos funcionais dos genes *EGFR* e *EGF* podem, potencialmente, responder de forma diferente aos EGFR-TKIs, embora esta se mantenha uma questão por responder. Existe ainda escassa informação sobre

a influência dos polimorfismos genéticos nos níveis de expressão do EGFR e EGF no sangue periférico e no tecido tumoral. Assim, a pesquisa adicional para se compreender a importância do *EGF* e do seu receptor mantém-se uma prioridade.

O CPNPC está associado a elevados custos económicos. Os novos medicamentos são dispendiosos e geralmente eficazes apenas para um subgrupo relativamente pequeno de doentes tratados. Por esta razão, previamente à introdução de um novo fármaco no mercado, o racional para a utilização destes novos fármacos deve incluir o cálculo da sua eficácia num determinado tipo de doentes e do seu índice de custo-efectividade para a sociedade.

O erlotinib foi o último fármaco introduzido em Portugal para o tratamento de segunda e terceira linhas do CPNPC avançado ou metastático, pelo que se realizou uma análise de custo-minimização e de custo-utilidade comparando os custos e os benefícios clínicos do erlotinib nesta indicação com as três alternativas de tratamento possíveis - docetaxel, pemetrexedo e melhor cuidado de suporte. O modelo mostrou que o erlotinib era superior em termos de QALY quando comparado com o docetaxel, o pemetrexedo ou o melhor cuidado de suporte, e tinha um custo inferior relativamente aos tratamentos activos. Concluiu-se, ainda, pela necessidade de estudos randomizados, prospectivos de fase III, que comparem todos os tratamentos activos em termos de eficácia, utilidade, toxicidade e utilização de recursos da saúde.

Foram estimados os custos do tratamento do cancro em Portugal, porque tal estudo era crucial para os nossos decisores políticos poderem dirimir de uma forma informada e racional sobre os fundos a alocar à área da oncologia do orçamento nacional para a saúde. A percentagem gasta com o cancro do total do orçamento da saúde foi pouco superior à metade e o valor *per capita* está mesmo abaixo da metade da média da União Europeia. Quando se compara o valor total gasto com as doenças cardio-vasculares e com o cancro, verifica-se que o primeiro é mais do dobro.

A medicina oncológica personalizada tem o potencial de poder reduzir os custos às seguradoras e aos governos. A possibilidade de se usar informação genómica para excluir de um tratamento com um fármaco em particular um grande número de doentes, sabendo de antemão que não beneficiariam deste, pode poupar os doentes a tratamentos desnecessários e poderá ter um impacto substancial na comparticipação dos custos associados a estes tratamentos relativamente dispendiosos. Por outro lado, uma análise farmaco-económica formal poderá dar uma noção mais aprofundada sobre o verdadeiro valor dos tratamentos. Estudos que possibilitem esta avaliação são uma ferramenta muito importante para os decisores, permitindo uma utilização racional dos recursos disponíveis de modo a obter o melhor rácio custo/benefício.

1. Introduction

1. Incidence and mortality rates of cancer

The world population is increasing, from the estimated 6.7 billion in 2008 to 8.3 billion by 2030 (Figure 1) (Boyle, P. et al. 2008). For this same period, the International Agency for Research on Cancer (IARC) estimated that for the year 2008 there were 12.4 million incident cases of cancer, 7.6 million deaths from cancer and 28 million persons alive with cancer within five years from initial diagnosis. These numbers will rise in 2030, with an estimated 26.4 million incident cases of cancer, 17.0 million deaths from cancer and 80 million persons living with cancer more than 5 years from diagnosis (Boyle, P. et al. 2008).

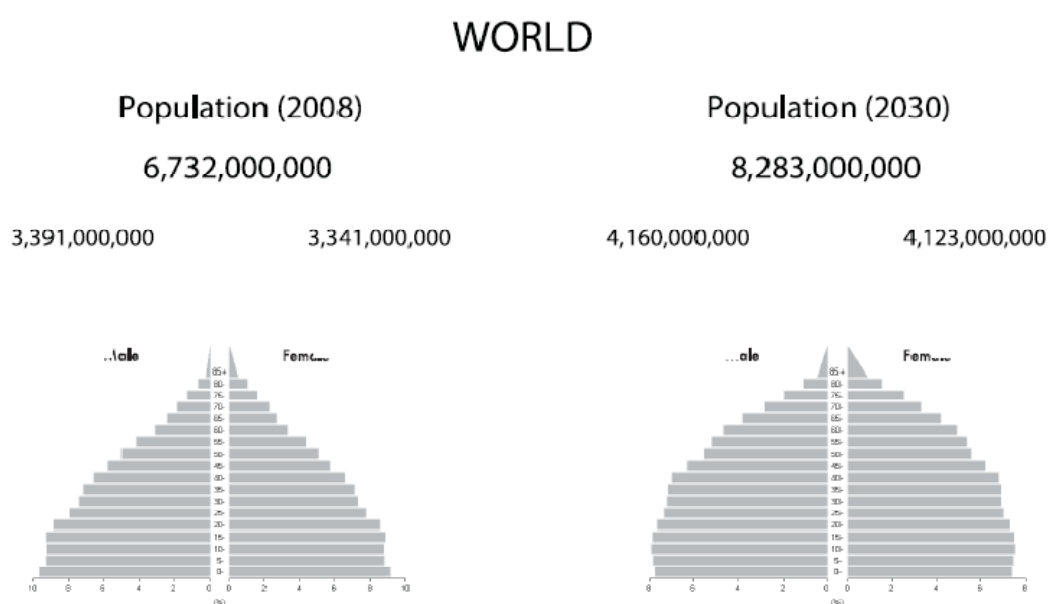


Figure 1 – Estimates of global population by gender and age, 2008 and 2030 (Boyle, P. et al. 2008).

The growth and ageing of the world's population and the continual increase in the underlying incidence rates will contribute to the rise in the global cancer burden. Globally, lung cancer was the commonest incident cancer and cause of cancer-related mortality in men; in women, the most common incident cancer and cause of cancer-related death was breast cancer (Boyle, P. et al. 2008).

In the European Union (EU) total cancer mortality has peaked in the late 1980s and has declined from 1988 to 2002 by approximately 15% in both sexes, corresponding to the avoidance of more than 150.000 deaths per year from the late 1980s to the early 2000s (Figure 2).

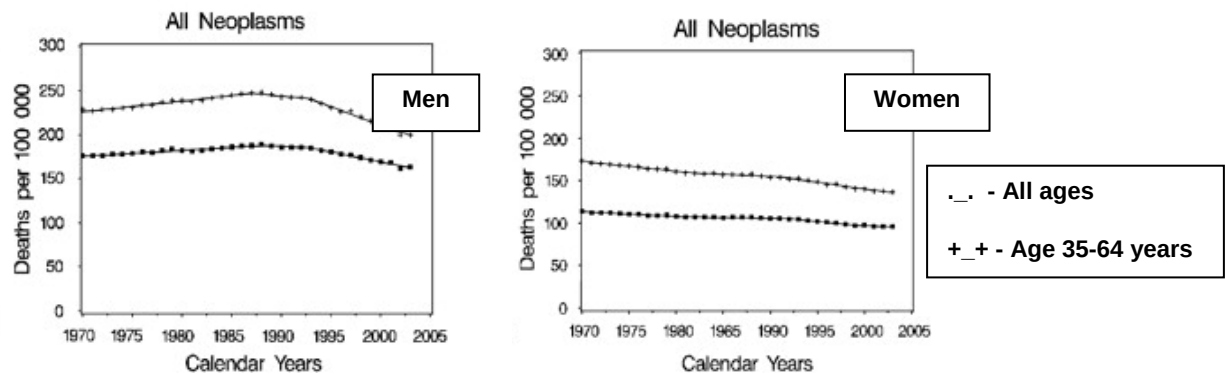
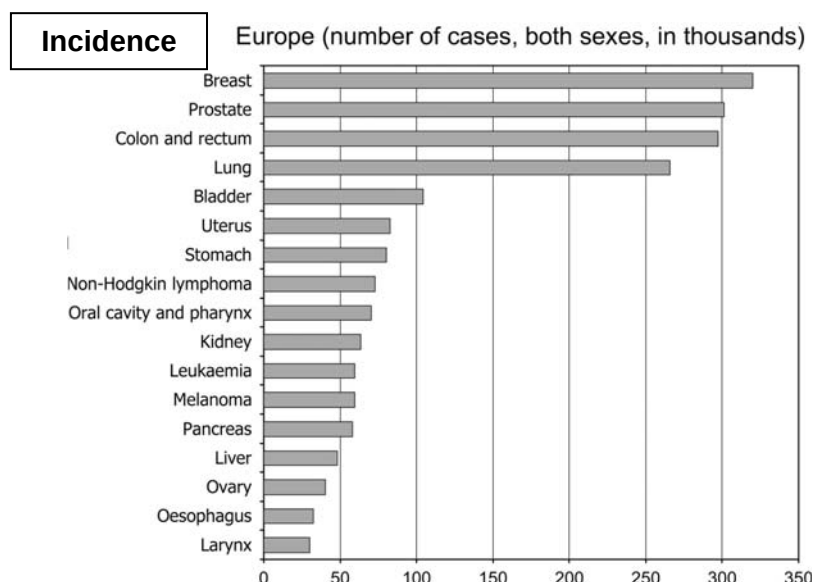


Figure 2 – Joinpoint analysis for cancer mortality in men and women (all ages and age 35-64 years) from the European Union, 1970-2002 (Bosetti, C. et al. 2008).

These favorable trends were mainly due to the decline in three major neoplasms, stomach, intestines and lung in men. Other contributions to this decline in cancer mortality included improvement in diagnosis and/or treatment of colorectum, breast, uteri, prostate, testis, Hodgkin's lymphoma and leukemia (Levi, F. et al. 2004a; Levi, F. et al. 2004b; 2007; Bosetti, C. et al. 2008). Nevertheless, in 2006, in the EU, lung cancer occupied the forth place in incidence after the breast, prostate and colorectal cancers but it was the leading cause of cancer dead (Figure 3) (Ferlay, J. et al. 2007).



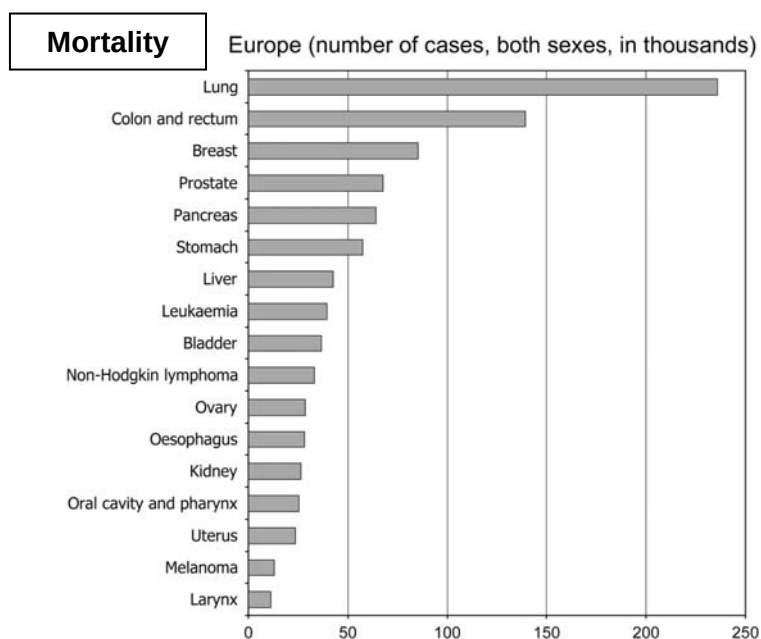


Figure 3 – Estimated incidence and mortality in European Union, 2006 (Ferlay, J. et al. 2007).

In Portugal, the National Institute of Statistics (INE) states the resident population is increasing from 9.970.441 estimated for 1990 to 10.627.250 in 2008 and is ageing (Figure 4) (INE 2009).

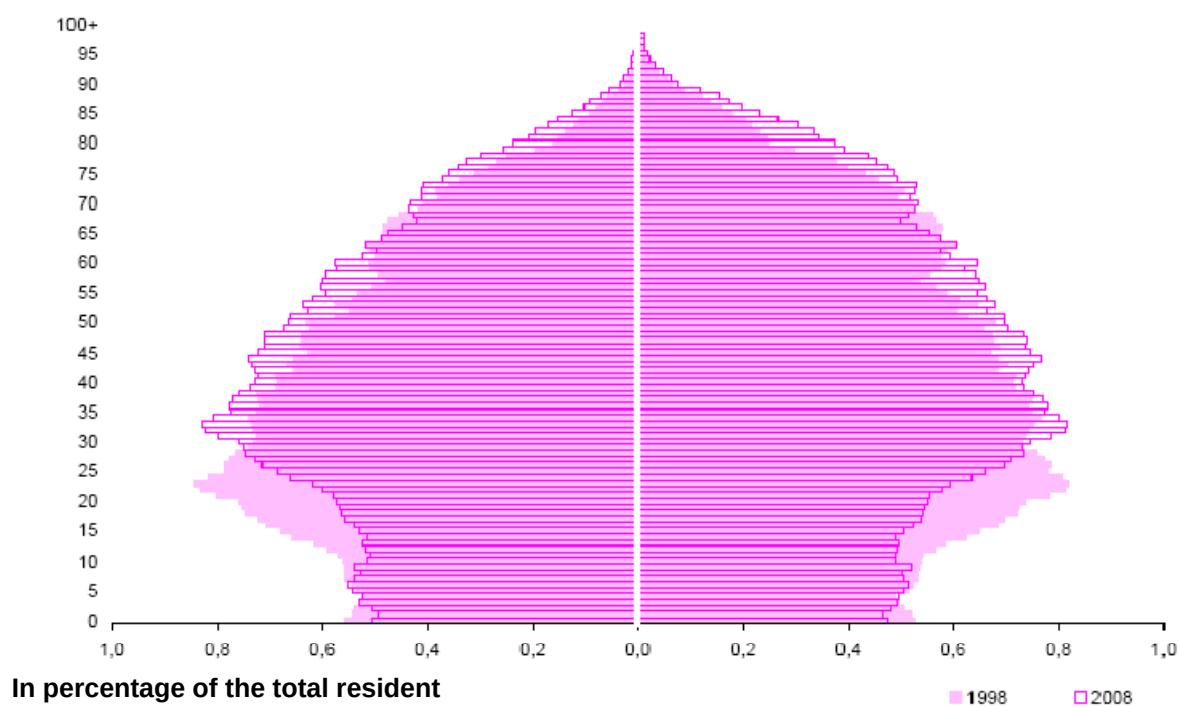


Figure 4 – Estimates of global population by age, 1998 and 2008, Portugal (INE 2009).

The mortality rates from 1990 to 2005 have decreased in the neonatal, infantile and circulatory system diseases mortality rates, but have increased in the cancer mortality rate (INE 2008a) (Table 1).

Table 1 – Mortality rates from the estimated Portuguese resident population, recomputed from the final results of the Census 2001 and adjusted to coverage ratios (INE 2008a)

1990	10,9	6,9	4,6	1,8	1990
1991	10,8	6,9	4,7	1,8	1991
1992	9,2	5,9	4,4	1,9	1992
1993	8,6	5,5	4,6	1,9	1993
1994	7,9	4,7	4,3	1,9	1994
1995	7,4	4,7	4,3	2,0	1995
1996	6,8	4,1	4,4	2,0	1996
1997	6,4	4,1	4,2	2,0	1997
1998	6,0	3,7	4,2	2,1	1998
1999	5,6	3,6	4,1	2,1	1999
2000	5,5	3,4	4,0	2,1	2000
2001	5,0	2,9	4,0	2,1	2001
2002	5,0	3,4	4,0	2,1	2002
2003	4,1	2,7	3,9	2,2	2003
2004	3,8	2,6	3,5	2,1	2004
2005	3,5	2,2	3,5	2,2	2005
					‰
					Infant
					Neonatal
					Circulatory system diseases
					Malignant neoplasms

Portugal is the second European country with the lowest lung cancer incidence. Lung cancer share of cancer incidence was about 7.8% and is ranked in fourth place among cancers in Portugal (Table 2) (Ferlay, J. et al. 2007).

Table 2 – Estimated age-standardized incidence rates in lung cancer (European age standard) per 100 000 inhabitants, 2006 (Ferlay, J. et al. 2007)

	Male	Female	Total*	Lung cancer share of cancer incidence	Rank in incidence among cancers
Sweden	28.6	23.8	26.2	6.7%	4
Portugal	44.5	11.7	28.1	7.8%	4
Finland	45.8	14.7	30.3	8.4%	4
Austria	54.0	22.3	38.2	10.3%	4
Switzerland	52.7	26.2	39.5	9.1%	4
Germany	61.2	20.8	41.0	10.4%	4
Spain	68.3	13.8	41.1	12.1%	2
Norway	53.8	33.7	43.8	10.4%	4
France	75.5	15.0	45.3	10.6%	4
United Kingdom	57.1	34.6	45.9	12.1%	3
Ireland	60.2	34.1	47.2	10.5%	4
The Netherlands	63.4	32.5	48.0	12.1%	4
Italy	84.7	15.6	50.2	12.2%	3
Greece	88.7	12.7	50.7	14.8%	1
Czech Republic	78.9	22.9	50.9	12.3%	2
Russian Federation	92.7	11.2	52.0	16.0%	1
Denmark	65.0	48.7	56.9	13.3%	2
Belgium	93.0	22.9	58.0	13.1%	3
Poland	103.0	28.6	65.8	17.4%	1
Hungary	119.3	42.4	80.9	16.0%	1
Europe	75.3	18.3	46.8	12.6%	2

In the latest National Cancer Registry of 2001, Portugal registered 3054 new lung cancer cases, comprehending the second major cancer in men (after the prostate cancer) and the tenth place in women. From these, 731 were in the north region, 384 in the center and 1270 in the south region of Portugal (Bento, M.J. 2008). In another study published in 2007, between 2000 and 2002 4396 new lung cancer cases were registered from 22 hospital units all over the country (Parente, B. et al. 2007). From these, 2133 were from the north, 690 from the center and 1573 from the south hospitals. Unfortunately, in Portugal there is no reliable national cancer registry and even those who are in practice have a delay of several years.

2. The importance of tobacco

Tobacco is the leading cause of preventable death. More than 4000 chemicals have been identified in tobacco smoke, at least 250 of which are known to be harmful and more than 60 of which are known to cause (US Department of Health and Human Services 2005). Tobacco smoke is the most common source of carcinogens to human, including polycyclic aromatic hydrocarbons (i.e. benzo[a]pyrene) and tobacco specific nitrosamines (i.e. NNK). The chronic presentation of carcinogens to the airway epithelial cells, through sustained smoking, can lead to molecular lesions which, in the presence of reduced metabolic detoxification, can diminish repair capability, overwhelming cellular defenses and leading to lung cancer (Wogan, G.N. et al. 2004; IARC 2007; Watanabe, K.H. et al. 2009).

Almost one billion men in the world smoke – about 35 percent of men in developed countries and 50% of men in developing countries. About 250 million women in the world are daily smokers – 22% in developed countries and 9% in developing countries. Most of the current smokers worldwide are between the ages of 20 and 40 years (Jha, P. et al. 2002). Trends in developed and developing countries show that male smoking rates have now peaked and, slowly but surely, are declining. Cigarette smoking among women is declining in many developed countries but is still increase or has not shown any decline in several southern, central and eastern European countries (WHO 2002; Jha, P. 2009). Nevertheless, the full effects of smoking can take 50 years to measure in individuals and up to 100 years to measure in populations (Jha, P. 2009).

Worldwide, tobacco use kills 5-6 million people annually, accounting for 1 in every 5 male deaths and 1 in 20 female deaths in individuals over 30 years of age (Ezzati, M. et al. 2004; Ezzati, M. et al. 2005). The consumption of tobacco causes nearly four times as many deaths from causes other than cancer than it does from cancer, like cardiovascular diseases, strokes and chronic lung diseases (Jha, P. 2009).

It is estimated that 25-30% of all cancers in developed countries are tobacco-related. From the results of several studies conducted in Europe, Japan and North America, between 87 and 91% of lung cancers in men, and between 57 and 86% of lung cancers in women, are attributable to cigarette smoking. In the 1990s it is estimated that smoking killed four million people each year in the world and that altogether some 60 million deaths were caused by tobacco in the second half of the

20th century. It was estimated that the number of annual tobacco deaths will reach an average of nearly 6 million in 2000-2024, and will be twice this number in 2025-2049 (Jha, P. 2009). Because of the length of the latency period, tobacco-related cancers observed today are related to the cigarette smoking patterns over several previous decades (Boyle, P. et al. 2008). The risk among smokers relative to the risk among never-smokers is in the order of 8-15 in men and 3-10 in women (Boffetta, P. et al. 2002). The strongest determinant of the risk is the duration of smoking, but this is also increase in proportion to the number of cigarettes smoked (IARC 2003).

Trends of cigarette smoking consumption in each country nicely predict the respective lung cancer incidence, with a gap of almost 20 years between the two curves (Lopez, A. et al. 1994) (Figure 5).

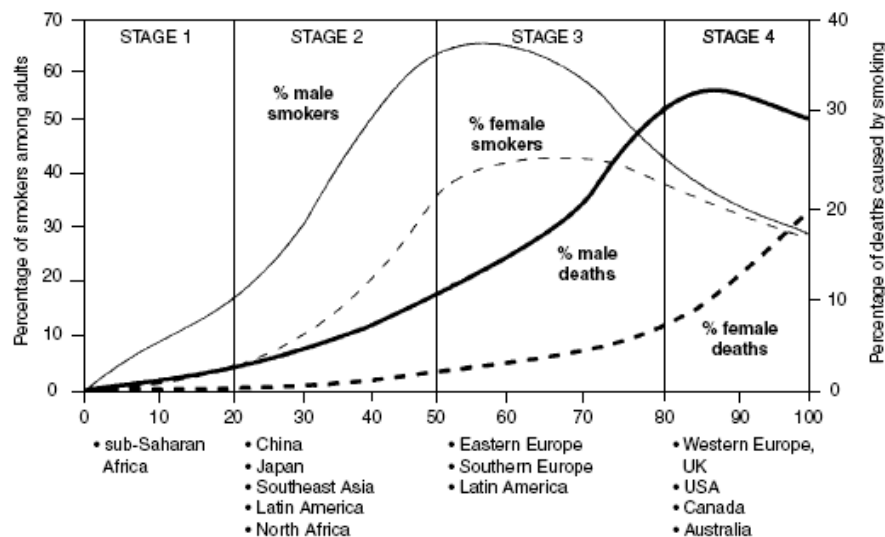


Figure 5 – A descriptive model of the cigarette epidemic (Lopez, A. et al. 1994).

Currently, tobacco smoking represents a less common cause of death in developing continents, such as Africa and Eastern Asia, where competing causes of death remain present, but in countries such as India and China, lung cancer will become a relevant social disease in the next 20 years (Araujo, A. et al. 2007) (Figure 6).

Cessation before middle age (defined as around 30 years) avoids more than 90% of the lung cancer mortality attributable to smoking, and individuals who stop smoking show a similar pattern of survival to that of individuals who have never smoked, but an excess risk throughout life likely persists even on long-term quitters (Jha, P. 2009).

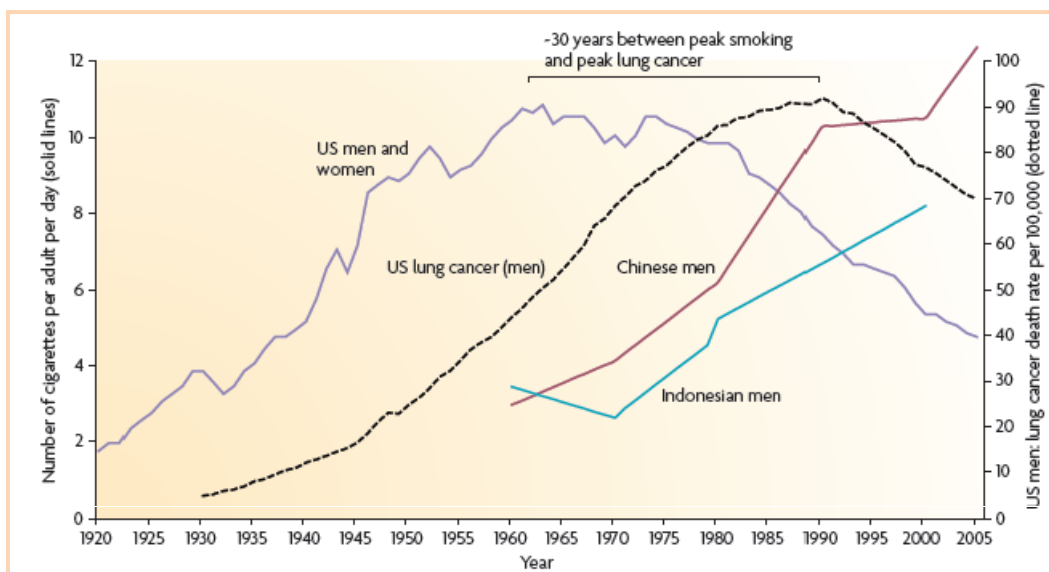


Figure 6 – Trends in cigarette consumption and male lung cancer rates, 1920-2005 (Jha, P. 2009).

The death rate of long-term cigarette smokers in middle age (from 30 to 69 years of age) is three times that of non-smokers. Half the deaths take place in middle-age, when smokers lose approximately 20-25 years of life expectancy compared to non-smokers, and the other half occurs late in life when loss of expectation of life is 7-8 years. It is known that the rate at which young people start to smoke will be a major determinant of ill-health and mortality in the second half of this century, but it will be the extent of current smokers that give up the habit who determine the mortality in the next decades (WHO International Agency for Research of Cancer 2004).

In Portugal, according to the INE, there were an estimated 1.664.073 current smokers in 2006, 1.428.487 ex-smokers and 6.154.423 never-smokers. Comparing with the rest of Europe, Portugal has one of the lowest rates of cigarette consumption which justifies the compared lower rate of lung cancer (INE 2008b).

3. The Non-Small-Cell Lung Cancer (NSCLC)

Cancer is typically diagnosed by pathologists on histological sections or on cytological smears routinely stained with hematoxylin and eosin (H&E) as well as by immunotechniques, complemented by their genetic profiles that permit to predict prognosis and response to therapy (Walk, E.E. 2009).

Non-small-cell lung cancer (NSCLC) accounts for 75%-85% of all histotypes of lung cancer. Adenocarcinoma has surpassed squamous carcinoma as the most common histologic subtype of lung cancer in many countries. The proportion of the two principal histological sub-types of NSCLC differs by sex: squamous cell carcinomas comprise 44% of lung cancers in men and 25% in women, while adenocarcinomas comprise 28% cases in men and 42% in women. But the incidence of adenocarcinomas has raised, mainly due to an ever-increasing proportion of ex-smokers in the population (the declining in risk of lung cancer on smoking cessation is faster for squamous cell tumors than for adenocarcinomas) and changes in cigarette composition (low tar, low nicotine, filtered cigarettes resulted in addicted smokers in more puffs and deeper inhalation) (Wynder, E.L. et al. 1995; Stellman, S.D. et al. 1997; Khuder, S.A. 2001; Janssen-Heijnen, M.L. et al. 2003; Patel, J.D. 2005; B'Chir, F. et al. 2007).

For a normal cell to become malignant it must acquire some specific capabilities such as independence from growth signaling, insensitivity to growth inhibitory signals, no limit on proliferation, development of angiogenic ability, evasion of apoptosis and capabilities for invasion and for originate distant metastases (Hanahan, D. et al. 2000). Cancer is a multi-step process during which cells undergo profound metabolic and behavioral changes, leading them to proliferate in an excessive and untimely way, to escape surveillance by the immune system, and ultimately to invade distant tissues to form metastases (Merlo, L.M. et al. 2006). These changes arise through the accumulation of modifications in cell's genetic program which controls cell proliferation and lifespan, relationships with neighboring cells, and capacity to escape the immune system (Merlo, L.M. et al. 2006).

Proliferative activity of cancer cells may be maintained through several mechanisms, including autocrine loops, leading to cancer cells exhibits a reduced requirement for exogenously supplied growth factors (Sporn, M.B. et al. 1985). This independence from external supply is, at least partially, secondary to the ability of

cancer cells to produce high levels of their own peptide growth factors, and this depends, in turn, on the activation of cellular proto-oncogenes (Goustin, A.S. et al. 1986; Aaronson, S.A. 1991). Similarly, the involvement of growth factors in sustaining the survival of cancer cells and in promoting tumor-induced neoangiogenesis has been definitively established, contributing to tumor progression through different mechanisms (Sporn, M.B. et al. 1985; Aaronson, S.A. 1991; Favoni, R.E. et al. 2000).

The stage of the disease is important for prognosis and treatment planning. The staging system for NSCLC is now changing, from the old 1997 of the American Joint Committee on Cancer and the Union Internationale Contre le Cancer revised in 2002 (Sobin, L.H. et al. 2002) to the more recent 2009 version of the International Association for the Study of Lung Cancer (Goldstraw, P. et al. 2007; Groome, P.A. et al. 2007; Postmus, P.E. et al. 2007; Rami-Porta, R. et al. 2007; Rusch, V.W. et al. 2007; Detterbeck, F.C. et al. 2009). However it is still generally based on T (tumour size), N (location of the lymph nodes involved) and M (distant metastatic disease). Unfortunately, in the daily clinical practice most patients present at late stages of their disease. In Portugal, only 8,9% of the patients presented at stage I, 5,3% at stage II, 30,0% presented at stage III and 46,9% at stage IV (Parente, B. et al. 2007).

Despite extensive preclinical and clinical research, the overall prognosis for patients with NSCLC remains poor, with a 5-year survival rate of only 14% (Spira, A. et al. 2004). Surgery remains the most effective therapeutic modality with curative intent in early-stage NSCLC, but postoperative survival remains unsatisfactory, with a 5-year survival rate less than 70% even in pathologic stage I. Consequently, more than 70% of NSCLC patients are candidates for neoadjuvant, adjuvant, or palliative systemic treatment at some point in their disease progression (Visbal, A.L. et al. 2005; Burdett, S. et al. 2006; Wakelee, H. et al. 2008).

Nowadays, the main challenge is the ability to identify in advance the subpopulation of patients most likely to respond to a particular therapy that would not only increase the likelihood of response, but would also avoid needlessly treating those patients who have little probability of benefiting from treatment.

4. Medical treatment for NSCLC

In the past, many patients with advanced NSCLC received no therapy, since toxicity was thought to outweigh the benefits. Several meta-analyses have reported moderate gains in survival when chemotherapy is used, as compared with the best supportive care. Increases in median survival appear to be in the range of two to four months, and increases in the one-year survival rate appear to range from 10 to 20 percent (Grilli, R. et al. 1993; NSCLC Collaborative Group 1995; 2008).

Although many agents are active against NSCLC, single-agent platinum therapy remained the backbone of treatment until the 1990s. Phase 3 studies in the 1980s did not show that adding a second or third agent was beneficial (Ruckdeschel, J.C. et al. 1985; Ruckdeschel, J.C. et al. 1986). With the development of additional cytotoxic drugs, such as gemcitabine, vinorelbine, paclitaxel, and docetaxel, combination therapy was reevaluated. Several randomized trials evaluating these newer agents in combination with cisplatin compared with cisplatin alone, showed response rates favoring combination therapy, with little additional toxicity (Spira, A. et al. 2004).

In 2002, a randomized phase III study reported a comparison of four commonly used two-drug regimens for advanced lung cancer, showing that all four treatment groups had virtually identical rates of survival and adverse effects, and all response rates were higher than historical response rates with the use of a single agent (Schiller, J.H. et al. 2002). It was the entering on the era where “one size fits all”.

The first randomized phase III trial demonstrating that the addition of a novel drug, the monoclonal antibody against vascular endothelial growth factor bevacizumab, to the standard regimen of chemotherapy with carboplatin and paclitaxel for first line treatment of NSCLC, has a significant survival benefit was published in 2006 (Sandler, A. et al. 2006). In this trial of 878 advanced or recurrent NSCLC patients, median survival was improved 2 months with the addition of bevacizumab (12.3 months versus 10.3 months; HR, 0.79; 95% CI, 0.67-0.92; $P=0.003$). The response rate (RR) was also improved (35% versus 15%, $P<0.001$). But the population under study was restricted to patients who had good performance status (ECOG 0-1), did not have brain metastases, or dominant squamous cell histology or hemoptysis, and who had no history of bleeding diathesis or coagulopathy.

Another recent phase III, randomized, noninferiority study compared overall survival (OS) of the standard regimen cisplatin plus gemcitabine (CG) versus cisplatin

plus pemetrexed (CP) in 1725 chemotherapy-naïve patients with advanced NSCLC (Scagliotti, G.V. et al. 2008). The primary end point of the trial was met, showing that OS for CP was noninferior to CG (median survival 10.3 months in both arms; pemetrexed HR, 0.94; 95% CI, 0.84-1.05). Prespecified analyses demonstrated that histology was also predictive for CP efficacy, but not CG. Patients with nonsquamous histology had statistically superior OS with CP compared with CG (for adenocarcinoma, n=847, median 12.6 versus 10.9 months; HR, 0.84; 95% CI, 0.71-0.99; for large cell carcinoma, n=153, median 10.4 versus 6.7 months; HR, 0.67; 95% CI, 0.48-0.96), whereas patients with squamous cell carcinoma had shorter survival with CP compared with CG (n=473, median 9.4 versus 10.8 months; HR, 1.23; 95% CI, 1.00-1.51). In the CP arm, patients with nonsquamous histology had longer survival than patients with squamous cell carcinoma, whereas in the CG arm, survival differences by histology were not observed. The treatment-by-histology interaction necessitated separate analyses by treatment arm, which prevented an exact determination of the prognostic role for histology, independent of treatment. With the progress toward individualized patient care, increased attention to tumor histology will aid in maximizing survival in patients with advanced NSCLC (Scagliotti, G.V. et al. 2008).

Since virtually all patients with advanced disease initial therapy will ultimately fail, second-line therapy will often be necessary. For second-line treatment, three agents have been approved so far, based on randomized phase III trials: two cytotoxic drugs, docetaxel and pemetrexed, and one targeted therapy, erlotinib. These drugs, although providing a modest 1-year survival benefit (ranging from 6 to 10%), significantly improve quality of life and cancer-related symptoms (Shepherd, F.A. et al. 2000; Hanna, N. et al. 2004; Shepherd, F.A. et al. 2005).

The randomized phase III trial that compared docetaxel with best supportive care (BSC), was initially designed to compare docetaxel at a dose of 100 mg/m² three-weekly (D100); however, an excess of treatment-related deaths led to a dose reduction to 75 mg/m² (D75) for patients enrolled in the second half of the trial (Shepherd, F.A. et al. 2000). Comparison of the survival outcomes revealed a significant benefit for treatment for the combined docetaxel arms over BSC, and for D75 versus BSC75 (7.5 versus 4.6 months; $P=0.01$), but no difference in survival for D100 versus BSC100. This survival benefit was seen despite a low overall tumor response rate of 5.8% and an overall stable disease rate of 43% for the combined docetaxel arms. The quality of life (QoL) analysis revealed a significant difference in mean patient-rated pain scores, favoring the combined docetaxel treatment arms over BSC ($P=0.005$), and trends in

favor of treatment for observer-rated scales for fatigue and pain (Dancey, J. et al. 2004).

The other land-marker randomized phase III trial with chemotherapy for second-line of treatment of NSCLC, was designed to test for non-inferiority with respect to survival of pemetrexed at a dose of 500 mg/m² versus docetaxel at 75 mg/m², each administered on a three-weekly schedule (Hanna, N. et al. 2004). The median number of cycles of chemotherapy administered was four in both groups. Median follow-up for all patients was 7.5 months, and 71.6% of patients had died by the time of the analysis. The primary test for non-inferiority required that survival with pemetrexed be ≤10% worse than with docetaxel (corresponding to a true hazard ratio [HR] of 0.83 and an upper 95% confidence limit [CI] of <1.11 for pemetrexed over docetaxel). This test for non-inferiority was not met (HR 0.99; 95% CI 0.82 to 1.2; non-inferiority *P*=0.226). However, a second pre-planned test of non-inferiority (percent retention method), which required that pemetrexed retain ≥50% of the survival benefit of docetaxel over BSC observed in the precedent clinical trial (Shepherd, F.A. et al. 2000) was statistically significant (102% survival benefit retained with a lower 95% confidence limit of 52%, *P*=0.047). In a multivariate analysis, survival was also shown to be similar for both treatment groups (HR 0.93; 95% CI 0.76–1.13; non-inferiority *P*=0.051) after adjusting for variables associated with increased survival (PS, disease stage, and time since last chemotherapy). QoL assessments indicated no significant differences between the treatment groups.

Erlotinib is the only specifically approved agent for third-line treatment, as half of the patients included in the landmark trial comparing erlotinib with best supportive care had previously received two chemotherapy regimens (Shepherd, F.A. et al. 2005). The double-blind randomized phase III trial, conducted by the National Cancer Institute of Canada Clinical Trials Group (BR.21), assigned patients in a 2:1 ratio to erlotinib at a dose of 150 mg daily or placebo until disease progression or unacceptable toxicity. Eligible patients were required to have received one or two prior chemotherapy regimens and be unsuitable for further chemotherapy. The study was initially powered to detect a 50% improvement in median survival but before analysis the sample size was adjusted to provide power to detect a 33% improvement in median survival. The comparison of survival outcomes revealed a significant survival benefit for erlotinib over placebo, after adjustment for stratification factors (except center) and EGFR status. The difference in RR was also statistically significant. Analysis of the clinical predictors of response to erlotinib suggested a higher response rate for patients of female gender, Asian ethnicity, adenocarcinoma histology, and a history of never smoking, although

only adenocarcinoma histology ($P=0.01$) and a history of never smoking ($P=0.001$) were significantly associated with response in a multivariate analysis. In a multivariate analysis, the factors associated with longer survival included treatment with erlotinib ($P=0.002$), Asian origin ($P=0.01$), adenocarcinoma ($P=0.004$), and non-smoking history ($P=0.0048$). Analysis for predictors of survival benefit indicated that erlotinib had a beneficial effect in most subgroups, and the only significant factor that predicted differential survival benefit for erlotinib therapy was smoking history. A similar survival benefit was found for both second- and third-line patients (adjusted HR, 0.8; 95% CI, 0.6–1.1 for both). The molecular analysis of tumor samples was only performed to 328 of 731 study participants (Tsao, M.S. et al. 2005). The analysis performed included the quantification of EGFR protein expression, estimation of *EGFR* gene copy number, and sequencing of exons 18–21 to identify *EGFR* gene mutations, which was successful for only 325, 125, and 177 samples, respectively. Univariate analysis of the results suggested an association between *EGFR* gene amplification/polysomy, but not EGFR gene mutation, and the likelihood of response to erlotinib, although EGFR expression was the only molecular marker significantly associated with response, in a multivariate analysis ($P=0.03$). The survival of patients with EGFR-expressing tumors (EGFR-positive), and those with *EGFR* gene amplification/polysomy, was longer with erlotinib than placebo, while survival for patients with EGFR-negative or non-amplified tumors was not different between treatment groups. However, neither EGFR expression nor *EGFR* gene mutation or copy number were significantly associated with survival benefit for erlotinib, in a multivariate analysis. The QoL analysis reported for the BR.21 trial indicated a significant benefit for erlotinib in time to deterioration in several patient-reported symptoms, including cough (adjusted $P=0.04$), dyspnea (adjusted $P=0.03$), and pain (adjusted $P=0.04$). Treatment with erlotinib was also associated with more frequent improvement in overall physical function ($P=0.01$), overall emotional function ($P=0.01$), and global QoL ($P=0.01$), compared with placebo. Grade 3/4 toxicities occurred with similar incidence in both treatment arms, with the exception of rash and diarrhea, which occurred more frequently with erlotinib, and infection, which occurred more frequently with placebo (Bezjak, A. et al. 2006).

The clinical improvements provided by first- and second-line treatment in NSCLC have led a higher proportion of patients to be considered for third-line treatment, rising from 6% in 1990s (Massarelli, E. et al. 2003) to 26% after 2000 (Murillo, J.R., Jr. et al. 2006). Although a survival benefit may also exist in some cases, the main aim of third-line treatment should be palliation of symptoms with minimum side effects.

A recent analysis of the Surveillance, Epidemiology, and End Results data from 1990–2005 does demonstrate a significant but modest improvement in the treatment of stage IV lung cancer over the last 15 years, with 1-year survival rates improving by 6% and 2-year survival rates improving by 3% (Figure 7). Moreover, this study showed that different histologic subtypes of NSCLC had differential improvements (Morgensztern, D. et al. 2009).

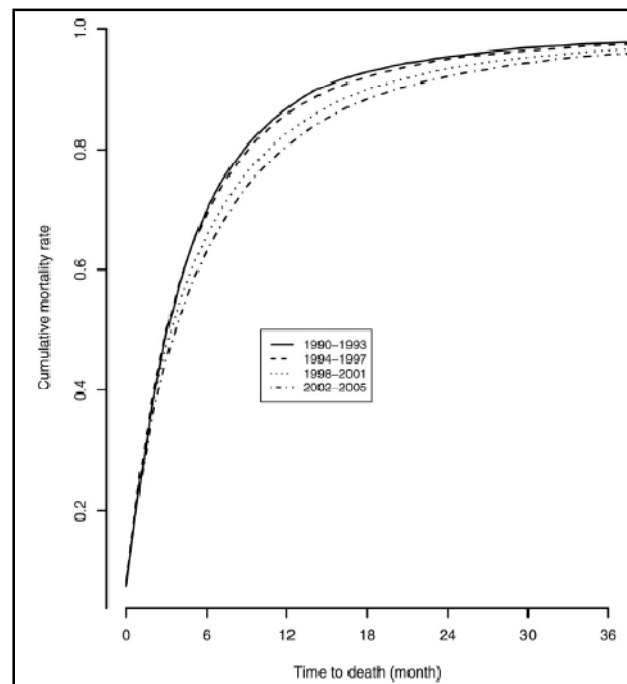


Figure 7 – Cumulative mortality rate according to diagnostic period (Morgensztern, D. et al. 2009).

Patients with adenocarcinoma histology have seen an 8% improvement in their 1-year survival rate, from 15% to 23%, even in an era when the clinical significance of histology was not recognized. Much of this benefit was achieved during the 2002–2005 period, in which erlotinib, gefitinib, and pemetrexed were approved. During that period, the observed survival duration for patients with the adenocarcinoma and squamous cell histologic subtypes diverged for the first time in history. With multiple new treatments that appear safer and more effective in patients with adenocarcinoma, this difference is likely to widen in the coming years. It is clear that histology is critical in choosing the appropriate therapy for NSCLC patients. Going forward, that is a real chance that improved molecular testing will augment and even replace histologic classification alone.

5. Prognostic and predictive factors to personalized therapy for NSCLC

Prognostic factor is a tumor or patient's characteristic that provides information on outcome (usually survival), regardless of the therapy used. Predictive factor is a clinical cellular or molecular marker, which provides information on outcome with regards to a specific therapy. These factors are relevant for the patient and for the physician, because they can give an accurate prognosis (in terms of recurrence or progression of the disease and survival), help in establishing the best treatment choice, help to design the right clinical trials and in interpreting the results (Shepherd, F.A. et al. 2006).

Classic prognostic factors include a history of tobacco consume (Kawaguchi, T. et al. 2010), the performance status (Kawaguchi, T. et al. 2010), co-morbidities of the patient (Asmis, T.R. et al. 2008) and disease stage (Sculier, J.P. et al. 2008).

Smoking is well known to be the main cause of lung cancer and therefore an increase of lung cancer mortality is significantly associated with the increase in the number of smokers (Huxley, R. et al. 2007). The influence of smoking in the prognosis of the patients with NSCLC was investigated in a study with 770 patients who underwent resection of primary NSCLC (Hanagiri, T. et al. 2008). The authors described a 5-year survival rate after surgery of 66,8% in the never-smokers group, 56,2% in the smokers with Packet Year Inhaled (PYI) less than or equal to 20 and 55,1% in those with PYI more than 20 (Figure 8). The prognosis was significantly poorer in the smokers with PYI more than 20 than that of the never smokers ($P=0.001$). In another study of a single institution, 141 never-smokers patients and 542 current smokers were analyzed. A statistically significant difference in the 5-year survival was observed between current smokers and never-smokers (16% versus 23%, $P=0.004$). Smoking was identified as an independent and negative prognostic factor by multivariate analysis (Nordquist, L.T. et al. 2004) (Figure 9).

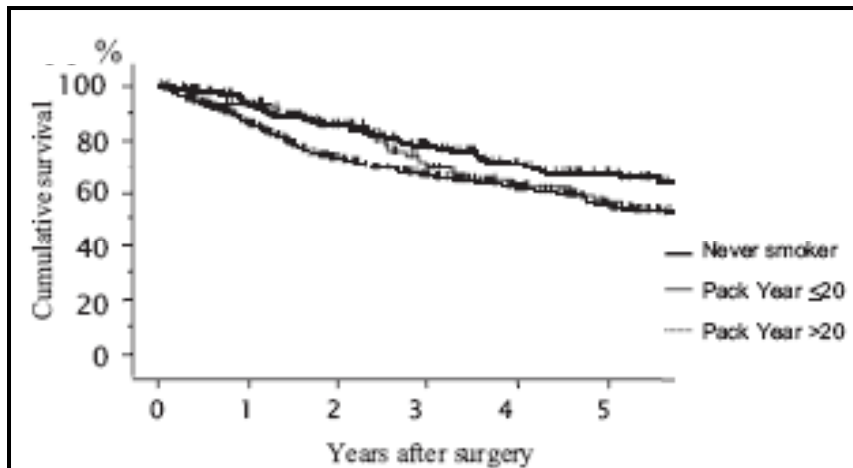


Figure 8 – Overall survival curves of all patients according to smoking history (Hanagiri, T. et al. 2008).

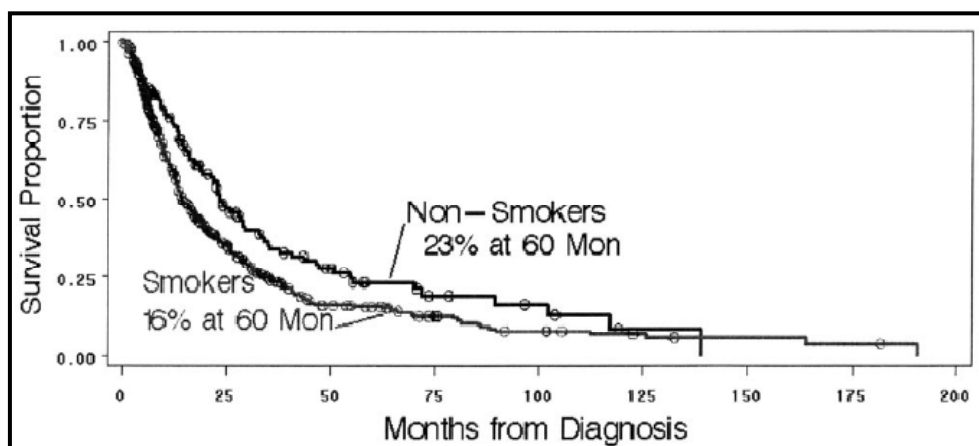


Figure 9 – Overall survival of never-smokers (nonsmokers) versus current smokers (Nordquist, L.T. et al. 2004).

The prognostic value of the performance status of the patients was evaluated in a study involving 109 stage III or IV NSCLC patients and which permitted also the determination of the congruency between physician-rated performance status (MD-PS) and patient-rated performance status (Pt-PS) (Dajczman, E. et al. 2008). Performance status was associated with survival irrespective of whether MD-PS or Pt-PS was used ($P=0.001$ for MD-PS and $P=0.001$ for Pt-PS) (Figure 10). The survival of patients with PS 0 to 1 was the same irrespective of rater. However, the median survival in 31 patients with MD-PS ≥ 2 was 3.3 (CI; 1.7– 4.9) months, whereas 49 patients with Pt-PS ≥ 2 had a median survival of 6.2 (CI; 5.4–6.9) months. The level of agreement between

MD-PS and Pt-PS with respect to entry into a hypothetical clinical trial where eligibility required a performance status of ≤ 1 , was only moderate (kappa coefficient = 0.42). In 79 (72%) cases, MD-PS and Pt-PS were congruent both rating PS as 0 to 1, whereas in 30 (28%) cases there was a lack of agreement on eligibility for the trial.

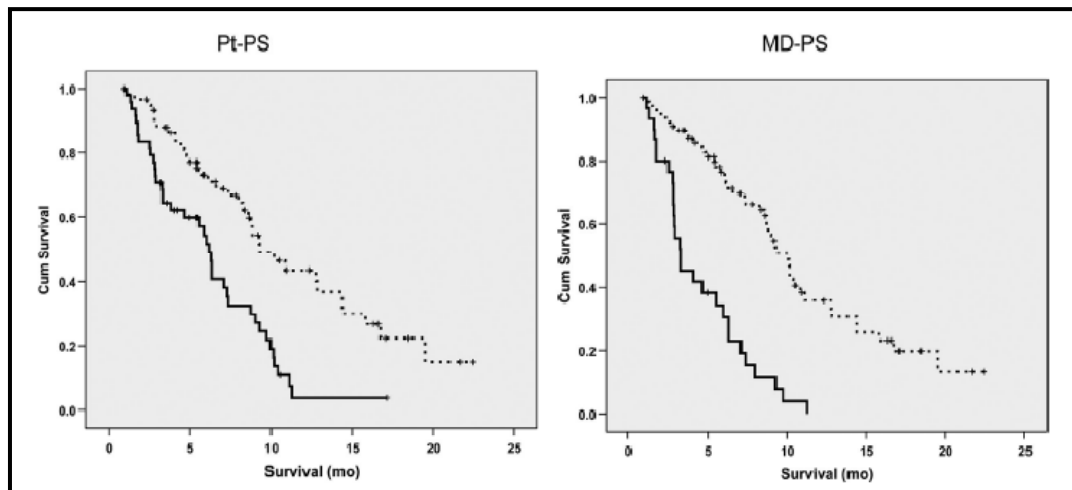


Figure 10 – Kaplan-Meier survival curves of performance status rated by patients (Pt-PS) and by physicians (MD-PS) (..... PS 0 to 1; ____ PS ≥ 2) (Dajczman, E. et al. 2008).

‘Comorbidity’ refers to non-cancer-related physical and mental disorders that may also affect a patient outcome and treatment safety. Comorbidity should be distinguished from functional status, because the latter is a measure of a patient’s ability to perform daily activities or other tasks (Firat, S. et al. 2002a; Firat, S. et al. 2002b). Comorbidities may prevent the physician from delivering optimal therapy because of possible treatment-related side effects. Furthermore, for cancer in the elderly, comorbidities can have a major impact on survival (Extermann, M. et al. 1998). There are some scales to assess the possible impact of comorbidities on the prognostic (Colinet, B. et al. 2005; Asmis, T.R. et al. 2008).

Another prognostic factor is the stage of the disease at the time of diagnosis. The importance of this factor is well known and was the motif for the recent re-evaluation by the International Association for the Study of Lung Cancer (IASLC) International Staging Committee (ISC) and proposals for revision of the tumor, node, metastasis (TNM) descriptors (Rusch, V.W. et al. 2006; Goldstraw, P. et al. 2007;

Postmus, P.E. et al. 2007; Rusch, V.W. et al. 2007) and stage groupings (Goldstraw, P. et al. 2007) for lung cancer in the forthcoming (7th) edition of the International Union Against Cancer and American Joint Committee on Cancer TNM Classification of Malignant Tumors (Figure 11).

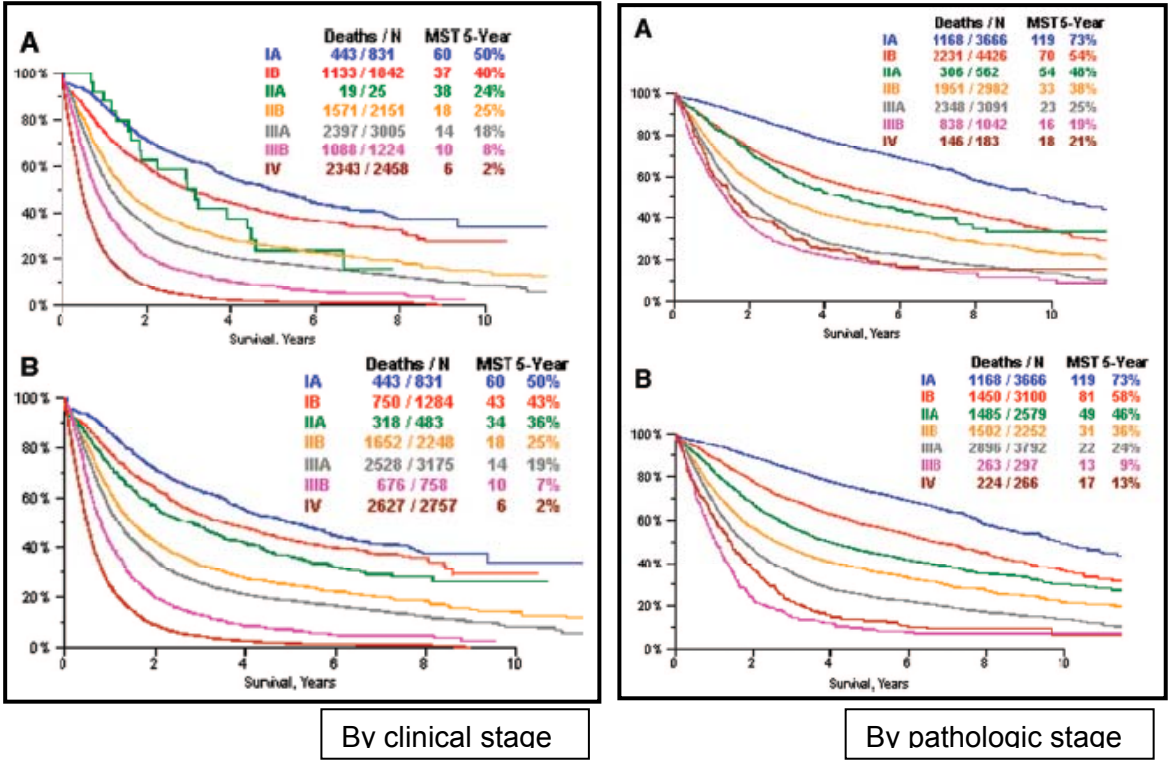


Figure 11 – Overall survival, expressed as median survival time (MST) and 5-year survival, by clinical stage and by pathologic stage using sixth edition of TNM (A) and proposed International Association of the Study of Lung Cancer recommendation (Goldstraw, P. et al. 2007).

Several molecular markers, such as the epidermal growth factor receptor (*EGFR*), the excision repair cross-complementing 1 (*ERCC1*), the ribonucleotide reductase subunit M1 (*RRM1*) and the breast cancer susceptibility gene1 (*BRCA1*), are still a matter of extensive debate as lung cancer prognostic factors (Dziadziuszko, R. et al. 2008; Perez-Soler, R. 2009; West, H. et al. 2009).

EGFR is a tyrosine kinase receptor (TK) expressed in the majority of NSCLCs. Tumor somatic mutations in exons 18 through 21 of the TK domain of EGFR may define a subset of tumors that are highly dependent on EGFR signaling and more responsive to EGFR inhibition. In a recent phase III randomized trial (TRIBUTE) with

1079 advanced or metastatic NSCLC patients treated in first-line with carboplatin and paclitaxel with or without concurrently erlotinib, no advantage for survival, overall response rate (ORR), time to progression (TTP) and duration of response was observed for the arm containing erlotinib over the carboplatin and paclitaxel alone (Herbst, R.S. et al. 2005). Eberhard and co-workers performed an elegant study sequencing *EGFR* and *KRAS* in lung cancer tissue samples obtained from the patients enrolled in the TRIBUTE trial, not preselected based on response or other clinical characteristics. They observed that patients with *EGFR* mutations showed significantly better clinical outcomes than those with wild type *EGFR* in all assessed endpoints (ORR, TTP, and survival) (Eberhard, D.A. et al. 2005).

ERCC1 is a structure-specific DNA repair endonuclease responsible for the 5-prime incision and for the removal of adducts from genomic DNA caused by the action of cisplatin and other cancer chemotherapeutic agents (Reardon, J.T. et al. 1999; Niedernhofer, L.J. et al. 2004). Pivotal data from primary NSCLC specimens suggest a different, but not contradictory, prognostic significance for ERCC1 in treated (Lord, R.V. et al. 2002) and untreated patients (Simon, G.R. et al. 2005). Taken together, all these studies show that the relative ERCC1 messenger RNA (mRNA) level could be inversely associated with response and survival as an independent indicator of cisplatin efficacy. Theoretically, high levels of ERCC1 in untreated patients, better DNA repair, better prognosis (Simon, G.R. et al. 2005). But low levels of ERCC1, worst efficiency in DNA repair, more efficacious the treatment with platinum are and so better prognosis for treated NSCLC patients (Ceppi, P. et al. 2006; Olaussen, K.A. et al. 2006; Rosell, R. et al. 2006).

Ribonucleotide reductase M1 (RRM1), a key enzyme of the DNA synthesis, catalyzing the biosynthesis of deoxyribonucleotides from the corresponding ribonucleotides, is involved in tumor invasiveness and metastasis (Fan, H. et al. 1997; Gautam, A. et al. 2003), and data indicates that higher levels of RRM1 are associated with chemoresistance to gemcitabine-based therapies (Ceppi, P. et al. 2006; Rosell, R. et al. 2006). It has been demonstrated that low levels of expression of the gene are associated with poor survival among patients with NSCLC (Bepler, G. et al. 2004). It is interesting to observe that the RRM1 protein in NSCLC cells is nuclear, highly correlated with ERCC1 expression, and significantly associated with disease-free and overall survival. The coordinate high expression of RRM1 and ERCC1 defines a subgroup of patients with an excellent outcome (Zheng, Z. et al. 2007).

BRCA1 expression is important in DNA repair, activation of cell-cycle checkpoints and maintenance of chromosomal stability (Liu, S. et al. 2008). Classically,

BRCA1 has been implicated as a modulator of response to DNA damage induced by chemotherapy and radiation therapy (Reguart, N. et al. 2008). It is known that upregulated *BRCA1* is part of a characteristic gene signature in aggressive lung cancers (Deeb, K.K. et al. 2007). Patients whose tumors had high BRCA1 expression had significantly worse survival (Rosell, R. et al. 2007).

All these molecular markers, together with *KRAS* mutation, are also predictive factors. *EGFR* mutations, gene copy number or overexpression helps to identify patients more likely to respond to EGFR tyrosine kinase inhibitors, ERCC1 could guide chemotherapy choice (platinum-based versus other chemotherapy), *KRAS* could identify patients unlikely to respond to EGFR tyrosine kinase therapy and unlikely to respond to adjuvant vinorelbine/cisplatin chemotherapy, and RRM1 could guide chemotherapy choice for gemcitabine-based versus other chemotherapy (Shepherd, F.A. et al. 2007).

In 2008, the histology emerged as another strong prognostic and predictive factor. In a retrospective analysis of the second-line phase III study comparing pemetrexed with docetaxel (Hanna, N. et al. 2004), patients with nonsquamous cell cancers had a better survival with pemetrexed (n=399, median 9.3 versus 8.0 months; HR, 0.778; 95% CI, 0.607–0.997), whereas those with squamous carcinomas had an inferior survival with pemetrexed (n=172, median 6.2 versus 7.4 months; HR, 1.56; 95% CI, 1.079–2.264) (Peterson, P. et al. 2007). Such differences, also observed in the first-line phase III trial that compare cisplatin plus gemcitabine versus cisplatin plus pemetrexed, may be related to increased expression of thymidylate synthase in squamous carcinoma (Scagliotti, G.V. et al. 2008).

Pharmacogenetics and pharmacogenomics are promising areas that, in the near future, will be crucial for personalized medicine, ultimately leading to drug prescription based on a patient's individual genetic and molecular profile (Yan, L. et al. 2005). Their aim is to establish a meaningful relationship between genotype (i.e., polymorphisms and genetic mutations), gene expression profiles (i.e., level of gene expression of all or of target genes in the genome), and phenotype, interpreted as the variability among individuals in terms of response and toxicity to different drugs. Pharmacogenetics commonly refers to the effects that involve a limited number of genes, often connected to drug metabolism, whereas pharmacogenomics involves the study of complex multigene patterns within the genome (Araujo, A. et al. 2007).

Genetic polymorphisms are variants in individual genomes, present in more than 1.5% of the population, that remain constant throughout a person's lifetime (Yan, L. et al. 2005). There are more than 1.4 million single nucleotide polymorphisms (SNPs) identified in the human genome, and many of them contribute to variability in both pharmacokinetic and pharmacodynamic of drugs (Sachidanandam, R. et al. 2001). Genetic mutations are acquired changes in gene sequences and occur only in certain cells. The interindividual genetic variation may also be an important factor in the characterization of susceptibility for the development of cancer and of variability to drug response (Kikuchi, T. et al. 2003; Evans, W.E. et al. 2004; Medeiros, R. et al. 2004; Efferth, T. et al. 2005; Coelho, A. et al. 2006; Ribeiro, R. et al. 2006; Jain, L. et al. 2009; O'Donnell, P.H. et al. 2009).

Gene expression profiling has a potential use for "personalized" medicine in the years to come, functioning as a diagnostic tool, predictive and prognostic biomarker (Singhal, S. et al. 2008; Santos, E.S. et al. 2009). It may identify patient groups with significantly different prognosis and also have value in determining, more selectively than stage, which patients will benefit from adjuvant chemotherapy (Custodio, A.B. et al. 2009; Santos, E.S. et al. 2009). A number of prognostic gene expression signatures have been reported to predict survival in NSCLC. Gene expression profiling by means of microarrays (Schena, M. et al. 1995; Meyerson, M. et al. 2004; Hoheisel, J.D. 2006; Singhal, S. et al. 2008) and reverse-transcriptase polymerase chain reaction (RT-PCR) (Endoh, H. et al. 2004; Singhal, S. et al. 2005; Singhal, S. et al. 2008) as well as by other techniques such as SNP chips (Huang, Y.T. et al. 2009) will be useful for classifying tumors and formulating a prognosis for patients with various types of cancer, including lung cancer. The use of microarrays in clinical practice is yet limited, however, by the need for complicated methods, the large number of genes used in genes profiling, the need for fresh-frozen tissue and the lack of both reproducibility and independent validation of the results (Ramaswamy, S. 2004; Singhal, S. et al. 2008). The genes selected for profiling in studies of lung cancer have varied considerably and only a few genes have been consistently included (Chen, J.J. et al. 2001; Garber, M.E. et al. 2001).

Subramanian et al. recently published a review focused in the evaluation of studies that reported prognostic gene expression signatures in NSCLC. They found little evidence that any of the signatures are ready for clinical application. Critical points that need to be clearly addressed by studies reporting prognostic signatures from gene expression data are the statistical validation and reproducibility of the signatures and their actual medical utility (Subramanian, J. et al.).

6. The Portuguese reality

Cancer was considered one of the priorities of the Health National Plan for 2004-2010, with very specific objectives such as the reduction of mortality rates, promotion the expansion of the therapeutic rationality, promotion of equitable access to drugs and improvement of the access to innovative medicines.

Portugal has a surface with 92.090 Km² with a population of 10.627.250 inhabitants and about 427 thousands of unemployed, according the last data of the National Institute of Statistic. In 2008, the gross domestic product (GDP) was 155.446,2 million euro, the GDP *per capita* was 19.800 euro, the unemployed rate was 7,6% (with a rate of long term unemployed of 49,8% of total) and the inflation rate was 2,6%. The GDP and the GDP *per capita* are very well below the mean of the EU (Figure 12).

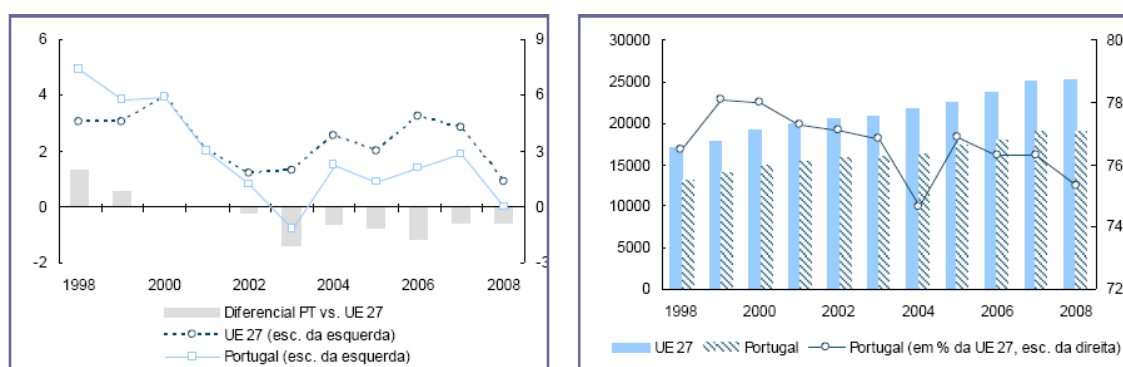


Figure 12 – Gross domestic product (GDP) and GDP per capita of Portugal and of European Union (GPEARI 2009).

In 2006, the GDP was 155.323 million euro and 17.153,3 million euro (about 5,6% of the total) was spent in the health care, which was below the mean average of Europe (Figure 13). The risk of poverty rate (median 60%) before any social transfer, i.e. proportion of population whose equivalent income is below the poverty line defined as 60% of median income per adult equivalent, was 41% in 2008.

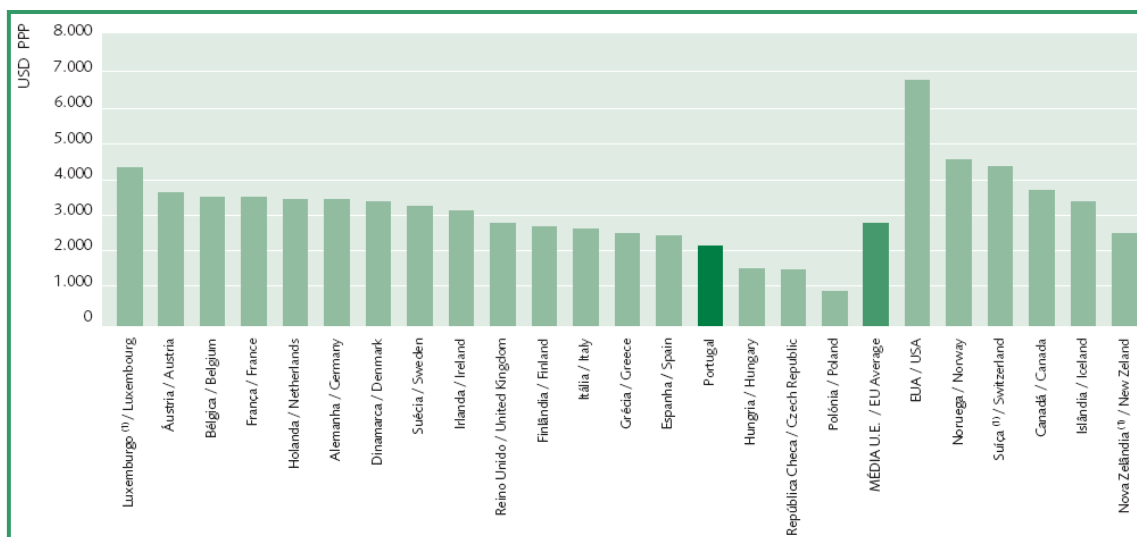


Figure 13 – Health care spending per capita, 2006 (APIFARMA 2008).

In Portugal, the bulk of the health system is a public model. The National Health Service has 30 years and the advantage of having managed to harmonize health outcomes between the Portuguese and the other Europeans, but became heavy and little agile. In 2008, Portugal had 366 medical doctors and 534 nurses per 100.000 inhabitants, with a total of 38.932 medical doctors and 56.709 nurses. In 2007, there were 198 hospitals, 99 publics and equal number of privates, 377 health centers, and 3,5 beds for 1000 inhabitants. In 2008, 24033 deaths from cancer were registered, corresponding to the second cause of death in Portugal just after the cardio-vascular diseases. In 2010, the life expectancy was 75,4 years for men and 82,2 years for women. In 2007, the average approval time for Marketing Authorizations were for centralized procedures of 387 days, for decentralized procedures of 338 days, for mutual recognition procedures of 356 days and for national procedures of 270 days. The Reimbursement average approval time for centralized procedures was of 553 days and for national procedures was 121 days. From the total market of prescription, 79,4% was from ambulatory drugs and 20,6% was from the hospital market. The ambulatory market represented 3.577 million euros, 337 euros *per capita*, which is slightly below the average of the EU (Figure 14). The hospital market represented 930 million euros.

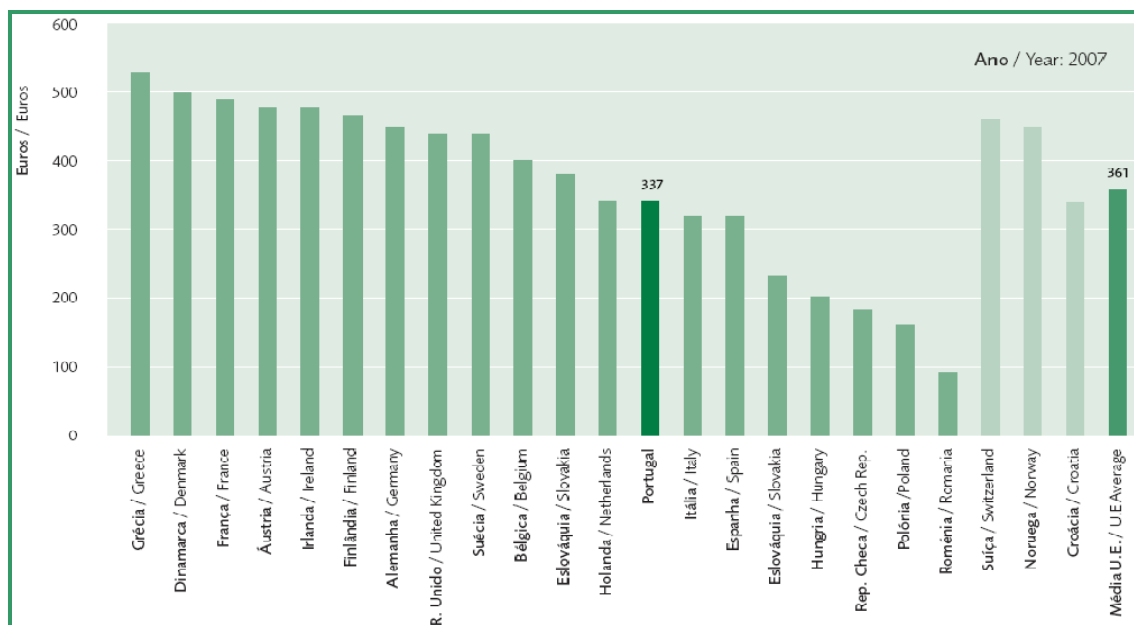


Figure 14 – Ambulatory medicinal products consumption per capita (retail price) in European Union (APIFARMA 2008).

In the Health National Plan for 2004-2010 it is possible to read that the present situation regarding the quality of the provision of health services involves: sparse culture of quality; organizational deficit of health services; lack of performance indicators and for decision support; insufficient structured support to areas of diagnostic and therapeutic decision.

In the Portuguese Great Options for the Plan 2010-2013, defined by the actual government, health is not a priority. In the Portuguese State Budget for 2010 one of the underlines will be the investment in new hospitals, with the goals of a better access to the health and a great rationalization of resources. They write the following lines of action: “financial sustainability of our National Health System, reform of primary health care, technologies of information and communication, rehabilitation of infrastructures, the drug policy (including the unidose sales) and development of the national net of palliative care”. Portuguese governments believe that this is the way to augment the sustainability of the National Health System, increasing the quality and efficiency of the services provided. The total consolidated expenditure of the Ministry of Health will be about 9504,5 million euros (10% more than in 2009), representing 5,7% of GDP and 15,9% of central government expenditure. The national funding of the Investment Plan to further remodeling facilities and health care equipment showed a decline of 1.5 million euros, which corresponds to a negative growth of 4,2% of the previous year.

2. Aims and Research Questions

1. Identification and evaluation of second and third line treatments for non-small-cell lung cancer in Portugal.

Which are the drugs currently used in Portugal in second and third lines of treatment for non-small-cell lung cancer on the daily clinical practice and what is its effectiveness?

2. Evaluation of the role of *EGF* and its receptor and other polymorphisms in non-small-cell lung cancer outcomes.

Is it possible to establish *EGF* and *EGFR* or other polymorphisms as prognostic or predictive factors for non-small-cell lung cancer outcomes and if so can it condition therapy?

3. Evaluation of the costs of cancer treatment in Portugal and of the second and third lines of treatment for non-small-cell lung cancer.

What are the costs of cancer treatment and what is the cost-effectiveness of the second and third lines for the treatment of non-small-cell lung cancer in Portugal?

4. Integration of all the information from the afore described studies in clinical practice, aiming to alert the policy makers for the costs of cancer and the best way to provide to the general population drugs of added therapeutic value.

Can evidence be provided in order to overcome the constraints of cancer funding, to promote equity and rationality of the treatment?

3. Non-Small-Cell Lung Cancer in Portugal

The last Portuguese National Cancer Registry dates back from 2001 and have many flaws in the registration. In Portugal does not have a reliable cancer registry and the one that is published has several years of delay. This makes it very difficult to know the lung cancer Portuguese reality and to acknowledge the current clinical practice in terms of treatment of NSCLC.

A systematic registration of the lung cancer patients in the period between 2000 and 2002 was carried out by the Oncologic Pulmonology Committee of the Portuguese Society of Pulmonology in order to elucidate the Portuguese reality of the lung cancer (Parente, B. et al. 2007) .

After 2000 the only recommended second-line treatment for NSCLC was docetaxel, which, in comparison with the best support care or other cytostatic drugs (vinorelbine or ifosfamide), was associated with an improved survival rate and an acceptable toxicity profile (Fossella, F.V. et al. 2000; Shepherd, F.A. et al. 2000).

Pemetrexed (P), an antifolate antimetabolite with multiple enzyme targets involved in both pyrimidine synthesis and purine synthesis (Paz-Ares, L. et al. 2003), demonstrated similar activity to docetaxel in this patient group, but had a better adverse event profile (Hanna, N. et al. 2004).

Pemetrexed was introduced in Portugal in October 2004. The Portuguese Lung Cancer Study Group (GECP) decided to conduct a study evaluating its efficacy and safety as second-line treatment for advanced or metastatic NSCLC patients in the current clinical practice (Araújo, A. et al. 2008).

Documentos das Comissões de Trabalho

Working Committee Documents

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Estudo epidemiológico do cancro do pulmão em Portugal nos anos de 2000/2002

Epidemiological study of lung cancer in Portugal (2000/2002)

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Resumo

O cancro do pulmão é a causa mais comum de cancro no Mundo. A sobrevida global aos 5 anos é de cerca de 15%, sem grandes previsões de mudança. Em Portugal, relativamente à doença oncológica, situa-se em terceiro lugar, sendo a primeira causa de morte por cancro. O tabaco é responsável por cerca de 85% dos casos. Um estudo efectuado em Portugal durante 3 anos (2000/2002) pela *Comissão de Trabalho de Pneumologia Oncológica da Sociedade Portuguesa de Pneumologia* em 22 hospitais, mostrou que, de um total de 4396 doentes com cancro do pulmão, 81,8% se referem ao sexo masculino e 18,2% ao sexo feminino, com uma média etária de $64,49 \pm 11,28$ anos. Cerca de 70% dos doentes era fumador ou ex-fumador, com 50,3% com *performance status* (PS) grau I da escala de Zubrod.

Do ponto de vista histológico, 37,5% eram adenocarcinomas, seguido do carcinoma epidermóide com 30,5% dos casos e dos tumores de pequenas células com 12,5%; carcinomas neuroendócrinos em 1,4% dos casos; CPNPC 10,5%, mistos em 0,7%, carcino-

Abstract

Lung cancer is the most common form of cancer death in the world. Five-year survival is about 15%, without any change to this picture envisaged.

It is the 3rd most prevalent type of cancer in Portugal and the primary cause of cancer death. 85% of lung cancer cases are attributable to smoking.

One study performed in Portugal for 3 years (2000/2002) by the *Lung Oncology Work Committee of the Portuguese Society of Pulmonology* in 22 Hospitals showed that of a total of 4396 patients with lung cancer, 81.8% were male and 18.2% were female, with a mean age of 64.49 ± 11.28 years. About 70% of patients were smokers or former smokers, with 50.3% of patients presenting with performance status (*Zubrod*) 1. Histologically, 37.5% were adenocarcinoma, followed by squamous carcinoma in 30.5% of cases, and small cell lung cancer in 12.5%; neuroendocrine carcinoma presented in 1.4% of cases; non small cell lung cancer in 10.5%; mixed carcinoma in 0.7%; large cell carci-

¹ Coordenadora da Comissão de Trabalho de Pneumologia Oncológica (2000/2002). Relatora do documento.

² Participantes

mas de grandes células em 2,3% e outros e não especificados em 4,6% dos casos,

O estadiamento, efectuado em 4097 casos, mostrou 113 doentes no estágio IA (2,8%) e 250 (6,1%) no IB; no estágio IIA apenas 0,8 % e 4,5% no IIB; no estágio IIIA 9,1% dos doentes, comparativamente ao IIIB com 29,9% dos casos, encontrando-se 46,9 % dos doentes já no estágio IV na altura do diagnóstico.

Em 3855 dos casos foi possível determinar a primeira opção terapêutica.

Foi efectuada cirurgia em 8,2% e terapêuticas combinadas (combinações de cirurgia com quimioterapia, ou radioterapia, ou a associação de QT com RT) em 21,8% dos casos; a QT isolada como primeira opção terapêutica foi efectuada em 43,7% dos doentes e em 20,3% apenas terapêutica de suporte.

Rev Port Pneumol 2007; XIII (2): 255-265

Palavras-chave: Cancro do pulmão, epidemiologia, tabagismo, terapêutica, Portugal.

noma in 2.3%; and others/not specified in 4.6% of cases.

Staging (known in 4097 patients), showed 113 patients in stage IA (2.8%) and 250 patients in stage IB (6.1%); only 0.8% in stage IIA and 4.5% in stage IIB; 9.1% in stage IIIA and 29.9% in stage IIIB; 46.9% were already in stage IV by the time of diagnosis.

The first therapeutic option was known in 3855 patients.

Surgery was performed in 8.2% and 21.8% of cases were treated with combined therapies (surgery and chemotherapy or radiotherapy, or combination of chemotherapy and radiotherapy); chemotherapy alone was first choice in 43.7% of patients and in 20.3% only best support therapy was chosen.

Rev Port Pneumol 2007; XIII (2): 255-265

Key-words: Lung cancer, epidemiology, smoking, therapeutic, Portugal.

Introdução

A neoplasia do pulmão é uma das mais frequentes em Portugal, sendo responsável por um grande número de mortes, quer no sexo masculino quer no sexo feminino. É o mais frequentemente diagnosticado no mundo e a causa de morte mais comum por cancro, quer em homens quer em mulheres.

Em Portugal estima-se uma incidência de cerca de 3400 novos casos nos últimos anos, com aumento do número na mulher.

Os doentes são diagnosticados muito tardiamente, sendo que apenas cerca de 20% se encontra em estágio cirúrgico.

Em Portugal¹ estima-se incidência bruta actual de 34/100 000 com 28/100 000 novos

casos para o homem e 6/100 000 para a mulher.

A Comissão de Trabalho de Pneumologia Oncológica, da Sociedade Portuguesa de Pneumologia (SPP), decidiu efectuar um trabalho de recolha de dados de cancro do pulmão, diagnosticados em hospitais portugueses, tendo o referido estudo visado caracterizar os doentes com aquela neoplasia no período de 2000 a 2002.

Metodologia

Foi efectuado um registo sistematizado, numa base de dados do programa Excel, distribuída previamente aos hospitais e recolhidas anualmente, referente aos doentes com

cancro do pulmão, em 22 hospitais portugueses, localizados no Norte, Centro e Sul do país, tendo sido recolhidos dados relativos a características demográficas, hábitos tabágicos, tipo histológico, estadiamento e opção terapêutica.

Os dados foram estudados de acordo com a idade, sexo, tipo histológico da neoplasia, com o estadiamento, a escala de Zubrod (*performance status*) e a presença ou não de hábitos tabágicos.

As variáveis foram analisadas tendo-se utilizado métodos de estatística descritiva, nomeadamente tabelas de frequência e tabelas de contingência para as variáveis categóricas, e média, desvio-padrão, máximos e mínimos para as variáveis contínuas.

A análise da associação entre variáveis de caracterização global – hábitos tabágicos e variáveis de caracterização clínica – tipo histológico, estadiamento do tumor e *performance status* segundo a escala de Zubrod foi efectuada através de curvas de Kaplan-Meier.

Assumiu-se um nível de significância estatística de 95%.

Resultados

Foram analisados os registos de 4396 processos de doentes com neoplasia do pulmão observados em consulta nos anos de 2000, 2001 e 2002 nos seguintes hospitais: Centro Hospitalar de Vila Nova de Gaia, Hospital de São João (Porto), Hospital de Santa Maria (Lisboa), Centro Hospitalar de Coimbra, Hospitais da Universidade de Coimbra, Hospital de Pulido Valente (Lisboa), Hospital Pedro Hispano (Matosinhos), Hospital de Santa Luzia (Viana do Castelo), Hospital de S. Marcos (Braga), Hospital de Vila Real, Hospital Sra. da Oliveira (Guimarães), Hospital de Évora, Hospital da Guarda, Hospital Egas Moniz (Lisboa), Hospital Garcia de Orta (Almada), Hospital Joaquim Urbano (Porto), Hospital São Bernardo (Setúbal), Hospital Distrital de Faro, Hospital de São Sebastião (Sta Maria da Feira), Hospital de Vila Nova de Famalicão, IPO do Porto e IPO de Lisboa.

As **características globais dos doentes** foram resumidas no Quadro I.

Do total dos doentes avaliados, 81,8 % eram do sexo masculino e 18,1% do sexo femini-

Quadro I – Caracterização global dos doentes (n = 4396)

	Número (n)	Percentagem (%)
Sexo: Feminino / masculino	797/ 3596	18,1/ 81,8
Idade média ± desvio padrão	64,49 ± 11,28	
Habitos tabágicos	3847	
Fumador	2185	56,8
Ex-fumador	751	19,5
Não fumador	911	23,7
Estado geral / Zubrod	3737	
0	332	8,9
1	1879	50,3
2	948	25,4
3	442	11,8
4	136	3,6

no, com uma média etária global de 64,49 anos e um desvio-padrão de $\pm 11,28$ anos. De notar que apenas 23,7 % de doentes eram não fumadores, representando ainda os fumadores activos cerca de 56,8% (Quadro I). Relativamente à *performance status* dos doentes (escala de Zubrod), só 8,9 % se encontrava assintomático à data do diagnóstico (Zubrod 0), encontrando-se 50,3 % com Zubrod 1; com Zubrod 3 e 4 foram classificados 15,4% dos doentes.

O adenocarcinoma (Quadro II) foi o tipo histológico mais frequente. O carcinoma epidermóide e o CPPC, tumores mais na dependência do tabaco, têm vindo a reduzir sucessivamente aos longos dos anos, representando (este último) nestes três anos cerca de 12,6 % do total dos casos.

A maioria dos doentes analisados (Quadro III) tinha neoplasia em estágio IIIB/ IV (76,8%).

Quadro II – Caracterização por tipo histológico (n= 4396)

Tipo histológico	n	%
Adenocarcinoma	1656	37,5
Carcinoma epidermóide	1320	30,5
CPPC/NE	553/63	12,5/1,4
CPNPC	464	10,5
Carcinomas mistos	33	0,7
Carcinomas de grandes células	99	2,3
Outros	128	2,8
N/especif.	80	1,8

Quadro III – Caracterização dos estádios

Estadiamento (n=4097)	Número de doentes	Percentagem (%)
IA / IB	113 / 250	2,8 / 6,1
IIA / IIB	32 / 184	0,8 / 4,5
IIIA / IIIB	373 / 1223	9,1 / 29,9
IV	1922	46,9

Quadro IV – Relação sexo / estágio (n=4097)

Estádio	Sexo feminino	Sexo masculino	P (sig) §
I A	35 31,0%	78 69,0%	< 0,001
I B	52 20,8%	198 79,2%	
II A	1 3,1%	31 96,9%	
II B	32 17,4%	152 82,6%	
III A	58 15,5%	315 84,5%	
III B	184 15,0%	1039 85,0%	
IV	380 19,8%	1542 80,2%	

§ Pearson qui-quadrado

Restando 23,2% para estádios eventualmente cirúrgicos (única terapêutica até agora potencialmente curável).

Na apreciação que efectuámos da relação sexo e tipo histológico (Quadro V), verificou-se que o adenocarcinoma, comparativamente ao carcinoma epidermóide, tem uma muito maior expressão no sexo feminino 28,3% *vs* 7,2 %, apresentando-se o CPPC nas mulheres apenas em 10,5% dos casos, dado ser um tipo histológico eminentemente ligado aos hábitos tabágicos.

Análise por hábitos tabágicos

Apesar do aumento crescente dos hábitos tabágicos na mulher (20,9% das doentes são fumadoras ou ex-fumadoras), continua a verificar-se ainda um aumento acentuado dos hábitos tabágicos do homem, comparativamente à mulher, situação que tem tendência a reduzir de uma forma progressiva. Nesta série, 10,3% dos homens era não fumador

Quadro V – Relação sexo / tipo histológico (n=4393)

Tipo histológico	Sexo feminino	Sexo masculino	p (sig) §
Não especificado	23 72,9%	62 27,1%	< 0,001
Adenocarcinoma	468 28,3%	1188 71,7%	
CPNPC	71 15,3%	393 84,7%	
Carcinoma epidermóide	95 7,2%	1225 92,8%	
Carcinoma de grandes células	10 11,2%	79 88,8%	
Carcinoma misto	8 24,2%	25 75,8%	
Carcinoma neuroendócrino	24 38,1%	39 61,9%	
Outros	39 30,5%	89 69,5%	
Carcinoma de pequenas células	58 10,5%	495 89,5%	

§ Pearson qui-quadrado

versus 79,1% das mulheres não fumadora (Quadro VI).

Contudo, ser fumador (Quadro VII) era uma característica comum à maioria dos doentes, independentemente do tipo de carcinoma, ou seja, o número de fumadores em qualquer tipo histológico era significativamente superior ao de não fumadores e ex-fumadores, excepto no carcinoma neuroendócrino (maioria de doentes não fumadores). Relativamente aos ex-fumadores, foi possível verificar que a maioria tinha carcinoma epidermóide.

Não existe relação entre o estágio da doença e o hábito ou não de fumar (Quadros VIII e IX), bem como com o estado geral (Zubrod). O número de doentes fumadores foi estatisticamente superior aos outros doentes, independentemente da classificação do estado geral segundo a escala de Zubrod. Por outro lado, a análise da *performance status* (PS) permite concluir que o número de doentes de PS 1 é estatisticamente superior ao dos outros níveis, quaisquer que sejam os seus hábitos tabágicos.

Quadro VI – Sexo / hábitos tabágicos

	Fumador	Não fumador	Ex-fumador
Sexo masculino n=3100	2065 (66,6%)	715 (23,1%)	320 (10,3%)
Sexo feminino n=747	120 (16,1%)	36 (4,8%)	591 (79,1%)

ESTUDO EPIDEMIOLÓGICO DO CANCRO DO PULMÃO EM PORTUGAL NOS ANOS DE 2000/2002

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Quadro VII – Tipo histológico / hábitos tabágicos

	Fumador	Não fumador	Ex-fumador	p (sig) §
Não especificado	28 47,5%	23 39,0%	8 13,6%	< 0,001
Adenocarcinoma	683 48,1%	513 36,2%	223 15,7%	
CPNPC	237 56,7%	83 19,9%	98 23,4%	
Carcinoma epidermóide	752 64,1%	122 10,4%	299 25,5%	
Carcinoma grandes células	46 58,2%	15 19,0%	18 22,8%	
Misto	18 54,5%	7 21,2%	8 24,2%	
Neuroendócrino	18 30,5%	33 55,9%	8 13,6%	
Outros	53 44,9%	50 42,4%	15 12,7%	
Carcinoma de pequenas células	349 71,7%	64 13,1%	74 15,2%	

§ Pearson qui-quadrado

Quadro VIII – Hábitos tabágicos / estágio

	Fumador	Não fumador	Ex-fumador	p (sig) §
I A	42 2,0%	42 4,9%	20 2,8%	< 0,001
I B	109 5,3%	62 7,2%	52 7,2%	
II A	17 0,8%	5 0,6%	6 0,8%	
II B	88 4,3%	32 3,7%	40 5,5%	
III A	192 9,4%	61 7,1%	80 11,0%	
III B	652 31,8%	233 27,1%	209 28,9%	
IV	950 46,3%	426 49,5%	317 43,8%	

§ Pearson qui-quadrado

Quadro IX – Hábitos tabágicos / estado geral (Zubrod)

	Fumador	Não fumador	Ex-fumador	p (sig) §
0	135 7,3%	78 9,9%	53 7,9%	0,007
1	895 48,2%	391 49,6%	355 52,8%	
2	519 28,0%	177 22,4%	174 25,9%	
3	226 12,2%	114 14,4%	71 10,6%	
4	81 4,4%	29 3,7%	19 2,8%	

§ Pearson qui-quadrado

Análise por tipos histológicos

A análise do tipo histológico pelo PS dos doentes mostrou que todos os tipos histológicos se encontravam em número significativamente mais elevado no PS 1 (Quadro X). Em todos os tipos histológicos, a percenta-

gem de doentes com idade superior a 60 anos ultrapassou os 50% (Quadro XI).

Nos tumores epidermóides, 73,2% dos doentes tem mais de 60 anos, o que está de acordo com os números relativos, quer à Europa, quer ao resto do mundo ².

Quadro X – Tipo histológico / estado geral (Zubrod)

Tipo histológico	0	1	2	3	4	p (sig) §
Não especificado	7 12,3%	22 38,6%	10 17,5%	14 24,6%	4 7,0%	< 0,001
Adenocarcinomas	168 11,7%	730 50,9%	348 24,3%	159 11,1%	28 2,0%	
CPNPC	23 6,0%	186 48,3%	93 24,2%	56 14,5%	27 7,0%	
Epidermóide	74 6,5%	585 51,8%	306 27,1%	118 10,4%	47 4,2%	
Grandes células	9 13,0%	27 39,1%	23 33,3%	10 14,5%	0	
Misto	4 12,9%	18 58,1%	4 12,9%	5 16,1%	0	
Neuroendócrino	8 15,1%	36 67,9%	5 9,4%	3 5,7%	1 1,9%	
Outros	14 13,1%	43 40,2%	22 20,6%	19 17,8%	9 8,4%	
Pequenas células	23 4,9%	232 49,4%	137 29,1%	58 12,3%	20 4,3%	

§ Pearson qui-quadrado

ESTUDO EPIDEMIOLÓGICO DO CANCRO DO PULMÃO EM PORTUGAL NOS ANOS DE 2000/2002

Bárbara Parente, H Queiroga, E Teixeira, R Sotto-Mayor, F Barata, A Sousa, MJ Melo, F João, R Neveda, J Cunha, A Fernandes, M Manuel, T Cardoso, L Ferreira, F Nogueira, J Duarte, E Semedo, U Brito, F Pimentel, S Barros, F Costa, T Almodôvar, A Araújo

Quadro XI – Grupo etário / tipo histológico (n=4337)

Tipo histológico	< 30 anos	30-40 anos	41-50 anos	51-60 anos	> 60 anos	p (sig) §
Não especificado		1 1,4%	4 5,6%	11 15,3%	56 77,8%	<0.001
Adenocarcinomas	1 0,1%	45 2,7%	208 12,7%	368 22,5%	1016 62,0%	
CPNPC		9 2,0%	47 10,3%	91 19,9%	311 67,9%	
Carcinoma epidermóide		12 0,9%	93 7,1%	247 18,8%	961 73,2%	
Carcinoma de grandes células	1 1,1%	2 2,3%	8 9,1%	29 33,0%	48 54,5%	
Carcinoma misto			1 3,0%	10 30,3%	22 66,7%	
Carcinoma neuroendócrino	4 6,3%	4 6,3%	12 19,0%	7 11,1%	36 57,1%	
Outros	3 2,4%	5 4,0%	10 7,9%	16 12,7%	92 73,0%	
CPPC		14 2,6%	55 10,1%	135 24,8%	340 62,5%	

§ Pearson qui-quadrado

Análise por regiões

Relativamente ao número de doentes por região geográfica (Quadro XII), do universo de hospitais que participaram neste trabalho (como referido na listagem dos hospitais), 10 pertencem geograficamente à região Norte, 4 à região Centro e 9 à região Sul.

Os estádios não mostraram diferenças com significado estatístico de região para região, quer nos estádios localizados, quer na doença avançada (Quadro XIII).

Quadro XII – Distribuição dos doentes por regiões

Região geográfica	Número de doentes	Porcentagem
Norte	2133	48,5
Centro	690	15,7
Sul	1573	35,8

Quadro XIII – Estádios por regiões

	Norte	Centro	Sul	p (sig) §
I A	45 2,3%	18 2,7%	50 3,3%	< 0,001
I B	89 4,6%	54 8,1%	107 7,1%	
II A	13 0,7%	4 0,6%	15 1,0%	
II B	75 3,9%	28 4,2%	81 5,4%	
III A	169 8,8%	52 7,9%	152 10,1%	
III B	665 34,4%	160 24,2%	398 26,5%	
IV	876 45,3%	346 52,3%	700 46,6%	

§ Pearson qui-quadrado

Relativamente à distribuição dos tipos histológicos pelas três regiões do país, também não foram encontradas diferenças com significado estatístico (Quadro XIV).

Também em relação aos hábitos tabágicos não se verificou haver diferenças no hábito de região para região (Quadro XV).

Quadro XIV – Tipo histológico por regiões

Tipo histológico	Norte	Centro	Sul	p (sig) §
Não especificado	25 1,2%	6 0,9%	57 3,6%	< 0,001
Adenocarcinoma	813 38,1%	265 38,4%	578 36,7%	
CPNPC	228 10,7%	43 6,2%	193 12,3%	
Carcinoma epidermóide	617 28,9%	231 33,5%	472 30,0%	
Carcinoma de grandes células	43 2,0%	23 3,3%	23 1,5%	
Carcinoma misto	11 0,5%	13 1,9%	9 0,6%	
Neuroendócrino	32 1,5%	11 1,6%	20 1,3%	
Outros	63 3,0%	7 1,0%	58 3,7%	
Carcinoma de pequenas células	301 14,1%	91 13,2%	161 10,2%	

§ Pearson qui-quadrado

Quadro XV – Hábitos tabágicos por regiões

Estado tabágico	Norte	Centro	Sul	p (sig) §
Fumador	1200 61,1%	259 41,2%	726 57,9%	< 0,001
Não fumador	461 23,5%	221 35,1%	229 18,3%	
Ex-fumador	303 15,4%	149 23,7%	299 23,8%	

§ Pearson qui-quadrado

Análise das terapêuticas efectuadas

De referir (Quadro XVI) que a percentagem média dos doentes submetidos a ressecção cirúrgica se apresenta baixa relativamente a outros países (8,2 %), embora cerca de 40 % das terapêuticas combinadas se refira à cirurgia associada a outras terapêuticas adjuvantes. Atendendo ao estágio avançado da grande maioria dos doentes à data do diagnóstico, é a quimioterapia (QT) a terapêutica mais frequentemente efectuada (43,7% dos casos). Fomos avaliar em que grupos etários se encontravam os doentes que efectuaram a melhor terapêutica de suporte (Quadro XVII). Não sendo a idade uma contra-indicação a nenhuma das terapêuticas, é nas idades mais avançadas que o risco de co-morbilidades é maior, daí que 81,2 % das terapêuticas de suporte fosse efectuada em doentes com mais de 60 anos.

Quadro XVI – Terapêuticas efectuadas

Terapêutica	Frequência	Percentagem
Cirurgia	315	8,2
Combinada	842	21,8
Quimioterapia	1684	43,7
Radioterapia	230	6,0
Suporte	784	20,3
Total	3855	100,0

Quadro XVII – Melhor terapêutica de suporte (n = 784 / 20,3%): Frequência com a idade

Grupos etários	Frequência	Percentagem
< 30 anos	1	0,1
30 – 40 anos	6	0,8
41 – 50 anos	42	5,4
51 – 60 anos	91	11,7
> 60 anos	640	82,1
Total	784	100,0

Comentário final e agradecimentos

Da comparação deste trabalho com um outro publicado em 1993³, e referente aos anos de 1988/90, também da responsabilidade da *Comissão de Trabalho da Pneumologia Oncológica*, verifica-se a participação de um maior número de hospitais (10 *versus* 22), o que torna a amostra mais representativa, a que não é alheio factores como o desenvolvimento da tecnologia do registo de dados e também a criação de novos centros em Portugal que tratam o cancro do pulmão.

No entanto, a idade de aparecimento da doença mantém-se sem alterações importantes, mas nota-se já uma tendência (após 13 anos) para o aumento de cancro de pulmão na mulher (15,5% *vs* 18,1%). Os hábitos tabágicos também não mostram tendência a reduzir nesta população (provavelmente porque embora estabilize no homem, está a aumentar na mulher), apesar das actuais campanhas anti-tabágicas e das múltiplas consultas de desabilitação tabágica.

Nos tipos histológicos verifica-se nesta série, como na Europa em geral e no resto do Mundo⁵ um aumento muito acentuado do adenocarcinoma, com uma correspondente redução do carcinoma epidermóide. Em 1998/90, o tipo histológico que se situava em primeiro lugar era o carcinoma epidermóide, com 46% *vs* 30% da série actual, e o adenocarcinoma, com 25,2% *vs* 37,5%, o que actualmente o coloca no primeiro lugar, situação que é atribuída hoje a causas multifactoriais⁴.

O CPPC não tem sofrido alterações significativas ao longo dos anos.

Também a nível do estadiamento⁵, não encontramos alterações entre as duas séries, nomeadamente nos estádios cirúrgicos (I e II), embora se admita que o a correlação não

se possa efectuar duma forma exacta, dado que hoje se realiza um mais rigoroso estadiamento, pelos meios que temos ao nosso dispor.

Continua a verificar-se o diagnóstico tardio na grande maioria dos doentes, o que configura dificuldades de diagnóstico precoce.

Apesar de todas as dificuldades encontradas na elaboração deste trabalho, parece-nos que o mesmo se reveste de maior interesse, dadas as limitações ainda hoje existentes na obtenção dum alargado leque de ítems, que melhor nos permita caracterizar o cancro do pulmão em Portugal, não só nas suas vertentes demográficas, como também nos tipos histológicos, estadiamento e orientações terapêuticas dos doentes portugueses.

Queríamos assim agradecer a todos os colegas que gentilmente, e ano após ano, foram registando os doentes das suas unidades, pois, sem o esforço de todos, este trabalho não teria sido possível.

Os profissionais envolvidos estão motivados para o diagnóstico precoce da CP, verificando-se já uma uniformização de metodologias de estudo e tratamento; ficou expressa a adesão progressiva ao trabalho de grupo.

Esta parece-nos ser uma forma de avançarmos no conhecimento e melhoria da reali-

dade no diagnóstico e tratamento do cancro do pulmão em Portugal.

É pois um trabalho que merece ter continuidade, alterando e aperfeiçoando o que se mostrar importante.

Bárbara Parente

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Pelo Grupo de Estudos do Cancro
do Pulmão

Pemetrexed na segunda linha de tratamento do carcinoma do pulmão de não pequenas células – A experiência portuguesa

Pemetrexed in second line treatment of non-small cell lung cancer – The portuguese experience

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Resumo

Até 2004, docetaxel em monoterapia era o tratamento *standard* de segunda linha para o carcinoma do pulmão de não pequenas células (CPNPC). O pemetrexed (P) mostrou, neste grupo, actividade semelhante com uma melhor tolerância. Em Portugal, foi introduzido em Outubro de 2004.

Abstract

Until 2004, docetaxel in monotherapy was the standard for second-line treatment of non-small cell lung cancer (NSCLC). Pemetrexed (P) has shown similar activity in this setting with a better adverse event profile. In Portugal, it was introduced in October of 2004.

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Realizou-se uma análise retrospectiva dos doentes que receberam P para a segunda linha de CPNPC em Portugal de Outubro de 2004 a Dezembro de 2006. Os dados foram recolhidos dos registos dos doentes com CPNPC localmente avançado ou metastático, tratados nos centros que participam no Grupo de Estudos do Cancro do Pulmão (GECp), que falharam uma primeira linha de quimioterapia. A resposta objectiva (OR; resposta completa [CR] ou parcial [PR]) foi avaliada segundo RECIST e a avaliação da segurança usando os registos dos acontecimentos adversos graves e não graves (SAE/AE).

Até Dezembro de 2006, os 19 centros GECp registaram 244 doentes que receberam P ≥ 1 ciclo e que foram considerados avaliáveis. Demografia: masculino/feminino, 175/69; idade mediana, 57,0 anos (variação 20-81); história de tabagismo, s/ex/n, 116/57/71; adenocarcinoma/carcinoma células escamosas/outras histologias, 141/72/31; tempo médio até progressão (TTP) 8,07 meses. O controlo da doença, avaliável em 209 doentes, foi observado em 116 (55.5%): 2 CR, 45 PR e 69 SD; TTP médio 4,70 meses. A maioria dos AE foi anemia (15 doentes) e neutropenia (18 doentes) de grau 3. A sobrevivência global média foi de 17,27 meses.

Esta análise retrospectiva revelou uma taxa de controlo da doença (55,5%) e um TTP (4,7 meses) na nossa população não seleccionada semelhante ao descrito na literatura. P é uma opção para a segunda linha do CPNPC com uma boa tolerabilidade.

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Palavras-chave: Carcinoma do pulmão de não pequenas células, pemetrexed, quimioterapia de segunda linha.

We have carried out a retrospective analysis of patients (pts) who received P for second-line NSCLC in Portugal from October 2004 to December 2006. Data were collected from the records of pts with locally advanced or metastatic NSCLC and failed first-line chemotherapy enrolled in centers participating in the Portuguese Lung Cancer Study Group (GECp). Objective response (OR; complete [CR] or partial [PR] response) was evaluated using RECIST and safety was assessed using serious or non-serious adverse events (SAEs/AEs).

By December 2006, 19 GECp centers had enrolled 244 pts who had received P for ≥ 1 cycle, and were considered evaluable for both objective response and safety. Demography: male/female, 175/69; median age, 57.0 years (range 20-81); smoking status, y/ex/n, 116/57/71; adenocarcinoma / squamous-cell carcinoma/other histology, 141/72/31; mean time to progression (TTP) 8.07 months. Disease control in 209 evaluable pts was observed in 116 (55.5%): 2 CR, 45 PR and 69 SD; mean TTP 4.70 months. The majority of AEs were grade 3 anemia (15 pts) and neutropenia (18 pts). The mean overall survival was 17.27 months.

Our retrospective analysis has observed a similar disease control rate with P in 2nd line (55.5%), and TTP (4.7 months) in our current unselected population to that published in the literature. P is an option for second-line NSCLC with a good tolerability.

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Key-words: Non-small cell lung cancer, pemetrexed, second-line chemotherapy

Introdução

Na Europa, em 2006, estima-se que tenham sido diagnosticados 3 191 600 novos casos de cancro. Destes, o cancro do pulmão é o terceiro mais frequente, logo a seguir ao da mama e ao do cólon e recto, com 412 000 novos casos. Neste período, estimam-se que tenham ocorrido cerca de 1,7 milhões de mortes por cancro, sendo as mais frequentes causadas pelo do pulmão (334 800), que contabiliza 1/5 do total do número de mortes por cancro¹.

Para os doentes com carcinoma do pulmão de não pequenas células (CPNPC) com um bom estado geral (bom *performance status*), em estágio IIIB (com derrame pleural) ou IV, o tratamento *standard* é a quimioterapia baseada na platina^{2,3}. No entanto, esta confere um tempo de sobrevivência que não ultrapassa os 10 meses⁴ e uma taxa de sobrevivência média no 1.º ano de cerca de 10%⁵. Em ensaios clínicos, aproximadamente 30-40% dos doentes recidiva ou progride após esta primeira linha de tratamento, vindo a receber uma segunda linha de tratamento⁶⁻⁸.

Para o tratamento de segunda linha do CPNPC, a partir de 2000, recomendava-se o docetaxel na dose de 75 mg/m² que, quando comparado com o melhor cuidado de suporte ou com outros fármacos citostáticos (vinorelbina ou ifosfamida), mostrou estar associado a um aumento significativo da sobrevivência e com um perfil de toxicidade aceitável^{9, 10}. Em 2004, surgiu o pemetrexed (P), um antifolato multialvo que mostrou uma actividade semelhante ao docetaxel neste grupo de doentes, na dose de 500 mg m², mas com um perfil de tolerabilidade mais favorável¹¹. Este último fármaco foi introduzido em Portugal em Outubro de 2004, pelo que o Grupo de Estudos do Cancro do Pulmão (GECP) decidiu realizar uma avaliação da sua eficácia em segunda

Introduction

An estimated 3 191 600 new cases of cancer were diagnosed in Europe in 2006. Lung cancer was the third most frequent of these, with 412 000 new cases, following breast cancer and colon/rectal cancer. An estimated 1.7 million cancer deaths occurred during this period, with the majority caused by lung cancer (334 800), which make up 1/5 of the total number of cancer deaths¹.

The standard treatment for non-small cell lung cancer patients (NSCLC) with a good performance status in stage IIIB (with pleural effusion) or IV is platin-based chemotherapy^{2,3}. This gives a maximum survival time of 10 months⁴ and a mean first year survival rate of approx. 10%⁵. In clinical trials, approximately 30-40% of patients relapse or progress after this first-line treatment and receive a second-line treatment⁶⁻⁸.

A 75 mg/m² dose of docetaxel was recommended for second-line NSCLC treatment after 2000, which, in comparison with the best support care or other cytostatic drugs (vinorelbine or ifosfamide), was associated with an improved survival rate and an acceptable toxicity profile^{9,10}. Pemetrexed (P), a multi-target anti-folate, arrived in 2004 and demonstrated similar activity to docetaxel in this patient group in a 500 mg/m² dose, but had a better adverse event profile¹¹. Pemetrexed was introduced in Portugal in October 2004, and the Portuguese Lung Cancer Study Group (GECP) decided to conduct a study evaluating its efficacy as second-line treatment in randomised Portuguese NSCLC patients.

linha nos doentes portugueses com CPNPC não seleccionados.

Material e métodos

Este foi um estudo retrospectivo realizado nos centros que estão representados no GECP através da consulta dos processos clínicos dos doentes seleccionados. Foram avaliados os seguintes parâmetros: demografia dos doentes, resposta objectiva (OR; resposta completa [CR] ou parcial [PR]) usando os critérios RECIST (*Response Evaluation Criteria in Solid Tumors*), tempo até progressão (TTP), taxa de sobrevida global (OS) e avaliação da segurança usando os registos dos acontecimentos adversos graves e não graves (SAE/AE). As toxicidades foram graduadas de acordo com o NCI-CTC (*National Cancer Institute Common Toxicity Criteria*), versão 2.0.

Os doentes elegíveis tinham um diagnóstico de CPNPC localmente avançado ou metastático, que tinha progredido após uma primeira linha de quimioterapia e que receberam uma segunda linha de tratamento com P. O P foi administrado na dose de 500 mg/m², com suplementos de vitamina B12 e de ácido fólico, de 3 em 3 semanas. O reestadiamento dos doentes, para avaliação da resposta, foi realizado de acordo com o estabelecido em cada instituição.

Todos os doentes tratados foram considerados para a análise estatística. O teste exacto de Fisher e o teste de Mann-Whitney foram usados para investigar o significado das relações entre as variáveis qualitativas e as quantitativas, respectivamente.

O TTP foi definido como o tempo desde o primeiro dia da administração da medicação até à data da primeira observação de progressão ou morte devido à doença. A OS foi defi-

Material and methods

We carried out a retrospective analysis of patients enrolled in centres participating in the Portuguese Lung Cancer Study Group (GECP) through collecting data from selected clinical files. We evaluated patient characteristics, objective response (OR; complete [CR] or partial [PR] response) using RECIST (*Response Evaluation Criteria in Solid Tumors*) criteria, time to progression (TTP), overall survival (OS) and safety, using records of serious or non-serious adverse events (SAEs/AEs).

The toxicities were graded in line with the NCI-CTC (*National Cancer Institute Common Toxicity Criteria*), version 2.0.

Eligible patients had locally advanced or metastatic NSCLC which had progressed after failed first-line chemotherapy and who had received second-line treatment with P. 500 mg/m² doses of P were administered every 3 weeks along with a vitamin B12 and folic acid supplement. Patient re-staging to evaluate the response was carried out in line with the principles of each institution.

All patients treated were included in the statistical analysis. The Fisher exact test and the Mann-Whitney test were used to investigate the significance of the relationships between the qualitative and quantitative variables respectively.

The TTP was defined as the time from the first day of medication administration to the date of the first sign of progression or death caused by the disease. The OS was defined as the time from diagnosis to death. TTP and OS were analysed using the Kaplan-Meier method. The response rate was defined as the percentage of patients among all the eligible patients with a CR or PR. The response rate was calculated with a cor-

nida como o tempo desde a data do diagnóstico até à data da morte. TTP e OS foram analisados pelo método de Kaplan-Meier. A taxa de resposta foi definida como a percentagem de doentes com uma CP ou PR entre todos os doentes avaliáveis. A taxa de resposta ao tratamento foi calculada com o correspondente intervalo de confiança de 95% (CI). A análise estatística foi realizada usando o programa SPSS, na versão 15.0.

Resultados

Entre Outubro de 2004 e Dezembro de 2006, os 19 centros representados no GECP registaram 244 doentes que receberam P ≥ 1 ciclo e que foram considerados avaliáveis.

As características demográficas dos doentes foram resumidas no Quadro I.

Do total dos doentes, eram 175 do sexo masculino e 69 do feminino. A idade mediana foi de 57,0 anos, com uma variação entre 20-81 anos. Cento e setenta e três doentes tinham uma história de tabagismo e 222 apresentaram-se com um *performance status* de 0-1. Em termos histológicos, 141 eram adenocarcinomas e 72 carcinomas eram do tipo de células escamosas. O esquema de quimioterapia de primeira linha utilizado englobou platina em 239 doentes, gemcitabina em 155 e taxano em 58. O número médio de ciclos de quimioterapia administrado em primeira linha foi de 4,8 ciclos/doente. O TTP médio da primeira linha foi de 8,07 meses (Fig. 1), não se encontrando qualquer diferença estatisticamente significativa entre qualquer um dos esquemas de quimioterapia utilizados.

Com a utilização de P em segunda linha, administraram-se um total de 1041 ciclos, tendo em média cada doente recebido 4,3

responding 95% confidence interval (CI).

Statistical analysis was performed using the SPSS software package version 15.0.

Results

Between October 2004 and December 2006, the 19 GECP centres represented had enrolled 244 patients who had received P for ≥ 1 cycle, and were considered eligible. Table I shows the patients' characteristics.

175 of the patients were male and 69 female. The mean age was 57.0 years old, with a 20-81 year variation. 173 had a smoking status and 222 had a 0-1 performance status. 141 had adenocarcinomas and 72 squamous cell carcinomas. 239 patients had platin-based first-line chemotherapy, 155 gemcitabine-based and 58 taxane-based. The mean number of first-line chemotherapy cycles administered was 4.8 cycles/patient. Mean first-line TTP was 8.07 months (Fig. 1), with no statistically significant difference seen between any of the chemotherapy schemes used.

A total of 1041 cycles of second-line P was administered, with each patient receiving mean 4.3 cycles. Disease control in 209 eligible patients was observed in 116 (55.5%): 2 CR, 45 PR and 69 SD. Mean second-line TTP was 4.70 months (Figure 2). Mean overall survival was 17.27 months (Figure 3). In terms of tolerance, P was a drug with a good adverse events profile. The majority of the AEs were anaemia (15 patients) and grade 3 neutropaenia (18 patients) (Table II).

The authors also analysed the TTP and OS of the squamous cell carcinoma patient group and the adenocarcinoma and large-cell carcinoma patient group. The TTPs of these two groups were different and while

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Quadro I – Características iniciais dos doentes e da doença

Características	% de doentes (n=244)
Género	
Masculino	71,7
Feminino	28,3
Idade (anos)	
Mediana	57
Variação	20-81
História de tabagismo	
Não	29,1
Ex	23,4
Sim	47,5
Performance status	
0	16,8
1	74,2
2	9,0
Histologia	
Adenocarcinoma	57,8
Carcinoma de células escamosas	29,5
Outros	12,7
Estádio	
IIIB	32,4
IV	67,6
Esquema de primeira linha	
Platina prévia	98,0
Gemcitabina prévia	63,5
Taxano prévio	23,8

ciclos. O controlo da doença, avaliável em 209 doentes, foi observado em 116 (55,5%): 2 CR, 45 PR e 69 SD. O TTP médio da segunda linha foi de 4,70 meses (Fig. 2). A sobrevivência global média foi de 17,27 meses (Fig. 3). Relativamente à tolerância, o P mostrou-se um fármaco com poucos efeitos adversos, tendo sido a maioria dos AE constituídos por anemia (15 doentes) e neutropenia (18) de grau 3 (Quadro II).

this different attained statistical significance ($P=0.040$) (Figure 4), there was no statistically significant difference seen in the OS ($P=0.675$).

Discussion and conclusions

We carried out a retrospective analysis of randomised daily clinical practice patients who received second-line locally advanced

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Table I – Initial patient and disease characteristics.

Characteristics	% of Patients (n=244)
Type	
Male	71.7
Female	28.3
Age (years)	
Mean	57
Variation	20-81
Smoking status	
No	29.1
Ex	23.4
Yes	47.5
Performance status	
0	16.8
1	74.2
2	9.0
Histology	
Adenocarcinoma	57.8
Squamous cell carcinoma	29.5
Others	12.7
Stage	
IIIB	32.4
IV	67.6
1 st line scheme	
Previous platin	98.0
Previous gemcitabine	63.5
Previous taxane	23.8

Os autores analisaram também TTP e OS entre os grupos de doentes com carcinoma de células escamosas e o grupo com adenocarcinomas e carcinoma de grandes células. Verificou-se que o TTP nestes dois grupos era diferente e que essa diferença era estatisticamente significativa ($P=0,040$) (Fig. 4), não se observando qualquer diferença estatisticamente significativa na OS ($P=0,675$).

or metastatic NSCLC treatment with P. In comparing our results with those of the randomised phase III trial of pemetrexed *versus* docetaxel¹¹ we found no statistically significant differences in the two study populations. The response rates gleaned (CR/PR/SD) were similar to those found in the literature, with a 55.5% disease control in our study and 54.9% in a study published earlier¹¹. The TTP of P was 3.4

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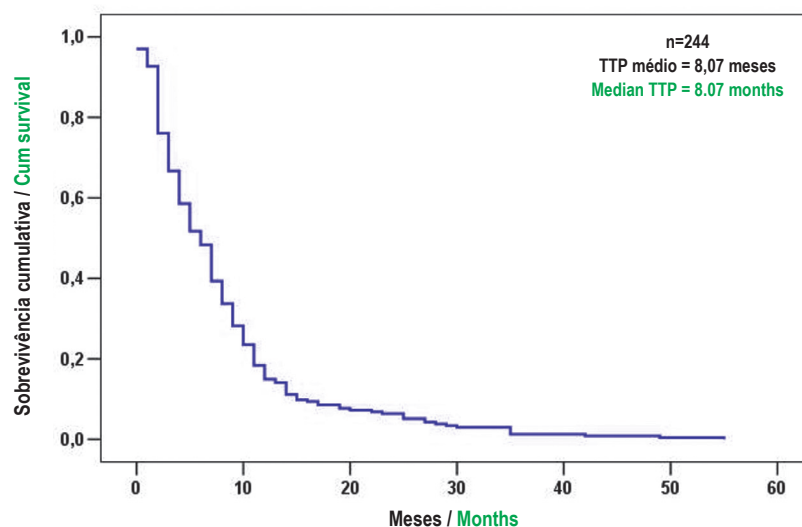


Fig. 1 – Tempo até progressão (TTP) da primeira linha de quimioterapia

Fig. 1 – Time to progression (TTP) of first-line chemotherapy

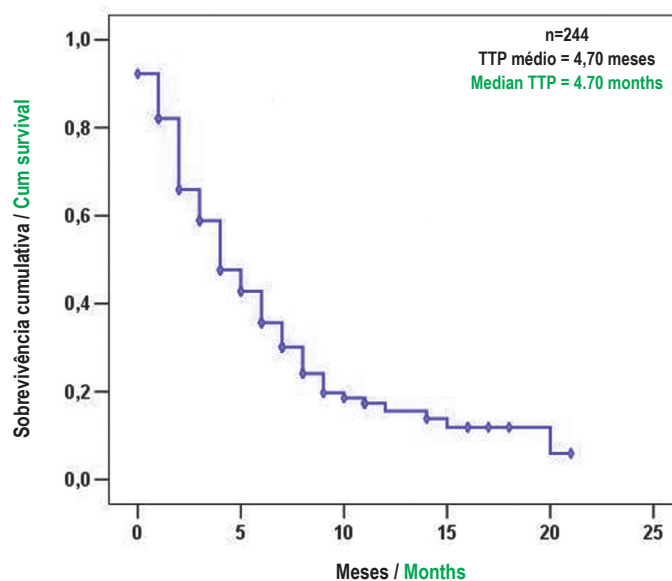


Fig. 2 – Tempo até progressão (TTP) da segunda linha de quimioterapia

Fig. 2 – Time to progression (TTP) of second-line chemotherapy

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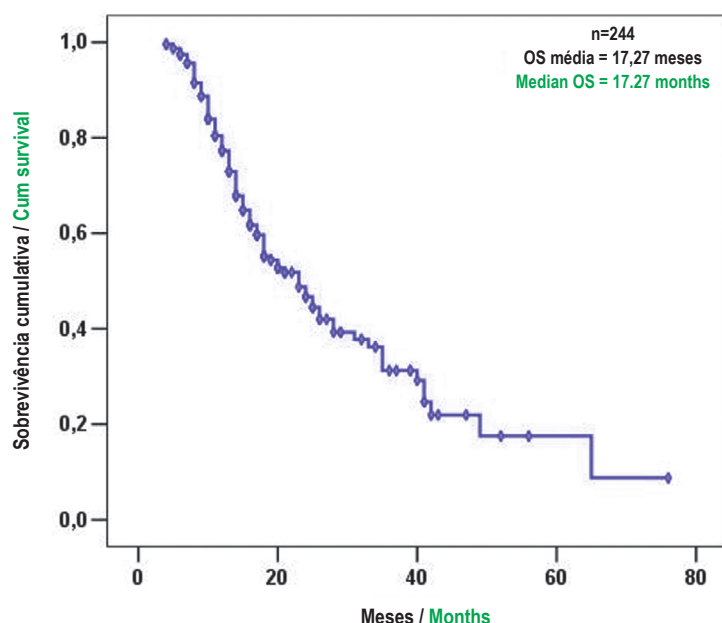


Fig. 3 – Sobrevivência global (OS)

FIG. 3 – Overall survival (OS)

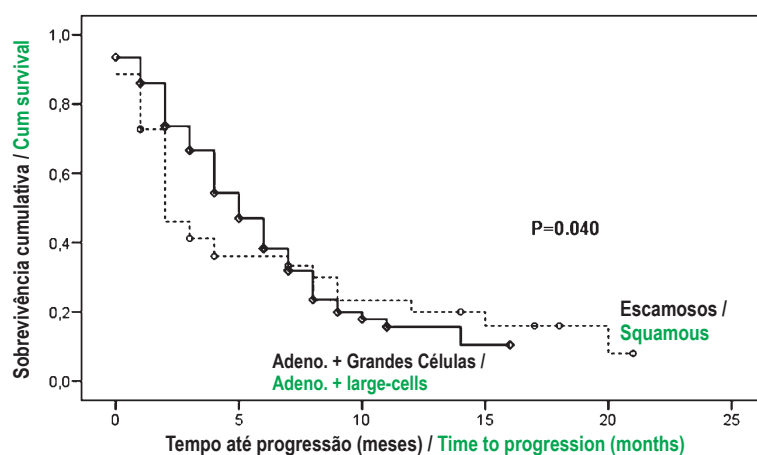


Fig. 4 – Tempo até progressão (TTP) da segunda linha de quimioterapia, nos grupos de doentes com carcinoma de células escamosas e com adenocarcinomas e carcinoma de grandes células

Fig. 4 – Time to progression (TTP) of second-line chemotherapy in the squamous cell carcinoma patient group and the adenocarcinoma and large-cell carcinoma patient group.

Quadro II – Acontecimentos adversos (AE) de grau 2 e 3, com o uso do pemetrexed

AE, n	Grau 3 (%)	Grau 4 (%)
Hematopoiético		
Anemia	15 (6,1%)	1 (0,4%)
Neutropenia	18 (7,4%)	0 (0%)
Trombocitopenia	2 (0,8%)	0 (0%)
Gastrointestinal		
Náusea / vômito	6 (2,5%)	1 (0,4%)
Outros		
Alopecia	8 (3,3%)	0 (0%)

Discussão e conclusões

Este é um estudo retrospectivo sobre o uso de P em segunda linha de tratamento do CPNPC localmente avançado ou metastático, em doentes não seleccionados da nossa prática clínica diária. Se compararmos os resultados com os do estudo de fase III, randomizado entre P e docetaxel¹¹, verifica-se que as populações dos dois estudos apresentam uma demografia sem diferenças estatisticamente significativas. As taxas de resposta obtidas (CR/PR/SD) foram em tudo semelhantes ao que está descrito na literatura, com um controlo da doença de 55,5% no presente estudo e de 54,9% no anteriormente publicado¹¹. O TTP do P foi de 3,4 meses, enquanto no presente estudo se verificou ser de 4,70 meses. Tal pode ficar a dever-se ao tempo que decorre entre as avaliações do tumor no ensaio clínico e na nossa prática diária. Relativamente à toxicidade encontrada, verifica-se um número ligeiramente superior de anemia e de neutropenia relativamente ao descrito, mas tal é logicamente decorrente de a nossa população não ter sofrido selecção e, portanto, poder ter um maior número de comorbilidades do que as descritas no ensaio clínico.

months, while we found it to be 4.70 months. This could be due to the time elapsing between tumour evaluations in clinical trial and in our daily practice. In terms of the toxicity found, we found a greater amount of anaemia and neutropenia than that described in earlier studies, but that would be a natural result of our population being randomised and consequently having a greater amount of co-morbidities that those described in clinical trial.

Unlike that found in a study into first-line treatment of NSCLC with P and cisplatin¹² we found a statistically significant difference in the TTP between the squamous cell carcinoma patient group and the adenocarcinoma and large-cell carcinoma patient group. This difference, however, was not seen in the OS.

Overall, our retrospective study in a randomised population in our daily clinical practice, showed similar results to those described in clinical trials. The results suggest that P is a sound choice for locally advanced or metastatic second-line NSCLC and one with a good adverse events profile.

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Table II – Grade 2 and 3 adverse effects (AE) with pemetrexed use

AE, n	Grade 3 (%)	Grade 4 (%)
Haematopoietic		
Anaemia	15 (6.1%)	1 (0.4%)
Neutropaenia	18 (7.4%)	0 (0%)
Thrombocytopaenia	2 (0.8%)	0 (0%)
Gastrointestinal		
Nausea / vomit	6 (2.5%)	1 (0.4%)
Others		
Alopecia	8 (3.3%)	0 (0%)

Ao contrário do descrito num estudo na primeira linha do tratamento do CPNPC com P e cisplatina¹², no presente estudo verificou-se que havia uma diferença estatisticamente significativa no TTP entre o grupo de doentes com carcinoma de células escamosas e o grupo com adenocarcinoma e carcinoma de grandes células. Essa diferença, no entanto, não tinha tradução na OS.

Globalmente, o presente estudo retrospectivo realizado numa população não seleccionada, da nossa prática clínica diária, apresenta resultados em tudo semelhantes aos descritos nos ensaios clínicos. Os resultados sugerem que o P é uma boa opção para a segunda linha de tratamento do CPNPC localmente avançado ou metastático e que este apresenta uma boa tolerabilidade.

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4. *EGF* and *EGFR* and Other Polymorphisms

In recent years, knowledge concerning the molecular mechanisms underlying cellular transformation and development of cancer has been greatly expanded. Therefore, new therapeutic agents, driven to specific intra- or extracellular targets, presumed to be crucial in the molecular pathways of carcinogenesis, have been developed.

Genetic polymorphisms are variants in individual genomes, present in more than 1.5% of the population, that remain constant throughout a person's lifetime (Yan, L. et al. 2005). There are more than 1.4 million single nucleotide polymorphisms (SNPs) identified in the human genome, and many of them contribute to variability in both pharmacokinetic and pharmacodynamic drugs (Sachidanandam, R. et al. 2001).

Among the different families of growth factors and growth factor receptors, the epidermal growth factor (EGF) and its receptor (EGFR) play a central role in lung carcinogenesis. Following stimulation by its ligands, EGFR initiates signal transduction cascades, which promote proliferation, invasion, metastasis, angiogenesis, and inhibition of apoptosis (Tabernero, J. et al. 2005; Lurje, G. et al. 2009). In the late 1990s, EGFR was discovered to play an important role in tumoral biology and to be an attractive therapeutic target. Therefore, different therapeutic strategies capable of interfering with the EGFR pathway activation were developed. Examples of these are different types (e.g., murine, chimeric, and humanized) of monoclonal antibodies (mAbs), which bind to the extracellular domain of the receptor and compete with the natural ligands (transforming growth factor α [TGF- α] and EGF), some of them currently in clinical trial (e.g., cetuximab, matuzumab, and panitumumab) (Lurje, G. et al. 2009). mAbs interact with receptor dimerization, resulting in receptor downregulation that may be important for their growth-inhibitory capacity (Fan, Z. et al. 1994). Another class of agents, the low molecular weight tyrosine kinase inhibitors (TKIs; e.g., gefitinib and erlotinib), competes with ATP binding to the TK portion of the intracellular domain of the receptor and abrogates the receptor's catalytic activity. These therapeutic strategies seem to be both equally effective in blocking the downstream receptor-dependent signaling pathways, including the phosphatidylinositol 3-kinase/ Akt, the janus kinase/ signal transducer and activator of transcription, and the mitogen-activated protein kinase pathways (Tabernero, J. et al. 2005).

In 2003, gefitinib (Cohen, M.H. et al. 2004), one of the EGFR-TKIs, was conditionally approved by the U.S. Food and Drug Administration for the treatment of CT-refractory locally advanced or metastatic NSCLC, based on clinical benefit data. But in 2004, a large randomized phase III study failed to demonstrate a survival advantage over placebo in overall population for gefitinib although some subgroups showed benefit (patients of Asian origin and those who had never smoke) (Thatcher, N. et al. 2005) and its application to the European market was withdrawn. It was also in 2004 that EGFR-TK mutations were first suggested as the reason for some of the exceptional responses seen at undertaken studies (Lynch, T.J. et al. 2004).

More recently, another EGFR-TKI agent, erlotinib, has been approved in the U.S. and Europe for second- and third-line treatment of NSCLC because of superiority over best supportive care as demonstrated by phase III clinical study (Shepherd, F.A. et al. 2005).

In 2009 the EU approved gefitinib for treatment of locally advanced or metastatic NSCLC with activating mutations of EGFR-TK across all lines of therapy, based on two large trials demonstrating the superiority of gefitinib versus doublet chemotherapy in EGFR mutation positive patients (Mok, T.S. et al. 2009) and the equivalence in second line treatment of NSCLC versus docetaxel (Kim, E.S. et al. 2008; Douillard, J.Y. et al. 2010).

A systematic review of data was conducted about EGF and EGFR, and its polymorphisms to define its influence in prognosis and in response to therapy for NSCLC (Araujo, A. et al. 2007).

The combination of pemetrexed and bevacizumab for second-line of non-squamous NSCLC is very promising. In a recently published study, Adjei and co-workers evaluated the impact of three single nucleotide polymorphisms (SNPs) in genes that code proteins linked to pemetrexed activity: *SLC19A1* codes a protein responsible for the transport, *FPGS* codes a protein linked to activation, and *GGH* codes a protein important for inactivation (Adjei, A.A. et al. 2010). The authors reported a promising progression-free survival of 4 months but no correlation of these polymorphisms with efficacy and toxicity. This study deserved attention and some critics and alerts for the need of a phase III trial with that combination analyzing the importance of these SNPs for the study population (Araujo, A.M. 2010).



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Genetic Polymorphisms of the Epidermal Growth Factor and Related Receptor in Non-Small Cell Lung Cancer—A Review of the Literature

António Araújo, Ricardo Ribeiro, Isabel Azevedo, Ana Coelho, Marta Soares, Berta Sousa, Daniela Pinto, Carlos Lopes, Rui Medeiros and Giorgio V. Scagliotti

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Genetic Polymorphisms of the Epidermal Growth Factor and Related Receptor in Non-Small Cell Lung Cancer—A Review of the Literature

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Key Words. Epidermal growth factor • Epidermal growth factor receptor • Polymorphism • Non-small cell lung cancer

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the role played by EGF and EGFR in lung carcinogenesis.
2. Discuss how different polymorphic alleles from the *EGF* and *EGFR* genes may affect drug response.
3. Evaluate the value of determining the presence of *EGF* and *EGFR* polymorphisms in NSCLC patients for daily clinical practice.

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ABSTRACT

Worldwide, approximately 1.3 billion individuals are current smokers, and smoking is the second major cause of death. Currently, lung cancer is the most common type of cancer in Europe, and the third in the U.S. Until now, cytotoxic chemotherapy has had a limited impact on survival in metastatic non-small cell lung cancer (NSCLC). The central role of epidermal growth factor (EGF) and its receptor (EGFR) in lung carcinogenesis is well recognized.

Genetic polymorphisms are variants in individual genomes that may be responsible for different functional molecular roles and contribute to variability in drug pharmacokinetic and pharmacodynamic processes. Herein, we review the literature on EGF and EGFR functions and activities, particularly the current role of their functional polymorphisms as related to NSCLC. *The Oncologist* 2007; 12:201–210

INTRODUCTION

In 2005, it was estimated that 11 million people were diagnosed with cancer worldwide. Currently, lung cancer is the

most common type of cancer in Europe (381,500 new cases in 2004) [1] and the third in the U.S. (172,570 new cases in 2005) [2]. During 2004, 341,800 deaths were attributable to

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lung cancer in Europe [1], whereas corresponding data in the U.S. for 2005 indicate 163,510 deaths [2].

Trends of cigarette smoking consumption in each country nicely predict the respective lung cancer incidence, with a gap of almost 20 years between the two curves. Furthermore, it is well known that lung cancer incidence and mortality rates are quite superimposed, making lung cancer the most common cause of cancer-related death in North America and Europe today [1]. Currently, tobacco smoking represents a less common cause of death in developing continents, such as Africa and Eastern Asia [3], where competing causes of death remain present. It has been estimated, however, based on current trends of cigarette consumption in countries such as India and China, that lung cancer will become a relevant social disease in those areas of the world in the next 20 years [4] (Fig. 1).

Non-small cell lung cancer (NSCLC) accounts for 75%–85% of all histotypes of lung cancer. Despite extensive preclinical and clinical research, the overall prognosis for patients with NSCLC remains poor, with a 5-year survival rate of only 14% [5]. Surgery remains the most effective therapeutic modality with curative intent in early-stage NSCLC, but postoperative survival remains unsatisfactory, with a 5-year survival rate less than 70% even in pathologic stage I disease [6]. Consequently, more than 70% of NSCLC patients are candidates for neoadjuvant, adjuvant, or palliative systemic treatment with chemotherapy (CT) at some point in their disease progression. Although patients with metastatic NSCLC clearly benefit from cytotoxic CT, the current limited impact on survival with an average prolongation of survival of no more than 2 months should also be recognized [7].

Proliferative activity of cancer cells may be maintained through several mechanisms, including autocrine loops; consequently, cancer cells exhibit a reduced requirement for exogenously supplied growth factors [8]. This independence from external supply is, at least partially, secondary to the ability of cancer cells to produce high levels of their own peptide growth factors, and this depends, in turn, on the activation of cellular proto-oncogenes [9, 10]. Similarly, the involvement of growth factors in sustaining the survival of cancer cells and in promoting tumor-induced neoangiogenesis has been definitively established, contributing to tumor progression through different mechanisms.

In recent years, knowledge concerning the molecular mechanisms underlying cellular transformation and development of cancer has been greatly expanded. Therefore, new therapeutic agents, driven to specific intra- or extracellular targets, presumed to be crucial in the molecular pathways of carcinogenesis, have been developed. Among the different families of growth factors and growth factor re-

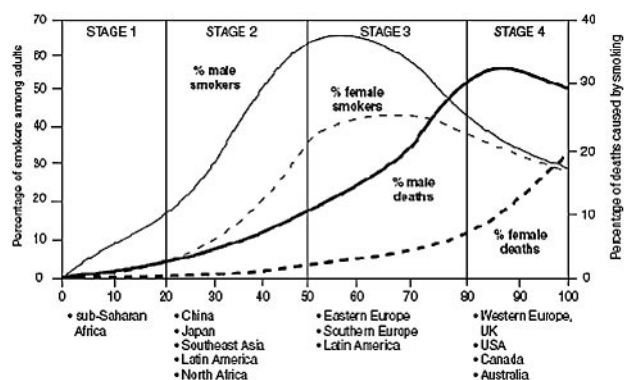


Figure 1. A descriptive model of the cigarette epidemic. From Lopez AD, Collishaw NE, Piha T. A descriptive model of the cigarette epidemic in developed countries. *Tobacco Control* 1994;3:242–247. Reproduced with permission from the BMJ Publishing Group.

ceptors, the epidermal growth factor (EGF) and its receptor (EGFR) play a central role in lung carcinogenesis. Following stimulation by its ligands, EGFR initiates signal transduction cascades, which promote proliferation, invasion, metastasis, angiogenesis, and inhibition of apoptosis [11] (Fig. 2). In the late 1990s, EGFR was discovered to play an important role in tumoral biology and to be an attractive therapeutic target. Therefore, different therapeutic strategies capable of interfering with the EGFR pathway activation were developed. Examples of these are different types (e.g., murine, chimeric, and humanized) of monoclonal antibodies (mAbs), which bind to the extracellular domain of the receptor and compete with the natural ligands (transforming growth factor α [TGF- α] and EGF), some of them currently in clinical trial (e.g., cetuximab, matuzumab, and panitumumab). mAbs interact with receptor dimerization, resulting in receptor downregulation that may be important for their growth-inhibitory capacity [12]. Another class of agents, the low molecular weight tyrosine kinase inhibitors (TKIs; e.g., gefitinib and erlotinib), compete with ATP binding to the TK portion of the intracellular domain of the receptor and abrogate the receptor's catalytic activity. These therapeutic strategies seem to be both equally effective in blocking the downstream receptor-dependent signaling pathways, including the phosphatidylinositol 3-kinase/Akt, the janus kinase/signal transducer and activator of transcription, and the mitogen-activated protein kinase pathways [11]. In 2003, gefitinib [13], one of the EGFR-TKIs, was conditionally approved by the U.S. Food and Drug Administration for the treatment of CT-refractory locally advanced or metastatic NSCLC, based on clinical benefit data. More recently, another EGFR-TKI agent, erlotinib, has been approved in the U.S. and Europe for second- and third-line treatment of NSCLC because of a

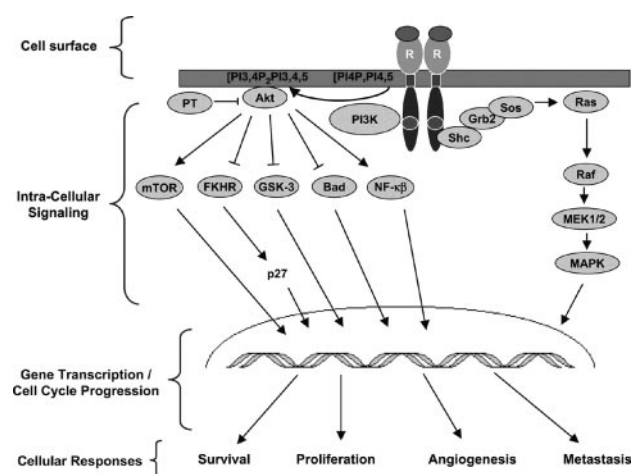


Figure 2. Epidermal growth factor receptor signal transduction pathways. From Tabernero J, Macarulla T, Ramos FJ et al. Novel targeted therapies in the treatment of gastric and esophageal cancer. *Ann Oncol* 2005;16:1740–1748. Reprinted with permission from Oxford University Press.

Abbreviations: FKHR, forkhead-winged helix protein; GSK-3, glycogen synthase kinase-3; Grb2, growth-factor receptor-bound protein 2; MAPK, mitogen-activated protein kinase; MEK1/2, MEK, mitogen-activated protein kinase kinase 1/2; NF- κ B, nuclear factor- κ B; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PT, phospho-threonine; Raf, serine kinase Raf; Ras, GTP-binding protein Ras; Shc, Src homologous and collagen protein; Sos, guanine nucleotide exchange factor Sos.

superiority over best supportive care as demonstrated by a phase III clinical study [14].

Pharmacogenetics and pharmacogenomics are emerging areas that will be crucial for personalized medicine, ultimately leading to drug prescription based on a patient's individual genetic and molecular profile [15]. Their aim is to establish a meaningful relationship between genotype (i.e., polymorphisms and genetic mutations), gene expression profiles (i.e., level of gene expression of all or of target genes in the genome), and phenotype, interpreted as the variability among individuals in terms of response and toxicity to different drugs. Pharmacogenetics commonly refers to the effects that involve a limited number of genes, often connected to drug metabolism, whereas pharmacogenomics involves the study of complex multigene patterns within the genome. Genetic polymorphisms are variants in individual genomes, present in more than 1.5% of the population, that remain constant throughout a person's lifetime [15]. There are more than 1.4 million single nucleotide polymorphisms (SNPs) identified in the human genome, and many of them contribute to variability in both pharmacokinetic and pharmacodynamic drugs [16]. Genetic mutations are acquired changes in gene sequences and occur only in certain cells. The interindividual genetic variation may also be an important factor in the characterization of

susceptibility for the development of cancer and of variability to drug response [17–23].

In the context of molecular epidemiology and pharmacogenomic investigation, it is also important to remember that prognostic factors are patient and tumor characteristics that predict patients' outcome (usually survival) and are independent from the type of administered treatment. Predictive factors are clinical, cellular, and molecular markers that predict response of the tumor to treatment (either in terms of tumor shrinkage or a survival benefit from treatment). Thus, prognostic factors define the effects of tumor characteristics on the patient, whereas predictive factors define the effect of treatment on the tumor [24].

EGFR

EGFR is a transmembranal glycoprotein encoded by a gene located in the short arm of chromosome 7 (chromosome 7p12.1–12.3). It has an M_r of 170,000 (1186 amino acids) [25] and contains 26 exons [26]. Exons 1–14 code the extracellular domain, exon 15 codes the transmembrane region, and exons 16–20 code the intracellular domain. This receptor belongs to the ErbB family of TK receptors, whose other members include ErbB2 (HER2/*neu*), ErbB3 (HER3), and ErbB4 (HER4) [27, 28]. Structurally, each protein of this family has an extracellular ligand-binding domain, a transmembrane hydrophobic domain, and an intracellular TK-containing domain. Except for ErbB3, they all have intrinsic TK activity [29]. The receptors exist as inactive monomers, and ligand binding causes dimerization, autophosphorylation of the adjacent intracytoplasmic domains (*trans*-autophosphorylation), and activation of the intracellular TK activity. This reaction is accompanied by recruitment of downstream signal transduction molecules, leading to activation of different pathways [30], and to effects in genetic expression, cellular proliferation, inhibition of apoptosis, and angiogenesis [31]. During carcinogenesis, the signaling system is frequently deregulated, and overexpression of EGFR is associated with aggressiveness, worse clinical prognosis, and chemo- and radioresistance in a variety of tumors [32–34].

The initial ErbB receptor-ligand and receptor-receptor interaction occurs on the cellular surface. ErbB receptors are activated by binding to growth factors of the EGF family, which are characterized by the presence of an EGF-like domain composed of three disulfide-bonded intramolecular groups that confer binding specificity, and additional structural areas such as immunoglobulin-like domains, heparin-binding sites, and glycosylation sites. These EGF-related growth factors, including amphiregulin and TGF- α , can specifically bind to EGFR. They can show dual specificity for EGFR and ErbB-4, such as the betacellulin, epiregulin,

and heparin-binding EGF. The third group is composed of the neuregulins (NRGs), divided into two subgroups based on their capacity to bind ErbB-3 and ErbB-4 (NRG-1 and NRG-2) or only ErbB-4 (NRG-3 and NRG-4) [35–38]. None of the EGF-family peptides binds directly ErbB-2.

This interaction induces the ErbB receptor to dimerization, which may occur between two receptors of the same family (heterodimerization; i.e., ErbB1-ErbB3) or between identical receptors (homodimerization; i.e., ErbB1-ErbB1). Stimulation by a specific ligand confers a unique dimerization profile that is also tissue- or tumor-specific [28]. The dimerization process leads to activation of the TK domain of the receptor and is followed by phosphorylation of multiple tyrosine residues, activating downstream proteins, and finally originating physiologic responses [28, 39].

Homodimers of EGFR signal weakly, in part due to receptor downregulation and degradation after ligand-mediated activation. The EGFR homologous HER2 receptor, which is highly expressed in several human cancers, can potentiate EGFR function by increasing EGF binding affinity, stabilizing and recycling EGFR-HER2 heterodimers, and expanding the repertoire of receptor-associated substrates and signaling responses [40, 41] (Fig. 3). In addition, the dimer degradation, initiated by ligand binding, induces receptors to cluster in clathrin-coated membrane pits, which is followed by endocytosis and eventual lysosomal degradation of the dimer [42]. However, in the kinase-negative mutants, recycling to the cell surface for reutilization is observed, and therefore, dimers are not degraded as much [43].

EGFR may crosstalk with heterologous receptors activated by neurotransmitters, lymphokines, and stress inducers. G-protein-coupled receptors can exert positive effects on EGFR signaling in several ways, including the activation of matrix metalloproteinases, which cleave membrane-bound EGFR ligands that can bind and activate EGFR [27].

Inhibition of EGFR Pathway by Low-Weight TKIs

EGFR is expressed in a variety of solid tumors, including NSCLC, cancer of the head and neck, and colorectal cancer. Overexpression of EGFR is found in 43%–83% of NSCLC, and it is more likely to occur in squamous cell carcinoma (70%), followed by adenocarcinoma (50%) and, to a lesser extent, in large-cell carcinoma [30]. It is a rare phenomenon in small-cell lung cancer.

Several phase II and phase III studies in second- and third-line treatment of NSCLC, in which gefitinib and erlotinib have been investigated as monotherapy, showed response rates ranging from 5% to 15% in different tumor types [14, 44, 45]. Since the time of pivotal phase II studies

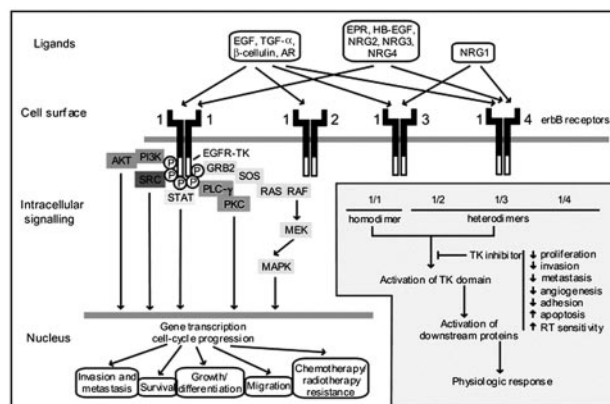


Figure 3. The erbB receptor dimerization, the epidermal growth factor receptor (EGFR) downstream signaling pathway, and the tyrosine kinase (TK) inhibitor's influence in cell outcome. Abbreviations: AR, amphiregulin; EPR, epiregulin; GRB2, growth-factor receptor-bound protein 2; HB-EGF, heparin-binding epidermal growth factor; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; NRG, neuregulin; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLC-γ, phospholipase C γ; RAF, serine kinase Raf; RAS, GTP-binding protein Ras; SOS, guanine nucleotide exchange factor Sos; STAT, signal transducer and activator of transcription; TGF-α, transforming growth factor α.

with gefitinib, a higher level of activity in selected subgroup of patients was clearly noted, including nonsmokers, Asian ethnicity, women, and patients with a diagnosis of adenocarcinoma. More recently, it was found that patients with NSCLC harboring somatic mutations in the TK domain receptor (the most common type is a short in-frame deletion of 9, 12, 15, 18, or 24 nucleotides in exon 19 or a point mutation, CTG to CGG, in exon 21 that results in substitution of leucine by arginine at codon 858, L858R) were extremely sensitive to EGFR inhibitors and obtained substantial and prolonged responses [46, 47]. There is also growing evidence suggesting that EGFR mutations are favorable prognostic markers of survival and that they are predictive markers of response in terms of tumor shrinkage. However, until now, there has been no evidence that suggests that they are predictive of a differential effect of EGFR inhibitor therapy on survival [24]. Other authors showed that the determination of *EGFR* gene copy numbers—by polymerase chain reaction or by fluorescence in situ hybridization (FISH)—could be a valuable tool in identifying a population of patients with NSCLC that will have a better response to EGFR-TKIs, time-to-progression, and an improved overall survival rate [48, 49]. At present, it is still unknown whether the determination of EGFR mutations in the TK domain by DNA sequencing, the number of copies of its gene by FISH, the determination of EGFR protein expression by immunohistochemistry, or a combina-

tion of these methods should be used in helping to predict which patients will benefit more from treatment with EGFR-directed drugs [50].

EGFR Polymorphisms

It is well known that interethnic differences are frequently observed in the distribution of polymorphisms in the drug-metabolizing enzymes, targets, receptors, and transporters. These may justify the interindividual variation in the response to the drugs and the obtained toxicity [51]. Overexpression of EGFR has been linked to amplifications of the *EGFR* gene located at 7p13-12. In most tumors, and especially in breast cancer, the main reason for overexpression has to be viewed at the gene transcription level.

In *EGFR*, the regulatory sequences of the gene have been demonstrated within the 5'-flanking region and intron 1 [52]. Two sequences with enhancer activity were located upstream in the promoter and downstream in intron 1. In this specific intron of *EGFR*, a highly polymorphic (CA)_n repeat was identified [53] (Fig. 4). Eight alleles with 14–21 (CA)_n repeats were found. Allele 16 (alleles are designated according to the number of repeats) showed the highest frequency (42%), followed by allele 20 (26%), allele 18 (20%), and allele 25 (5%). The other alleles are relatively rare [51].

Recent in vitro and in vivo studies showed that transcriptional activity of *EGFR* is reduced with more CA repeats [53] (Fig. 5). The longer allele 21 induced an 80% reduction in the gene expression compared with the shorter allele 16 [54, 55]. Thus, the length of this (CA)_n dinucleotide polymorphism is inversely related to the transcriptional activity of the gene. In addition, a constant decline of intratumoral EGFR protein expression was also observed to be associated with an increase in allele length [55].

Given the association between the expression of the gene and the polymorphic (CA)_n repeat, the response to therapy with EGFR inhibitors may vary among patients, due to their genotypic differences. The highest response rate to these therapies was observed in the Japanese population and may be due to a reduced expression of EGFR associated with the longer sequence of allele 20 (the most frequent allele in Asians) unlike the shorter sequence of 16 repeats associated with white and black ancestry [56]. Skin toxicity, the most common adverse effect of EGFR inhibitors, has not been uniformly associated with tumor response. By taking into consideration the elevated expression of EGFR in epidermis [57] and the proposed effect of the (CA)_n polymorphism, it seems reasonable to correlate these *EGFR* genotypes with sensitivity of both epidermal and tumor tissues, although other genetic determinants such as the effectors in the signal transduction cascade may also contribute to this association [56].

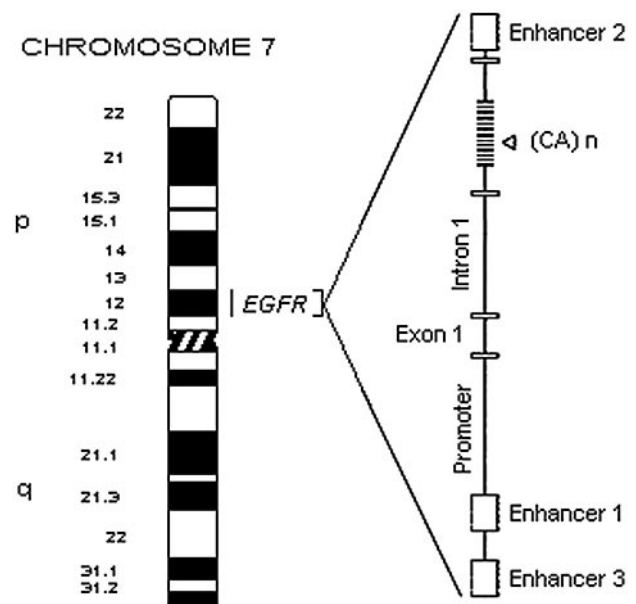


Figure 4. 5'-region of the *EGFR* gene (adapted from Gebhardt et al. [59]). Abbreviation: EGFR, epidermal growth factor receptor.

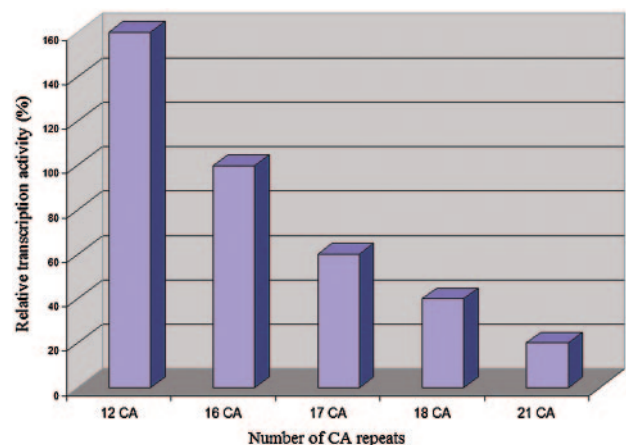


Figure 5. Relative transcription activity of the 5'-region of the *EGFR* gene in vitro (adapted from Gebhardt et al. [59]).

Furthermore, and in contrast, previously published data suggest a significant correlation between the polymorphic variations in intron 1 of *EGFR* and response to inhibitors. The reasons suggested by the authors for this discrepancy could be related to methodologic issues regarding the use of nonquantitative and poorly validated immunohistochemistry methods [58].

In breast cancer, allele length is inversely proportional to the level of EGFR transcription [55], and when there are 21 repeats, transcription decreases to about 80%, resulting in decreased cellular EGFR protein levels [54]. Furthermore, squamous cell histology in NSCLC is associated with higher EGFR content [49], and so it is expected to have shorter allele lengths.

In 2006, a study aimed at characterizing the frequency of *EGFR* polymorphisms in NSCLC specimens and determining the correlation of CA repeats with survival in the population of the Eastern Cooperative Oncology Group (ECOG) 3590 clinical trial was published [59, 60]. The ECOG 3590 clinical trial was a multicenter, randomized, prospective trial of adjuvant therapy following resection of stage II and IIIA NSCLC. Patients with complete tumor resection were randomized to receive either thoracic radiation (RT; 50.4 Gy) or RT concurrent with CT (four 28-day cycles of 60 mg/m² cisplatin on day 1 and 120 mg/m² etoposide on days 1–3). Survival was similar in both study arms. Of the 488 patients enrolled onto the ECOG 3590, 157 primary tumor samples were available for *EGFR* intron 1 analysis. In this subanalysis, it was demonstrated that patients with more than 35 (CA)_n repeats in *EGFR* intron 1 polymorphism had a significantly longer overall survival, with a median survival of 41 months compared with 29.2 months for the patients with the 35 or fewer (CA)_n alleles ($p = .03$). There was no difference in median survival between the groups of patients treated with RT alone, but a difference was seen between the groups in the RT-plus-CT group. Thus, although the authors concluded that *EGFR* dinucleotide polymorphisms (≤ 35 (CA)_n nucleotide repeats) was a good prognostic marker, it could also be interpreted as an unfavorable predictive marker associated with the combined treatment of RT plus CT [61]. The study addressed the use of dinucleotide repeats neither as a prognostic marker per se nor as a predictive factor for benefit from EGFR-TKIs.

The *EGFR* regulatory region has a high content in guanine-cytosine (G-C) and multiple transcriptional start sites, but there are no TATA or CAAT boxes [62, 63]. A TATA box serves to fix the transcription initiation site [64], and most genes whose promoter regions contain a TATA box have a single RNA start site. For genes with multiple start sites, such as *EGFR*, the promoters are often activated by Sp family proteins [65, 66]. The main role of the Sp1 in *EGFR* promoter activity has been extensively described [62, 67–69], and the requirement of Sp1 for *EGFR* transcription is well known [70].

EGFR intron 1 is 120 kilobases (kb) long, and it is believed that the sequences around exon 1 may have a separate effect on gene regulation [70]. The (CA)_n polymorphism in intron 1 of *EGFR* seems to be unstable, with five other frequent nucleotide polymorphisms in the 5' regulatory region, and thus may not be functional by itself. There are studies that support the hypothesis that *EGFR*-216G/T SNP has a functional relevance, including susceptibility to EGFR inhibitors [70]. Allele T in this polymorphism was associated with a 40% increase in

EGFR expression in vivo compared with allele G. The polymorphic allele is also expected to result in a stronger correlation between Sp1 and EGFR expression, potentially resulting in a different signaling network, probably because it is located in a Sp1-binding site, which is a critical region for the promoter activity [63, 67]. Thus, it is likely that *EGFR*-216G/T may, at least partially, contribute to the variability of EGFR expression in malignant cells and influence the reliance of cells upon EGFR. Conversely, EGFR expression seems to manifest interindividual variability, which may be related to *EGFR*-216G/T polymorphism [70]. Previously identified somatic mutations in *EGFR* are not capable of predicting those NSCLC patients who will likely respond to EGFR-TKIs. Data from published studies demonstrated that only 81% of lung cancer patients who were treated with gefitinib or erlotinib and who experienced partial responses or significant clinical improvement had EGFR somatic mutations [71] and that not all patients sensitive to gefitinib had EGFR mutations [46]. Furthermore, it was recently suggested that these mutations are not relevant in other types of tumors [72], although there is evidence of activity in other diseases such as colon cancer and brain tumors [73]. Thus, in spite of strong association, EGFR somatic mutations are neither sufficient nor necessary for drug response [70].

EGF

The ErbB receptors are activated through binding of EGF-family growth factors that are produced by the same cells that express the ErbB receptors (autocrine secretions) or by surrounding cells (paracrine secretions) [27, 28]. Proteins belonging to this family are characterized by the presence of an EGF-like domain, which is constituted by three joined disulphide intramolecular groups, conferring linkage specificity, and additional structural motifs such as immunoglobulin-like domains, heparin-binding locations, and glycosylation sites.

The *EGF* gene is located in chromosome 4q25-27, and its protein may activate DNA synthesis and cellular proliferation and stimulate mitosis in epidermal cells [74, 75]. EGF is encoded by a 4.8-kb mRNA transcribed from a 110-kb gene containing 24 exons [76].

It has been proposed that the interaction between EGF and EGFR may be a factor of susceptibility and prognosis in various tumors, such as melanoma, glioblastoma multiforme, or gastric cancer [77].

It has been shown that the treatment of tumor cells with oligonucleotide antisense combinations directed toward different EGF-like growth factors resulted in synergistic antitumoral effects in different tumors [78]. Recently, it has been documented that combined therapy with the EGFR-TKI ge-

fitinib and the monoclonal antibody anti-ErbB2 trastuzumab has a synergistic antitumor effect [77–89]. These results indicate a new possibility of treatment for cancer patients that may ultimately lead to a more efficient and prolonged control of tumor growth through the use of combinations of agents targeted toward ErbB receptors and their ligands.

EGF Polymorphisms

To the best of our knowledge, only one functional polymorphism in the *EGF* gene has been described and is associated with different types of tumors and with apparent functional consequences. Identified in 2002, this polymorphism is located in the 5′-untranslated region of the *EGF* gene. It consists of a substitution of guanine (G) for adenine (A) that leads to increased EGF expression by cultured peripheral-blood mononuclear cells. It has been identified 61 base pairs (bp) downstream of the EGF promoter and has been detected in 44% of the European white population and in almost 66% of patients with cutaneous malignant melanomas [80]. Carriers of the heterozygous G allele had a 2.7-fold relative risk for melanoma, whereas homozygous G individuals had an even higher risk compared with normal population (odds ratio, 4.9). The GG genotype was also significantly associated with a higher Breslow thickness index at the time of diagnosis [79], which is recognized as an adverse prognostic factor in malignant melanoma [81]. Nevertheless, the association between the *EGF*+61G/A polymorphism and the risk for malignant melanoma, as well as the association of the G/G genotype to Breslow's depth index, was not confirmed by other studies [82–85]. Therefore, no conclusive evidence supports the role of the *EGF* genotype in determining the susceptibility to cutaneous malignant melanoma, and its role in prognosis remains unclear [86].

The *EGF*+61G/A allele was associated with increased EGF expression observed in the resected specimens of primary or secondary glioblastoma multiforme [87]. It was shown that this association is independent from EGFR overexpression or gene mutation, which could indicate that this genetic variant on EGF does not depend on EGFR genetic alteration even in cases of increased activation of the receptor. However, because the *EGF*+61G/A allele is associated with increased EGF expression, it may promote development and progression of glioblastoma multiforme

and may ultimately be responsible for a more aggressive disease [87].

The mechanism by which increased EGF expression is associated with the polymorphism of the 5′-untranslated region of the *EGF* gene is currently unknown. One plausible explanation is the proximity of +61G locus to a region involved in *EGF* gene regulation [87]. A recent report suggests that the *EGF*+61G/A polymorphism could be involved in the development and malignant progression of gastric cancer [88], although another study failed to demonstrate such association [89].

CONCLUSION

Overexpression of EGFR is associated with a more aggressive phenotype, worse clinical prognosis, and chemo- and radioresistance in different solid tumors. The understanding of these molecular mechanisms has already led and, in the near future, will lead to the development of new therapies with significant clinical improvements. This is the case for EGFR inhibition in NSCLC, either by EGFR-TKIs or anti-EGFR antibodies that constitute a promising area of innovative treatment. At present, the factors that may be useful in predicting which patients will benefit from the treatment with EGFR-directed drugs is still largely unknown.

The low efficacy of some of these drugs in NSCLC patients led us to search for the explanation in patients' genetic background and tumor characteristics, keeping in mind that intricate and complex pathways may modulate response to treatment.

Patients carrying different functional polymorphic alleles from *EGFR* and *EGF* genes may potentially respond differently to EGFR-TKIs, although this remains an unanswered question. Furthermore, there is scant information regarding the influence of genetic polymorphism on EGFR and EGF expression levels in peripheral blood and tumor tissue. Therefore, further research to understand the field of EGF and its receptor remains a priority, and more studies are necessary and underway.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

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**Genetic Polymorphisms of the Epidermal Growth Factor and Related Receptor
in Non-Small Cell Lung Cancer—A Review of the Literature**

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Pemetrexed Plus Bevacizumab for Second-Line Therapy of Non–Small-Cell Lung Cancer: The Importance of Patient Selection

TO THE EDITOR: Pemetrexed is an antifolate drug that inhibits multiple enzymes involved in purine and pyrimidine synthesis, but thymidylate synthase is its primary target. Dihydrofolate reductase and glycinamide ribonucleotide formyl transferase are its secondary targets. The differential expression of thymidylate synthase between adenocarcinoma and squamous cell carcinoma could explain the differential efficacy according to histology in non–small-cell lung cancer (NSCLC).¹ The results of two published phase III trials with pemetrexed versus docetaxel² and cisplatin plus pemetrexed versus cisplatin plus gemcitabine³ were consistent with those of the phase III study comparing pemetrexed with placebo.⁴

Bevacizumab is a humanized monoclonal antivascular endothelial growth factor antibody with demonstrated significant clinical benefit in first-line treatment of nonsquamous NSCLC. This was observed in the phase III trials with the combination of carboplatin plus paclitaxel and bevacizumab and with cisplatin plus gemcitabine and bevacizumab over the same combinations without this antibody.⁵⁻⁶

On the basis of these studies, tumor histology should be carefully assessed when selecting treatment options for patients with advanced NSCLC. Both pemetrexed and bevacizumab have demonstrated significant clinical activity for nonsquamous NSCLC.

In the recent published North Central Cancer Treatment Group and Southwest Oncology Group study N0426, Adjei et al⁷ evaluated the combination of pemetrexed and bevacizumab as second-line therapy for NSCLC. Then they evaluated the impact of three single nucleotide polymorphisms (SNPs) in genes that code proteins linked to pemetrexed activity: *SLC19A1* codes a protein responsible for the transport, *FPGS* codes a protein linked to activation, and *GGH* codes a protein important for inactivation. The authors reported a promising progression-free survival of 4 months but no correlation of these polymorphisms with efficacy and toxicity. They concluded that the small sample size and the bevacizumab were confounding variables. The article was unclear about the histologic types of the patients' samples, and this is a main issue when evaluating the clinical importance of any treatment combination in NSCLC. We should evaluate

this combination for second-line treatment of nonsquamous NSCLC in a phase III trial versus the standard arm of pemetrexed alone and probably analyze the importance of these SNPs for this specific population.

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5. Costs of Cancer Treatment in Portugal

Currently second-line treatment for advanced or metastatic NSCLC includes docetaxel or pemetrexed (drug chemotherapy) or erlotinib (oral administration biological therapy) (de Marinis, F. et al. 2008; Arango, B.A. et al. 2009; Sheth, S. 2010), which are very expensive drugs (Capri, S. et al. 2007).

In face of the price of these drugs, it is urgent to define healthcare and drug policies and strategies for the use of them which will allow a rational utilization of available resources to obtain an optimal cost/benefit ratio. Several studies addressing this issue have already been published (Chouaid, C. et al. 2009; Asukai, Y. et al. 2010; Bradbury, P.A. et al. 2010; Ramsey, S.D. 2010), but further studies to attain a consensus in this matter are needed, to serve as an important tool for decision makers, especially when it comes to defining decisions over diseases such as lung cancer which take a great impact on patient quality of life .

A cost-minimization and cost-utility analysis was performed to compare the costs and clinical benefits of erlotinib as second or third line treatment of advanced or metastatic NSCLC with those of the three usual clinical care alternatives of docetaxel, pemetrexed and best supportive care (Araujo, A. et al. 2008).

This study received some criticisms such as differences in studied populations which makes them not comparable, after the change in the drug label of pemetrexed any conclusions on effectiveness in the second-line treatment of NSCLC are misleading, and that differences between the trials can result in bias and the direction of this bias is unknown, which means uncertainty of the results (Bartminski, W. 2009). These criticisms deserved some considerations on the subject (Araujo, A. 2009).

In the Portuguese National Health Plan of 2004-2010 a great deal was given to the oncologic diseases, setting them as a priority. After this period of time it turns necessary to evaluate if the allocated financial resources were in line with the burden of disease.

In times where spending on drugs continues to increase and the resources available to fund new therapies are limited, there was a need to conduct a study in the Portuguese context about the cost of cancer treatment in general and the cost of drugs used to treat NSCLC in particular. This study was crucial for making informed and reasoned decision with regard to the allocation of funds from the national health budget for the area of oncology. An estimation of the costs of cancer and the amount spent with the cancer treatment drugs in Portugal was made (Araujo, A. et al. 2009).

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Avaliação económica do erlotinib, docetaxel, pemetrexedo e tratamento de suporte no tratamento de segunda ou terceira linhas de doentes com cancro do pulmão de não pequenas células

An economic analysis of erlotinib, docetaxel, pemetrexed and best supportive care as second or third line treatment of non-small cell lung cancer

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Resumo

Objectivo: Avaliar o custo-efectividade de erlotinib na segunda ou terceira linha do tratamento do cancro do pulmão de não pequenas células (CPNPC) avançado ou metastizado *versus* docetaxel, pemetrexedo ou tratamento de suporte.

Material e métodos: Análises de minimização de custos e custo-utilidade. Horizonte temporal: dois anos.

Abstract

Aim: Evaluate costs and benefits of erlotinib as 2nd or 3rd line treatment of advanced or metastatic non-small cell lung cancer (NSCLC) *versus* docetaxel, pemetrexed and best supportive care.

Materials and methods: Cost-minimisation and cost-utility analysis were performed. Time horizon of two years. Portuguese National Health System (NHS)

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Perspectiva do Sistema Nacional de Saúde (SNS) português. Sobrevivência e tempo até progressão obtidos a partir de três ensaios clínicos. Análise-base inclui doentes com CPNPC avançado ou metastizado em segunda ou terceira linhas. Anos de vida ajustados pela qualidade (ou QALY) obtidos a partir de estudo no Reino Unido. Consumo de recursos estimado por painel de peritos portugueses. Incluíram-se apenas custos directos, obtidos a partir de fontes oficiais (preços actualizados para 2008). Taxa de actualização anual: 5%. Análises de sensibilidade: diferentes subpopulações, horizonte temporal a três anos e análise probabilística.

Resultados: O custo total/doente foi menor com erlotinib (26 478€) *versus* docetaxel (29 262€) ou pemetrexedo (32 762€) e superior *versus* tratamento de suporte (16 112€). Obtiveram-se QALY/doente mais elevados com erlotinib (0,250) *versus* docetaxel (0,225), pemetrexedo (0,241) ou tratamento de suporte (0,186). Assim, o erlotinib mostrou-se “dominante” em segunda ou terceira linhas *versus* docetaxel e pemetrexedo. A análise de sensibilidade comprova a robustez dos resultados.

Conclusões: A substituição de docetaxel ou pemetrexedo por erlotinib poderia contribuir para uma redução anual dos gastos do SNS que se estima (taxas substituição: 5%-65%) com uma variação entre 135 046€-1 755 602€ e entre 291 801€-3 793 409€, respectivamente, e com ganho em termos de QALY.

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Palavras-chave: Cancro do pulmão de não pequenas células, económico, Portugal, utilidade, custo-efectividade.

perspective was applied. Survival and time to progression were obtained from three clinical trials. Base-case analysis: 2nd or 3rd line patients with advanced or metastatic NSCLC. Quality Adjusted Life Years (QALYs) were obtained from a UK study. Resource consumption was estimated by a Portuguese panel of experts. Costs were calculated according to official Portuguese databases (updated to 2008). Only direct health costs were applied. Annual discount rate: 5%. Sensitivity analysis included different subpopulations, a three year time horizon and a probabilistic analysis.

Results: The cost per patient was lower with erlotinib (€26 478) than docetaxel (€29 262) or pemetrexed (€32 762) and higher than best supportive care (€16 112). QALYs per patient were higher with erlotinib (0.250) than docetaxel (0.225), pemetrexed (0.241) or best supportive care (0.186). Erlotinib was dominant in the cost-utility analysis, with a lower cost and a higher efficacy than docetaxel and pemetrexed. The sensitivity analysis confirmed the robustness of the base-case analysis results.

Conclusions: The use of erlotinib instead of docetaxel or pemetrexed could contribute to annual savings for the NHS (substitution rates: 5%-65%) ranging from €135 046-€1 755 602 (docetaxel replacement) and €291 801-€3 793 409 (pemetrexed replacement), with a gain in terms of QALYs.

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Key-words: Non-small cell lung cancer, economics, Portugal, utility, cost-effectiveness.

Introdução

No mundo, mais de meio milhão de novos casos de cancro do pulmão são diagnosticados anualmente. Aproximadamente 80% destes tumores são de tipo histológico de não pequenas células, incluindo adenocarcinomas, carcinomas de células escamosas e carcinomas de grandes células. Considerando-se todos os estádios, o cancro do pulmão de não pequenas células (CPNPC) apresenta uma sobrevivência a cinco anos de, aproximadamente, 12%¹. Em Portugal, estima-se que sejam diagnosticados cerca de 34 novos casos de cancro do pulmão/100 000 habitantes (homens: 28 casos/100 000; mulheres: 6 casos/100 000). Embora a incidência nos homens seja mais elevada, tem-se vindo a observar um aumento da incidência desta doença nas mulheres². A mortalidade por cancro continua a aumentar mais de 6% ao ano, nomeadamente a mortalidade por cancro do pulmão³.

Actualmente, a terapêutica de segunda linha do CPNPC em estágio avançado prevê a utilização de docetaxel ou pemetrexed (quimioterapia farmacológica) ou erlotinib (fármaco biológico de administração oral)⁴. O erlotinib é um inibidor da tirosina-quinase do receptor do factor de crescimento epidérmico/receptor tipo 1 do factor de crescimento epidérmico humano EGFR (igualmente designado por HER1) que se encontra indicado no tratamento de doentes com CPNPC, localmente avançado ou metastizado, após falência de pelo menos um regime de quimioterapia⁵.

Actualmente, torna-se premente definir políticas e estratégias de actualização na área da saúde e do medicamento que permitam uma utilização racional dos recursos disponíveis, na perspectiva de otimizar as despesas face aos benefícios obtidos mediante determinada opção. Estudos que permitam esta avaliação cons-

Introduction

Over half a million new lung cancer cases are diagnosed annually world-wide. Approximately 80% of these tumours are non-small cell lung cancer, including adenocarcinoma cell type, squamous cell cancer and large cell cancer. In terms of disease staging, non-small cell lung cancer (NSCLC) has a five year survival rate of approximately 12%¹.

It is estimated that around 34 new cases of lung cancer per 100 000 inhabitants (men: 28 cases/100 000; women: six cases/100 000) are diagnosed in Portugal. While the incidence in men is higher, an increased incidence of this disease has also been seen in women². Cancer mortality, particularly death due to lung cancer, continues to rise by over 6% a year in Portugal³.

Current 2nd line treatment for advanced stage NSCLC includes docetaxel or pemetrexed (drug chemotherapy) or erlotinib (oral administration biological therapy)⁴. Erlotinib inhibits the tyrosine kinase of the human epidermal receptor/growth factor receptor 1/ epidermal growth factor receptor (HER1/EGFR), approved for treating locally advanced or metastatic NSCLC with failure of at least one prior chemotherapy regimen⁵.

It is now urgent to define healthcare and drug policies and strategies for the use of erlotinib which will allow a rational utilisation of available resources to obtain an optimal cost/benefit ratio. Studies which allow this evaluation are thus a very important tool for decision makers, specially when it comes to defining decisions over diseases such as lung cancer which take a heavy toll of patient quality of life.

Em Portugal, estima-se que sejam diagnosticados cerca de 34 novos casos de cancro do pulmão/100 000 habitantes

tituem assim ferramentas muito importantes para os decisores, ainda mais quando se trata de definir tomadas de decisão relativas a doenças com marcado impacto na qualidade de vida dos doentes, como o cancro do pulmão.

O objectivo deste estudo consistiu em comparar os custos e os benefícios clínicos de erlotinib no tratamento do CPNPC avançado ou metastizado, em segunda ou terceira linhas, com outras três alternativas consideradas na prática clínica habitual (docetaxel, pemetrexedo e tratamento de suporte), através de uma análise de minimização de custos e de uma análise de custo-efectividade.

Material e métodos

Modelo fármaco-económico

Construiu-se um modelo com três estados de saúde “livre de progressão”, “progressão” e “morte”, com o objectivo de se estimar o custo-utilidade da terapêutica com erlotinib *versus* tratamentos alternativos (docetaxel, pemetrexedo ou tratamento de suporte) no tratamento do CPNPC avançado ou metastizado (Fig. 1). O modelo foi construído em Excel, sendo possível especificar tipo de população, tratamentos alternativos, custos relevantes, taxas de desconto, valores de utilidade e incidência de eventos adversos (EA).

População

Considera-se que a população deste estudo corresponde a uma coorte hipotética de doentes portugueses, de ambos os sexos e com diagnóstico de CPNPC avançado ou metastizado (estádios IIIA, IIIB ou IV), em que se observou falência de um ou mais regimes de quimioterapia no tratamento da doença. Esta população apresenta caracte-

This study aims to perform a cost-minimisation and cost-utility analysis to compare the costs and clinical benefits of erlotinib as 2nd or 3rd line treatment of advanced or metastatic NSCLC with those of the three usual clinical care alternatives of docetaxel, pemetrexed and best supportive care.

Material and methods

Pharmoeconomic model

A three-stage model of health (free of progression; progression; death) was constructed to estimate the cost/benefit ratio of erlotinib *versus* alternative treatment (docetaxel, pemetrexed and best supportive care) of advanced or metastatic NSCLC (Fig. 1). The model was constructed in Excel, specifying different subpopulations, alternative treatments, relevant costs, discount rates, utility values and incidence of adverse events (AEs).

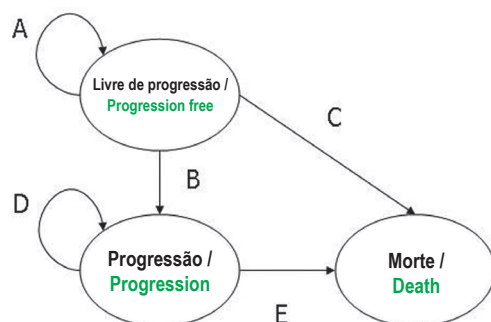
Population

The study population corresponds to a hypothetical cohort of male and female Portuguese patients with advanced or metastatic NSCLC (stages IIIA, IIIB or IV) that has at least one prior failed chemotherapy regimen. This population has similar characteristics to the patients of the three clinical trials whose efficacy results were used in this study.

The model, based on clinical trials with erlotinib, estimates results for the following subpopulations of advanced or metastatic NSCLC patients: a) patients with failure of at least one prior chemotherapy regimen (2nd and 3rd line); b) patients with

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No início da simulação todos os doentes se encontram no estado "livre de progressão", de onde poderão transitar para outro estado de saúde (B ou C) ou manter-se no mesmo (A). Após progressão, o doente pode manter-se neste estado (D) ou transitar para o estado "morte" (E).

Fig. 1 – Estrutura do modelo de decisão.

Fig. 1 – Structure of the model

rísticas semelhantes às dos doentes incluídos nos três ensaios clínicos, cujos resultados de eficácia foram utilizados neste estudo.

O modelo, que se baseia nos ensaios clínicos principais com erlotinib, pode estimar resultados para as seguintes subpopulações de doentes com CPNPC avançado ou metastizado: a) doentes após falência de um ou mais regimes prévios de quimioterapia (segunda e terceira linhas); b) doentes após falência de um ou mais regimes prévios de quimioterapia e com ECOG PS (*eastern cooperative oncology group performance status*) 0 ou 1 (segunda e terceira linhas); c) doentes após falência de um regime prévio de quimioterapia (segunda linha); e d) doentes após falência de dois ou mais regimes prévios de quimioterapia (terceira linha).

A análise-base refere-se à população de doentes com CPNPC avançado após falência de um ou mais regimes prévios de quimioterapia (segunda ou terceira linhas).

Estados de saúde

De acordo com a história natural do CPNPC foram considerados os seguintes estados de saúde no modelo: dois estados de transição

failure of at least one prior chemotherapy regimen plus ECOG PS (Eastern Cooperative Oncology Group Performance Status) 0 or 1 (2nd and 3rd line); c) patients with failure of prior chemotherapy regimens (2nd line) and d) patients with failure of at least two chemotherapy regimens (3rd line).

Base-case analysis refers to population of patients with advanced NSCLC with at least one failed chemotherapy regimen (2nd or 3rd line).

Stages of health

The model considered the following stages of health, according to progression of the NSCLC: two transition stages called “free of progression” (patients whose disease did not progress with initial treatment) and “progression” (patients whose disease progressed with initial treatment). Patients either remained in the same stages for several cycles (1 month) or transited to the stage “death” (end stage).

Fig. 1 shows that a progressing patient cannot return to the “free of progression” stage, that is, throughout the cycles, patients may

designados por estado “livre de progressão” (doentes que não progrediram no tratamento inicial) e estado “progressão” (doentes que progrediram durante o tratamento inicial). Os doentes poderão manter-se nestes mesmos estados em vários ciclos (1 mês) ou transitar para o estado “morte” (estado absorvente).

A Fig. 1 mostra que um doente ao progredir deixa de poder retornar ao estado “livre de progressão”, ou seja, ao longo dos ciclos os doentes poderão permanecer no estado “livre de progressão” ou transitar para os restantes estados.

O modelo foi construído para estimar o tempo que o doente permanece em sobrevivência livre de progressão e em sobrevivência após progressão nos diferentes regimes terapêuticos, assim como para estimar os custos associados aos estados de saúde “livre de progressão” e “progressão” (no estado “morte” não se consideram custos). No entanto, o modelo não utiliza as cadeias de Markov tradicionais, ou seja, não existem probabilidades de transição, uma vez que as estimativas de Kaplan-Meier para o tempo em sobrevivência livre de progressão e sobrevivência após progressão são utilizadas directamente no modelo. O modelo assume ainda que um doente que se encontra vivo, mas não no estado “livre de progressão”, deverá despendar tempo no estado “progressão”. Assim, o modelo calcula a área abaixo da curva de tempo em que os doentes se encontram vivos nos estados “livre de progressão” e “progressão”.

Dados de eficácia e tipos de análise

Não existem ensaios clínicos em paralelo que comparem directamente a eficácia de erlotinib com docetaxel e/ou pemetrexed. Desta forma, foram realizadas comparações indirectas da eficácia entre estes regimes com base

remain in the “free of progression” stage, or transit to the remaining stages.

The model was constructed to estimate the time a patient remains in free of progression survival and survival after progression on the different treatment regimens, and thus estimate the costs associated with the “free of progression” and “progression” health stages (costs are not considered in the “death” stage). However, the model does not use traditional Markov chains, meaning there is no possibility of transition once the Kaplan-Meier estimates for time in free of progression survival and survival after progression are used directly in the model. The model further assumes that a patient who is alive but not in the “free of progression” stage should spend time in the “progression” stage. The model thus calculates the area below the time curve in which the patients are alive in the “free of progression” and “progression” stages.

Efficacy data and type of analysis

There are no parallel clinical trials which directly compare the efficacy of erlotinib with docetaxel and/or pemetrexed. Accordingly, indirect comparisons of efficacy among these regimens were undertaken based on three clinical trials which compared docetaxel with best supportive care⁶, docetaxel with pemetrexed⁷ and erlotinib with best supportive care⁸. Table I shows the base characteristics of patients included in these clinical trials and the survival results. It is seen that prognostic factors such as age, disease stage and response to cisplatin were very similar among the clinical trials. The results, however, show a higher proportion of patients with ECOG PS 2-3 in the erlotinib trial (par-

em três ensaios clínicos que compararam docetaxel *versus* tratamento de suporte⁶, docetaxel *versus* pemetrexedo⁷ e erlotinib *versus* tratamento de suporte⁸. O Quadro I apresenta as características de base dos doentes incluídos nestes ensaios clínicos, assim como os resultados de sobrevivência. Verifica-se que factores de prognóstico, como a idade, o estágio da doença e a resposta à cisplatina foram muito semelhantes entre ensaios clínicos. No entanto, os resultados apresentados mostram uma proporção superior de doentes com ECOG PS 2-3 no ensaio com erlotinib (particularmente doentes ECOG PS 3), assim como uma maior proporção de doentes que receberam mais terapêuticas prévias para o CPNPC avançado ou metastizado, comparativamente aos doentes incluídos noutros ensaios clínicos. Isto poderá indicar que os doentes tratados com erlotinib se encontravam numa pior situação clínica, comparativamente aos incluídos nos ensaios clínicos com docetaxel e pemetrexedo.

Uma vez que não se demonstrou existirem diferenças em termos de sobrevivência entre os tratamentos activos descritos anteriormente, o custo por ano de vida ganho (AVG) foi comparado através de uma análise de minimização de custos. Para a comparação com o tratamento de suporte, uma vez que se verifica uma diferença em termos de sobrevivência, conduziu-se uma análise de custo-efectividade. Em termos de toxicidade, verificaram-se diferenças entre os tratamentos activos, o que pressupõe que as terapêuticas tenham diferentes impactos na qualidade de vida dos doentes. Assim, efectuou-se uma análise de custo-utilidade para se estimar o custo por anos de vida ajustados pela qualidade (AVAQ ou QALY – *Quality adjusted life years*).

ticularly ECOG PS 3 patients), and a higher proportion of patients who had received more prior treatments for advanced or metastatic NSCLC than the patients in the other clinical trials. This could indicate that the patients treated with erlotinib were in a worse clinical state than the patients in the docetaxel and pemetrexed clinical trials.

As differences in terms of survival among the abovementioned active treatments could not be demonstrated, the cost per Year of life Gained (YLG) was compared using a cost-minimisation analysis. As a difference in terms of survival was seen, a cost-effectiveness analysis was performed for the comparison with best supportive care. In terms of toxicity, there were differences seen among the active treatments, presupposing that the treatments have different impacts on patients' quality of life. Thus, a cost-utility analysis was performed to estimate the cost per Quality Adjusted Life Years (QALYs).

The comparison between costs and consequences of the alternative treatments was made by calculating the incremental cost-effectiveness ratio (ICER) using the formula:

$$\text{ICER} = \frac{\text{cost of treatment with erlotinib} - \text{cost of treatment with comparison item}}{\text{effectiveness of erlotinib} - \text{effectiveness of comparison item}}$$

The results are presented as incremental costs, cost per YLG (cost-effectiveness) and costs per QALY (cost-utility) for erlotinib compared to docetaxel, pemetrexed and best supportive care.

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Quadro I – Resultados dos ensaios clínicos considerados no modelo

Características dos doentes	Docetaxel vs tratamento de suporte ⁶		Docetaxel vs pemetrexedo ⁷		Erlotinib vs tratamento de suporte ⁸	
	Docetaxel 75 mg/m ²	Tratamento de suporte	Docetaxel 75 mg/m ²	Pemetrexedo 500 mg/m ²	Erlotinib	Tratamento de suporte
N.º de doentes	55	100	288	283	488	243
Masculino	63,6%	65,0%	75,3%	68,6%	64,5%	65,8%
Feminino	36,4%	35,0%	24,7%	31,4%	35,5%	34,2%
Idade média (min-max)	61 (37-73)	61 (28-77)	57 (28-87)	59 (22-81)	62 (34-86)	59 (32-88)
Estádio da doença						
IIIA/B	27,3%	19,0%	25,3%	25,1%	Não reportado	Não reportado
IV	72,7%	81,0%	74,7%	74,9%	Não reportado	Não reportado
ECOG-PS						
0	23,6%	22,0%	87,6%	88,6%	13,1%	14,0%
1	50,9%	53,0%			52,5%	54,3%
2	25,5%	25,0%	12,4%	11,4%	25,8%	23,0%
3	0,0%	0,0%	0,0%	0,0%	8,6%	8,6%
N.º de tratamentos prévios						
0	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%
1	80,0%	76,0%	100,0%	100,0%	50,0%	50,0%
2	12,7%	15,0%	0,0%	0,0%	49,0%	49,0%
3 ou +	7,3%	9,0%	0,0%	0,0%	1,0%	1,0%
Melhor resposta à cisplatina						
RP/RC	25,5%	37,0%	37,5%	34,7%	40,0%	40,0%
DE	56,4%	43,0%	Não reportado	Não reportado	39,0%	39,0%
DP	18,2%	20,0%	Não reportado	Não reportado	21,0%	21,0%
Resultados de sobrevivência						
Sobrevivência global (mediana)	7,5 meses	4,6 meses	7,9 meses	8,3 meses	6,7 meses	4,7 meses
Sobrevivência global (média)	9,4 meses	5,4 meses	Não reportado	Não reportado	Não reportado	Não reportado
Sobrevivência livre de progressão	10,6 semanas	6,7 semanas	2,9 meses	2,9 meses	9,7 semanas	8,0 semanas

RP – Resposta parcial; RC – resposta completa; DE – doença estável; DP – doença em progressão

A comparação entre custos e consequências das terapêuticas alternativas foi efectuada através do cálculo do rácio incremental de custo-efectividade (ICER) calculado de acordo com a seguinte fórmula:

$$ICER = \frac{\text{cost of treatment with erlotinib} - \text{cost of treatment with comparison item}}{\text{effectiveness of erlotinib} - \text{effectiveness of comparison item}}$$

Adverse events (AEs)

There are significant differences in the safety profile of erlotinib and its comparison items. Rash is the AE most frequently associated with erlotinib, while the AEs most frequently associated with docetaxel are neutropaenia, stomatitis, diarrhoea and nausea, and the AEs most frequently associated with pemetrexed are stomatitis, neu-

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Table I – Results of the clinical trials considered in the model

Patient profiles	Docetaxel vs. best supportive care ⁶		Docetaxel vs. pemetrexed ⁷		Erlotinib vs. best supportive care ⁸	
	Docetaxel 75 mg/m ²	Best supportive care	Docetaxel 75 mg/m ²	Pemetrexed 500 mg/m ²	Erlotinib	Best supportive care
No. of patients	55	100	288	283	488	243
Male	63.6%	65.0%	75.3%	68.6%	64.5%	65.8%
Female	36.4%	35.0%	24.7%	31.4%	35.5%	34.2%
Mean age (min-max)	61 (37-73)	61 (28-77)	57 (28-87)	59 (22-81)	62 (34-86)	59 (32-88)
Disease stage						
IIIA/B	27.3%	19.0%	25.3%	25.1%	Not reported	Not reported
IV	72.7%	81.0%	74.7%	74.9%	Not reported	Not reported
ECOG-PS						
0	23.6%	22.0%	87.6%	88.6%	13.1%	14.0%
1	50.9%	53.0%			52.5%	54.3%
2	25.5%	25.0%	12.4%	11.4%	25.8%	23.0%
3	0.0%	0.0%	0.0%	0.0%	8.6%	8.6%
No. of prior treatments						
0	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
1	80.0%	76.0%	100.0%	100.0%	50.0%	50.0%
2	12.7%	15.0%	0.0%	0.0%	49.0%	49.0%
3 or +	7.3%	9.0%	0.0%	0.0%	1.0%	1.0%
Best response to cisplatin						
PR/CR	25.5%	37.0%	37.5%	34.7%	40.0%	40.0%
SD	56.4%	43.0%	Not reported	Not reported	39.0%	39.0%
DP	18.2%	20.0%	Not reported	Not reported	21.0%	21.0%
Survival results						
Global survival (mediana)	7.5 months	4.6 months	7.9 months	8.3 months	6.7 months	4.7 months
Global survival (mean)	9.4 months	5.4 months	Not reported	Not reported	Not reported	Not reported
Free of progression survival	10.6 weeks	6.7 weeks	2.9 months	2.9 months	9.7 weeks	8.0 weeks

PR – Partial response; CR – Complete response; SD – stable disease; DP – disease in progression

Os resultados foram apresentados como custos incrementais, custo por ano de vida ganho (custo-efectividade) e custo por QALY (custo-utilidade) relativamente ao erlotinib em comparação com docetaxel, pemetrexedo e tratamento de suporte.

ropathy, diarrhoea and nausea (Table II). Treatment of the AEs associated with pemetrexed and docetaxel is possibly more expensive than treating those related to erlotinib and will have a major impact on the quality of life of NSCLC patients.

Eventos adversos (EA)

Existem diferenças relevantes no perfil de segurança entre erlotinib e os seus comparadores. O *rash* é o EA mais frequentemente associado ao erlotinib. Por outro lado, os EA mais frequentemente associados ao docetaxel são neutropenia, estomatite, diarreia e náusea, enquanto os EA mais frequentes associados ao pemetrexedo são estomatite, neuropatia, diarreia e náusea (Quadro II). O tratamento dos EA associados ao pemetrexedo e docetaxel será possivelmente mais caro do que os relacionados com erlotinib e os mesmos terão um maior impacto na qualidade de vida dos doentes com CPNPC.

A taxa de incidência de EA para o erlotinib, docetaxel e pemetrexedo não foi ajustada às diferenças observadas nas subpopulações do modelo, dada a pequena dimensão destes subgrupos nos ensaios clínicos com docetaxel e pemetrexedo.

Utilidades

As utilidades dos estados considerados no modelo foram obtidas a partir de um estudo

The rate of incidence of AEs for erlotinib, docetaxel and pemetrexed was not adjusted for the differences seen in the model's subpopulations, given the small size of these subgroups in the docetaxel and pemetrexed clinical trials.

Utilities

The utilities of the stages in the model were obtained from a utility study conducted in the UK by Roche (Table III). The stages of health related to NSCLC were developed by experts in the UK and based on the published literature. A total of 154 healthy subjects were recruited at four centres (Oxford, Glasgow, London and Cardiff) to evaluate each of the 13 health stages defined using the EQ-5D York tariff and the EQ-5D visual analogue scale. The model considers the utilities obtained from the EQ-5D visual analogue scale. The utility associated with the "free of progression" stage was 0.451 (standard deviation=0.170) and the "progression" stage 0.217 (standard deviation=0.011). The utility values associated to

Quadro II – Taxa de ocorrência de eventos adversos consideradas no modelo

Evento adverso	Erlotinib	Docetaxel	Pemetrexedo	Tratamento de suporte
<i>Rash</i>	9%	0%	0%	0%
Diarreia	6%	15%	15%	1%
Fadiga	18%	17%	16%	20%
Anorexia	9%	10%	10%	5%
Neutropenia (grau 3)	0%	25%	4%	0%
Neutropenia (grau 4)	0%	40%	1%	0%
Neutropenia febril	0%	2%	0%	0%
Náusea	3%	15%	15%	2%
Infecção	4%	10%	0%	2%
Estomatite	0%	26%	15%	0%
Neuropatia	0%	0%	0%	0%

Fonte: Resultados do ensaio clínico BR-21 (erlotinib, tratamento de suporte); Shepherd *et al.*, 2000 (docetaxel); Hanna *et al.*, 2004 (pemetrexedo)

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de utilidade conduzido no Roche Reino Unido (Quadro III). Os estados de saúde relacionados com o CPNPC foram desenvolvidos com peritos do Reino Unido e com base na literatura publicada. Foi solicitado a um total de 154 pessoas saudáveis de quatro centros (Oxford, Glasgow, Londres e Cardiff) que avaliassem cada estado de saúde definido (13 estados) utilizando o EQ-5D *York tariff* e a escala visual analógica do EQ-5D. No modelo consideraram-se as utilidades obtidas a partir da escala visual analógica do EQ-5D. A utilidade associada ao estado “livre de progressão” foi de 0,451 (erro padrão = 0,170) e de 0,217 (erro padrão = 0,011) para o estado de “progressão”. Os valores de utilidade associados aos estados de saúde e aos EA encontram-se descritos no Quadro III.

O cálculo dos QALY, em cada ciclo, é efectuada da seguinte forma: no estado “livre de progressão” existe uma proporção de doentes em que não se verifica a ocorrência de EA; a contribuição destes doentes para o valor do QALY é calculada multiplicando-se a proporção de doentes sem EA pela utilidade associada a esse

the health stages and the AEs are shown in Table III.

Each cycle's QALYs are calculated using the following formula: there is a proportion of patients in the “free of progression” stage who had no AEs; these patients' contribution to the QALY value is calculated by multiplying the proportion of patients without AEs by the utility associated with this stage. The contribution to the QALY value of patients with AEs in this health stage is calculated by multiplying the proportion of patients with each of the AEs with the corresponding utility (Table III). The QALYs gained in the “free of progression” stage in each cycle equal the sum of these 2 values.

The model assumes that the AEs are related to the treatments and do not onset after disease progression. Thus, the QALYs gained in each of the cycles in the “progression” stage are calculated by multiplying the proportion of patients in this stage by the corresponding utility.

Table II – Rate of occurrence of adverse events considered in the model

Adverse event	Erlotinib	Docetaxel	Pemetrexed	Best supportive care
Rash	9%	0%	0%	0%
Diarrhoea	6%	15%	15%	1%
Fatigue	18%	17%	16%	20%
Anorexia	9%	10%	10%	5%
Neutropaenia (level 3)	0%	25%	4%	0%
Neutropaenia (level 4)	0%	40%	1%	0%
Febrile neutropaenia	0%	2%	0%	0%
Nausea	3%	15%	15%	2%
Infection	4%	10%	0%	2%
Stomatitis	0%	26%	15%	0%
Neuropathy	0%	0%	0%	0%

Source: Results of the BR-21 clinical trial (erlotinib, best supportive care); Shepherd *et al.*, 2000 (docetaxel); Hanna *et al.*, 2004 (pemetrexed)

mesmo estado. A contribuição para o valor de QALY dos doentes que se encontrem neste estado de saúde com EA é calculada multiplicando-se a proporção de doentes com cada um dos EAs pela utilidade correspondente (Quadro III). Os QALY ganhos no estado “livre de progressão”, em cada ciclo, correspondem à soma destes dois valores.

O modelo assume que os EA se encontram relacionados com os tratamentos e que não ocorrem após a progressão da doença. Assim, os QALY ganhos em cada um dos ciclos no estado “progressão” são calculados multiplicando-se a proporção de doentes que se encontram nesse mesmo estado pela utilidade correspondente.

Duração dos ciclos, horizonte temporal e descontos

Considerou-se que as transições entre estados ocorrem em intervalos designados por ciclos, com uma duração de um mês. Para melhorar a aproximação à realidade, os custos e os benefícios no modelo são determinados no final de cada mês, utilizando-se uma correcção para meio ciclo.

Duration of cycles, time horizon and discount

The transitions between stages are considered to occur at intervals designated as cycles, lasting a month. To increase approximation to reality, the costs and benefits in the models are determined at the end of each month, using a correction for half-cycle.

The base-case analysis considers a time horizon of 24 months (two years). However, there is a significant proportion of patients in the erlotinib arm alive at 24 months (using Kaplan-Meier survival curves) and, as such, the model allows an extrapolation of the survival curves to 36 months (three years) for the populations in ITT and 3rd line treatment through Weibull or log-logistic distribution.

The costs and consequences were updated by a rate of 5%, as the model's time horizon exceeds the period of a year⁹.

Study perspectives and guidelines followed

We applied the Portuguese National Health System (NHS) perspective to this study, in-

Quadro III – Utilidades consideradas no modelo

Estado de saúde	Utilidade	Erro-padrão
Estados		
Livre de progressão	0,451	0,170
Progressão	0,217	0,011
Morte	0	0
Eventos adversos		
Neutropenia	0,324	0,156
Neutropenia febril	0,194	0,114
Diarreia	0,325	0,148
Náusea	0,315	0,146
Estomatite	0,321	0,136
Neuropatia	0,306	0,163
Rash	0,403	0,166

Fonte: Estudo de utilidade conduzido por Roche Reino Unido (n=154)

Table III – Utilities considered in the model

Health stage	Utility	Standard deviation
Stages		
Free of progression	0.451	0.170
Progression	0.217	0.011
Death	0	0
Adverse events		
Neutropaenia	0.324	0.156
Febrile neutropaenia	0.194	0.114
Diarrhoea	0.325	0.148
Nausea	0.315	0.146
Stomatitis	0.321	0.136
Neuropathy	0.306	0.163
Rash	0.403	0.166

Source: Utility study performed by Roche UK (n=154)

Na análise-base considerou-se um horizonte temporal de 24 meses (dois anos). No entanto, verificou-se existir uma proporção significativa de doentes no braço erlotinib que se encontrava viva aos 24 meses (através da análise de sobrevivência de Kaplan-Meier) e, como tal, o modelo permite efectuar uma extrapolação das curvas de sobrevivência até aos 36 meses (três anos) para as populações em ITT e em tratamento de terceira linha através da distribuição Weibull ou log-logística.

Os custos e consequências foram actualizados a uma taxa de 5%, uma vez que o horizonte temporal do modelo excede o período de um ano⁹.

Perspectiva do estudo e directrizes seguidas

A perspectiva adoptada neste estudo foi a do Sistema Nacional de Saúde (SNS) português, tendo-se incluído apenas os custos directos médicos suportados pelo SNS. Neste estudo foram seguidas as orientações metodológicas do Infarmed para estudos de avaliação económica em Portugal⁹.

Premissas do modelo

Assumiram-se algumas premissas, para além dos pressupostos enunciados nas secções anteriores, sobre a comparabilidade dos três ensaios clínicos: a) entre o erlotinib, docetaxel ou pemetrexed não existem diferenças no tempo que se permanece no estado “livre de progressão” nem na sobrevivência; b) a utilização mensal de recursos no estado “livre de progressão” e “progressão” foi estimada através um painel de sete especialistas clínicos em Portugal; c) o regime posológico de cada um dos fármacos comparados corresponde ao descrito no respectivo resumo das características do medicamento (RCM) respectivo^{5,10,11}.

cluding only the direct health costs borne by the NHS. The study followed Infarmed's (Portugal's National Medicine and Health Products Body) methodology orientations for economic evaluation studies in Portugal⁹.

Model presuppositions

Several presuppositions on the comparability of the three clinical trials other than those detailed above were assumed: a) there are no differences among erlotinib, docetaxel or pemetrexed in the time spent “free of progression” or survival stages; b) monthly use of resources in “free of progression” and “progression” stages was estimated by a panel of seven Portuguese clinical specialists; c) the dosing regimen of each drug was that described in its drug information summary (RCM)^{5,10,11}.

Cost estimation

The costs of patient per year resources consumed in treating advanced or metastatic NSCLC in each stage (“free of progression” and “progression”) and in treating adverse events were estimated by a Portuguese panel of experts composed of six pneumonologists and an oncologist. Consumption of chemotherapy drugs was estimated using clinical trial data and the medicines' RCM.

Unit cost was estimated from several official sources of data, namely the table in the *Grupos de Diagnósticos Homogéneos* (GHDs) published in ministerial dispatch no. 110-A/2007 of January 23 2007, hospital analytical accounting reports (RCAs)¹² and Infarmed¹³.

To calculate outpatients' treatment costs, the price at which the medicine is available to the public was multiplied by the

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Quadro IV – Custo mensal nos estados “livre de progressão” e “progressão” e custo dos tratamentos

Estados	Custo total/doente /mês	Componentes	
Livre de progressão	675,48 €	Consumo de recursos (hospitalizações, consultas, exames e procedimentos)	
Progressão	2.959,49 €	Consumo de recursos (hospitalizações, consultas, medicação concomitante, exames e procedimentos)	
Eventos adversos (EAs)	Custo total/episódio	Componentes	
Rash	865,45 €	Consumo de recursos por episódio (hospitalizações, consultas e medicação concomitante)	
Anorexia	632,75 €	Consumo de recursos por episódio (hospitalizações, consultas e medicação concomitante)	
Diarreia	2.958,12 €	Consumo de recursos por episódio (hospitalizações, consultas e medicação concomitante)	
Náusea	893,71 €	Consumo de recursos por episódio (hospitalizações, consultas e medicação concomitante)	
Infecção	1.908,65 €	Consumo de recursos por episódio (hospitalizações e consultas)	
Estomatite	2.245,75 €	Consumo de recursos por episódio (hospitalizações, consultas, medicação concomitante, exames e procedimentos)	
Neutropenia (grau 3)	41,36 €	Consumo de recursos por episódio (medicação concomitante)	
Neutropenia (grau 4)	602,24 €	Consumo de recursos por episódio (hospitalizações, consultas, medicação concomitante, exames e procedimentos)	
Neutropenia febril	3.311,25 €	Consumo de recursos por episódio (hospitalizações, consultas e medicação concomitante)	
Fadiga	197,14 €	Consumo de recursos por episódio (hospitalizações, consultas e medicação concomitante)	
Neuropatia	108,85 €	Consumo de recursos por episódio (hospitalizações, consultas e medicação concomitante)	
Medicação	Dose	Custo unitário (€)	Referência
Erlotinib	150 mg/dia (4 ciclos de 7 dias ao mês)	70,00 € por comprimido de 150 mg	Roche Farmacêutica Química Lda.
Docetaxel	75 mg/m², 1.º dia no ciclo de 21 dias	169,26 € e 666,74 € por 1 frasco de 20mg e 80 mg	Catálogo do IGIF
Pemetrexedo	500 mg/m², 1.º dia no ciclo de 21 dias	983,12 € por 1 frasco de 500mg	Média do preço de venda de dois hospitais

Estimação de custos

O consumo de recursos envolvido no tratamento do CPNPC avançado ou metastizado incorrido por um doente em cada um dos estados (“livre de progressão” e “progressão”) e no tratamento de eventos adversos foi estimado através de um painel de Delbecq constituído por sete especialistas clínicos (seis pneumologistas e um oncologista) em Portugal. O consumo de fármacos

rate of government subsidy set by In-farmed¹³. The costs of concomitant medicine reserved solely for hospital use, except for cancer treatment drugs, was taken from the Institute of IT and Financial Management (IGIF) database consulted January-February 2008, at VAT-free prices. In terms of cancer treatment drugs, the cost of erlotinib was supplied by Roche and the cost of pemetrexed estimated through the

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Table IV – Monthly cost of the “free of progression” and “progression” stages and treatment costs

Stages	Total cost/patient /month	Components	
Free of progression	€ 675.48	Resource consumption (hospital admissions, appointments, exams and procedures)	
Progression	€ 2,959.49	Resource consumption (hospital admissions, appointments, concomitant medication, exams and procedures)	
Adverse events (AEs)	Total cost /episode	Components	
Rash	€ 865.45	Resource consumption per episode (hospital admissions, appointments and concomitant medication)	
Anorexia	€ 632.75	Resource consumption per episode (hospital admissions, appointments and concomitant medication)	
Diarrhoea	€ 2,958.12	Resource consumption per episode (hospital admissions, appointments and concomitant medication)	
Nausea	€ 893.71	Resource consumption per episode (hospital admissions, appointments and concomitant medication)	
Infection	€ 1,908.65	Resource consumption per episode (hospital admissions and appointments)	
Stomatitis	€ 2,245.75	Resource consumption per episode (hospital admissions, appointments, concomitant medication, exams and procedures)	
Neutropaenia (level 3)	€ 41.36	Resource consumption per episode (concomitant medication)	
Neutropaenia (level 4)	€ 602.24	Resource consumption per episode (hospital admissions, appointments, concomitant medication, exams and procedures)	
Febrile neutropaenia	€ 3,311.25	Resource consumption per episode (hospital admissions, appointments and concomitant medication)	
Fatigue	€ 197.14	Resource consumption per episode (hospital admissions, appointments and concomitant medication)	
Neuropathy	€ 108.85	Resource consumption per episode (hospital admissions, appointments and concomitant medication)	
Medication	Dose	Unit cost (€)	Reference
Erlotinib	150 mg/day (4 cycles of 7 days per month)	€70.00 per 150 mg tablet	Roche Farmacêutica Química Lda.
Docetaxel	75 mg/m ² , 1st day of 21 days cycle	€169.26 and € 666.74 for 1 20 mg and 80 mg phial	IGIF Catalogue
Pemetrexed	500 mg/m ² , 1st day of 21 days cycle	€ 983.12 per 1 500mg phial	Mean sales price of two hospitals

de quimioterapia foi estimado através dos dados de ensaios clínicos e do RCM dos medicamentos.

O custo unitário foi estimado a partir de várias fontes oficiais de dados, nomeadamente tabela de grupos de diagnósticos homogéneos (GDH) publicados na Portaria n.º 110-A/2007, de 23 de Janeiro de 2007, relatórios de contabilidade analítica (RCA) dos hospitais¹² e Infarmed¹³.

prices supplied by two hospital pharmacies. The cost of docetaxel was taken from the IGIF database, consulted in January 2008.

The cost associated with the specialised medical consultations was taken from 2006 hospital RCAs¹². Costs of hospital stays and laboratory and complementary exams were estimated using the NHS table of prices as a base (GHDs)¹⁴.

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Quadro V – Custo-efectividade do erlotinib vs tratamento de suporte, docetaxel e pemetrexedo e custo total por doente: análise aos 2 anos

Análise aos dois anos	Erlotinib	Tratamento de suporte	Docetaxel	Pemetrexedo
Análise de minimização de custos				
Custo	26.478 €	16.112 €	29.262 €	32.762 €
Anos de vida ganhos	0,77	0,62	0,77	0,77
Custo incremental por ano de vida ganho	–	70.424 €	Erlotinib reduz os custos	Erlotinib reduz os custos
Análise custo-utilidade				
Custo	26.478 €	16.112 €	29.262 €	32.762 €
QALY	0,250	0,186	0,225	0,241
Custo incremental por QALY ganho	–	161.742 €	Erlotinib é dominante	Erlotinib é dominante
Tipo de recursos				
Livre de progressão	2.973 €	1.817 €	2.973 €	2.973 €
Após progressão	14.192 €	14.027 €	14.192 €	14.192 €
Aquisição do medicamento	8.625 €	0 €	7.236 €	12.114 €
Administração do medicamento	0 €	0 €	2.017 €	1.977 €
Eventos adversos	687 €	268 €	2.843 €	1.506€
Custo total	26.478 €	16.112 €	29.262 €	32.762 €
Custo incremental vs erlotinib	–	-10.365 €	2.784 €	6.284 €

Para o cálculo dos custos de medicação em ambulatório, utilizou-se o preço de venda ao público multiplicado pela taxa de comparticipação referenciada pelo Infarmed¹³. O custo da medicação concomitante de uso reservado a meio hospitalar, excepto antineoplásicos, foi extraído da base de dados do Instituto de Gestão Informática e Financeira (IGIF), consultada entre Janeiro e Fevereiro de 2008, considerando-se os preços sem IVA. Relativamente à terapêutica antineoplásica, o custo do erlotinib foi fornecido pela Roche e o custo do pemetrexedo estimado através dos valores indicados por duas farmácias hospitalares. O custo do docetaxel foi extraído da base de dados do IGIF, consultada em Janeiro de 2008. O custo associado às consultas de especialidade foi retirado do RCA dos hospitais de 2006¹². Os custos das hospitalizações, exames laboratoriais e complementares foram estimados com base na tabela de preços do SNS (GDH)¹⁴.

Prices obtained from 2006 and 2007 data were updated to 2008 prices using an annual inflation rate of approximately 3%. The estimations of the monthly cost in the “free of progression” and “progression” stages, the cost per episode of each adverse event and the unit cost and respective dosage of erlotinib, docetaxel and pemetrexed are shown in Table IV.

Sensitivity analyses

Sensitivity analyses with different patient sub-populations and for a three year time horizon were undertaken to prove the robustness of the results and the consistency of the estimates obtained in the base-case analysis. A probabilistic sensitivity analysis was performed using second-order Monte Carlo simulation 500 times. In this analysis it was necessary to set minimum and maxi-

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Table V – Cost-effectiveness of erlotinib vs. best supportive care, docetaxel and pemetrexed total cost per patient: 2 year analysis

Two year analysis	Erlotinib	Supportive care	Docetaxel	Pemetrexed
Cost minimisation analysis				
Cost	€ 26,478	€16,112	€ 29,262	€ 32,762
YLG	0.77	0.62	0.77	0.77
Incremental costs YLG	–	€ 70,424	Erlotinib reduces costs	Erlotinib reduces costs
Cost-utility analysis				
Cost	€ 26,478	€ 16,112	€ 29,262	€ 32,762
QALY	0.250	0.186	0.225	0.241
Incremental cost per QALY gained	–	€ 161,742	Erlotinib leads	Erlotinib leads
Type of resource				
Free of progression	€ 2,973	€ 1,817	€ 2,973	€ 2,973
After progression	€ 14,192	€ 14,027	€ 14,192	€ 14,192
Aquisition of medication	€ 8,625	€ 0	€ 7,236	€ 12,114
Administration of medication	€ 0	€ 0	€ 2,017	€ 1,977
Adverse events	€ 687	€ 268	€ 2,843	€ 1,506
Total cost	€ 26,478	€ 16,112	€ 29,262	€ 32,762
Incremental cost vs. erlotinib	–	-€ 10,365	€ 2,784	€ 6,284

Os preços obtidos a partir de dados de 2006 e 2007 foram actualizados para preços de 2008, considerando-se uma taxa de inflação anual de aproximadamente 3%.

As estimativas do custo mensal nos estados “livre de progressão” e “progressão”, do custo por episódio de cada evento adverso e do custo unitário e respectiva dosagem do erlotinib, docetaxel e pemetrexedo encontram-se descritos no Quadro IV.

Análise de sensibilidade

Para comprovar a estabilidade dos resultados e a consistência das estimativas obtidas na análise-base foram efectuadas análises de sensibilidade com diferentes subpopulações de doentes e para um horizonte temporal de três anos. Foi efectuada uma análise de sensibilidade probabilística, através de uma simulação de Monte Carlo de segunda ordem, com

mum values for resource consumption and costs, considering a presupposed +/- 20% variation.

Results

The base-case analysis of this study was performed for a population undergoing 2nd or 3rd line treatment, considering a Kaplan-Meier survival curve of two years.

At two years, QALYs per patient were higher with erlotinib (0.250) than with best supportive care (0.186), docetaxel (0.225) or pemetrexed (0.241). Table V shows the total cost per patient was lower with erlotinib (€26 478) than with docetaxel (€29 262; a difference of -€2784) or with pemetrexed (€32 762; a difference of -€6284) and higher than with best supportive care (€16 112; a difference of

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Quadro VI – Resultados da análise de sensibilidade determinística

	Erlotinib vs tratamento de suporte	Erlotinib vs docetaxel	Erlotinib vs pemetrexedo
Análise de minimização de custos (diferença entre custos)			
Análise-base	70.424 €	Erlotinib reduz os custos	Erlotinib reduz os custos
População de doentes			
Segunda linha de tratamento	67.215 €	Erlotinib reduz os custos	Erlotinib reduz os custos
Segunda linha com ECOG 0 a 1	58.056 €	Erlotinib reduz os custos	Erlotinib reduz os custos
Terceira linha de tratamento	73.062 €	Erlotinib reduz os custos	Erlotinib reduz os custos
Extrapolação dos resultados a 36 meses (ITT 2. ^a ou 3. ^a linha)			
Distribuição de Weibull	68.171 €	Erlotinib reduz os custos	Erlotinib reduz os custos
Distribuição Log-logística	103.685 €	Erlotinib reduz os custos	Erlotinib reduz os custos
Análise de custo-utilidade (custo por QALY)			
Análise-base	161.742 €	Erlotinib é dominante	Erlotinib é dominante
População de doentes			
Segunda linha de tratamento	170.425 €	Erlotinib é dominante	Erlotinib é dominante
Segunda linha com ECOG 0 a 1	157.574 €	Erlotinib é dominante	Erlotinib é dominante
Terceira linha de tratamento	148.516 €	Erlotinib é dominante	Erlotinib é dominante
Extrapolação dos resultados a 36 meses (ITT 2. ^a /3. ^a linha)			
Distribuição de Weibull	176.021 €	Erlotinib é dominante	Erlotinib é dominante
Distribuição log-logística	281.902 €	Erlotinib é dominante	Erlotinib é dominante

500 ensaios. Nesta análise foi necessário definir valores mínimo e máximo para o consumo e custo dos recursos, considerando-se como pressuposto uma variação de +/- 20%.

Resultados

A análise-base deste estudo foi realizada relativamente à população em segunda ou terceira linhas de tratamento, considerando-se a sobrevivência de Kaplan-Meier a dois anos. Aos dois anos, verificou-se um QALY por doente mais elevado com o erlotinib (0,250) do que com o tratamento de suporte (0,186), docetaxel (0,225) ou pemetrexedo (0,241). O Quadro V mostra que o custo total por doente foi menor com erlotinib (26 478€) do que com docetaxel (29 262€; diferença de -2784€) ou com pemetrexedo (32 762€; diferença de

+€10 366). The difference in costs between erlotinib and best supportive care is mainly explained by the cost of acquiring the drug. In fact, the cost of acquiring erlotinib represents 83% of the difference in the total cost between the two approaches over the two years.

Erlotinib has a higher cost associated to acquisition of the drug than docetaxel (+€1389). Here, the cost of acquiring erlotinib is offset by the costs associated with treating AEs, which are higher in the docetaxel arm (+€2156), and by the costs associated with docetaxel administration (+€2017). Erlotinib has lower acquisition, administration and AE costs than pemetrexed and pemetrexed has a higher total cost than docetaxel (€32 762 *versus* €29 262). Accordingly, erlotinib was domi-

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Table VI – Results of the deterministic sensitivity analysis

	Erlotinib vs. best supportive care	Erlotinib vs. docetaxel	Erlotinib vs. pemetrexed
Cost minimisation analysis (difference between costs)			
Base-case analysis	€ 70,424	Erlotinib reduces costs	Erlotinib reduces costs
Patient population			
2 nd line treatment	€ 67,215	Erlotinib reduces costs	Erlotinib reduces costs
2 nd line treatment with ECOG 0 – 1	€ 58,056	Erlotinib reduces costs	Erlotinib reduces costs
3 rd line treatment	€ 73,062	Erlotinib reduces costs	Erlotinib reduces costs
Extrapolation of results to 36 months (2 nd or 3 rd line ITT)			
Weibull distribution	€ 68,171	Erlotinib reduces costs	Erlotinib reduces costs
Log-logistic distribution	€ 103,685	Erlotinib reduces costs	Erlotinib reduces costs
Cost-utility analysis (cost per QALY)			
Base-case analysis	€ 161,742	Erlotinib leads	Erlotinib leads
Patient population			
2 nd line treatment	€ 170,425	Erlotinib leads	Erlotinib leads
2 nd line treatment with ECOG 0 – 1	€ 157,574	Erlotinib leads	Erlotinib leads
3 rd line treatment	€ 148,516	Erlotinib leads	Erlotinib leads
Extrapolation of results to 36 months (2 nd or 3 rd line ITT)			
Weibull distribution	€ 176,021	Erlotinib leads	Erlotinib leads
Log-logistic distribution	€ 281,902	Erlotinib leads	Erlotinib leads

-6284€) e mais elevado do que com o tratamento suporte (16 112€; diferença +10 366€). A diferença de custos entre o erlotinib e o tratamento de suporte é explicada sobretudo pelo custo de aquisição do medicamento. De facto, o custo de aquisição do erlotinib representa 83% da diferença no custo total entre estas duas abordagens, ao longo de dois anos.

Verifica-se que o erlotinib apresenta um custo associado à aquisição do medicamento superior ao docetaxel (+1389€). Neste caso, o custo da aquisição do erlotinib é compensado pelos custos associados ao tratamento dos EA, que se mostram muito mais elevados no braço do docetaxel (+2156€) e pelos custos associados à administração do docetaxel (+2017€). Verifica-se que o erlotinib apresenta custos inferiores ao pemetrexedo no que diz respeito à aquisição, administração e EA e que o pemetrexedo apresenta um custo total superior ao docetaxel

nant in having a lower total cost and a higher efficacy in terms of QALYs than docetaxel and pemetrexed.

The incremental cost associated with YLG and QALY with erlotinib is €70 424, and that of best supportive care is €161 742.

The deterministic sensitivity analysis shows similar results to those obtained in the base-case analysis (Table VI), namely, in the extrapolation of data for three years (Weibull or log-logistic distribution).

The mean results for the costs and probabilistic sensitivity analysis consequences are identical to those obtained in the deterministic analysis (base-case analysis), showing the robustness of the model (Table VII).

For the majority of simulations in the probabilistic analysis, the ICER between erlotinib and supportive care was above the €30 000 /QALY “willing to pay”

(32 762€ *versus* 29 262€). Assim, o erlotinib pode ser considerado como uma alternativa “dominante” face ao docetaxel e ao pemetrexedo, uma vez que apresenta um menor custo total e uma maior eficácia em termos de QALY.

O custo incremental associado a um ano de vida ganho e a um QALY com erlotinib, comparativamente com o tratamento de suporte, é de 70 424€ e 161 742€, respectivamente.

A análise de sensibilidade determinística mostra resultados semelhantes aos obtidos na análise-base (Quadro VI), nomeadamente na extrapolação dos dados para três anos (distribuição Weibull e log-logística).

Os resultados médios para os custos e consequências na análise de sensibilidade probabilística mostram-se idênticos aos obtidos na análise determinística (análise-base), o que constitui uma validação interna dos resultados do modelo e da sua consistência (Quadro VII).

Na análise probabilística, para a maioria das simulações o ICER entre o erlotinib e o tratamento de suporte encontra-se acima do limiar (*threshold*) da “disposição a pagar” de 30 000€/QALY, tanto para a análise dos anos de vida

threshold, both for the YLG (cost-effectiveness) and the QALY (cost-utility) analysis (Fig. 2).

Second or 3rd line treatment of 1000 patients with advanced or metastatic NSCLC with erlotinib instead of docetaxel or pemetrexed could contribute with annual savings for the NHS (with 5%-65% substitution rates) that would range from €135 046 -€1 755 602 and between €291 801-€3 793 409 respectively (Table VIII).

Discussion

The model shows that 2nd or 3rd treatment with erlotinib instead of docetaxel, pemetrexed and best supportive care could contribute with a gain in terms of QALYs and also have a lower cost than active treatments. In terms of the two abovementioned active schemes, erlotinib could be considered the 2nd and 3rd line treatment with the best cost-utility for patients with advanced or metastatic NSCLC.

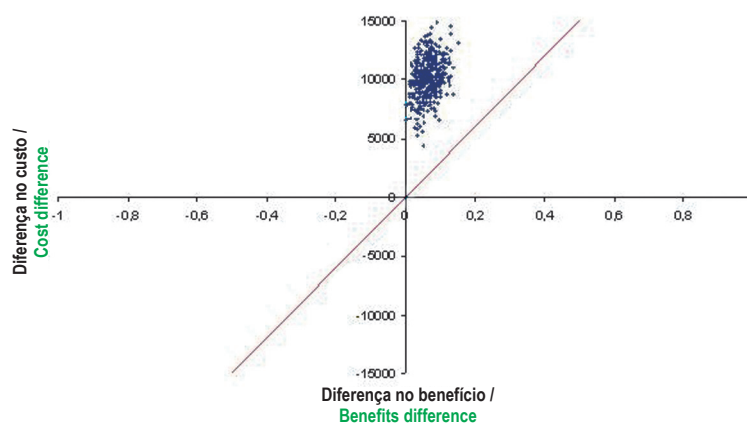


Fig. 2 – Gráfico de dispersão para erlotinib *versus* tratamento de suporte: análise aos 2 anos

Fig. 2 – Graph showing the dispersal of erlotinib *versus* best supportive care: 2 year analysis

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Quadro VII – Resultados da análise de sensibilidade probabilística aos dois anos

Resultados	Média	Percentil 2,5%	Percentil 97,5%
<i>Tratamento de suporte</i>			
Custo	15.994 €	12.815 €	19.570 €
Anos de vida	0,62	0,55	0,69
QALY	0,19	0,11	0,27
<i>Erlotinib</i>			
Custo	26.237 €	23.530 €	29.529 €
Anos de vida	0,77	0,71	0,83
QALY	0,25	0,12	0,38
<i>Docetaxel</i>			
Custo	28.653 €	25.487 €	31.724 €
Anos de vida	0,77	0,71	0,82
QALY	0,23	0,11	0,35
<i>Pemetrexedo</i>			
Custo	32.526 €	29.668 €	35.698 €
Anos de vida	0,77	0,71	0,83
QALY	0,25	0,14	0,38
ICER		Erlotinib vs tratamento de suporte	
Custo incremental por ano de vida ganho		71.152 €	
Custo incremental por QALY ganho		161.356 €	

Table VII – Results of the probabilistic sensitivity analysis over two years

Results	Mean	2.5% percentile	97.5% percentile
<i>Best supportive care</i>			
Cost	€ 15,994	€ 12,815	€ 19,570
Years of life	0.62	0.55	0.69
QALY	0.19	0.11	0.27
<i>Erlotinib</i>			
Cost	€ 26,237	€ 23,530	€ 29,529
Years of life	0.77	0.71	0.83
QALY	0.25	0.12	0.38
<i>Docetaxel</i>			
Cost	€ 28,653	€ 25,487	€ 31,724
Years of life	0.77	0.71	0.82
QALY	0.23	0.11	0.35
<i>Pemetrexed</i>			
Cost	€ 32,526	€ 29,668	€ 35,698
Years of life	0.77	0.71	0.83
QALY	0.25	0.14	0.38
ICER		Erlotinib vs. best supportive care	
Incremental cost per YLG		€ 71,152	
Incremental cost per QALY gained		€ 161,356	

ganhos (custo-efectividade) como para a dos QALYs (custo-utilidade) (Fig. 2).

Considerando-se o tratamento de 1000 doentes com CPNPC avançado ou metastizado em segunda ou terceira linhas com erlotinib, em substituição do tratamento com docetaxel ou pemetrexedo, estima-se que a poupança anual para o SNS (considerando taxas de substituição entre os 5% e 65%) variaria entre 135 046€-1 755 602€ e entre 291 801€-3 793 409€, respectivamente (Quadro VIII).

Discussão

De acordo com os resultados do modelo, o tratamento com erlotinib em segunda ou terceira linhas poderá trazer um benefício relativamente a QALY comparativamente ao docetaxel, pemetrexedo e tratamento de suporte, apresentando simultaneamente um menor custo do que os tratamentos activos. Relativamente aos dois esquemas activos referidos, o

We underline that this type of study is normally undertaken using a theoretical model which tries to mimic reality as simplistically as possible. In addition, the several sources of data used have some limitations from an economic evaluation perspective. The information contained in the literature does not necessarily represent normal clinical practice; the majority of the literature evaluated is based on data from clinical trials. These data do not necessarily have a high degree of external validity as the results are associated to patient inclusion and exclusion criteria and the adhesion of the patients themselves to the study protocol. The clinical situation may not be easy to reproduce outside a clinical trial context.

There are two further equally important aspects to consider when interpreting the results obtained: a) *Efficacy* – The comparison of erlotinib clinical data with that of active comparisons is based on an indirect

Quadro VIII – Análise do impacto da substituição de docetaxel/pemetrexedo por erlotinib (considerando 1000 doentes com CPNPC)

% de substituição	N.º de doentes a ser tratado com erlotinib	Poupança obtida com substituição de docetaxel por erlotinib	Poupança obtida com substituição de pemetrexedo por erlotinib
5%	50	-135.046 €	-291.801 €
10%	100	-270.093 €	-583.601 €
15%	150	-405.139 €	-875.402 €
20%	200	-540.185 €	-1.167.203 €
25%	250	-675.232 €	-1.459.004 €
30%	300	-810.278 €	-1.750.804 €
35%	350	-945.324 €	-2.042.605 €
40%	400	-1.080.371 €	-2.334.406 €
45%	450	-1.215.417 €	-2.626.200 €
50%	500	-1.350.463 €	-2.918.007 €
55%	550	-1.485.509 €	-3.209.808 €
60%	600	-1.620.556 €	-3.501.608 €
65%	650	-1.755.602 €	-3.793.409 €

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erlotinib pode ser considerado como o tratamento com melhor custo-utilidade para a população de doentes com CPNPC avançado ou metastizado em segunda e terceira linhas. Saliente-se que este tipo de estudos é, normalmente, efectuado sob um modelo teórico que tenta mimetizar a realidade de forma simplista. Adicionalmente, as várias fontes de dados utilizadas apresentam algumas limitações na perspectiva da avaliação económica. A informação contida na literatura não representa necessariamente a prática clínica habitual, uma vez que a maioria da literatura avaliada se baseia em dados de ensaios clínicos. Estes dados não terão necessariamente um elevado grau de validade externa, uma vez que os resultados estão associados a critérios de inclusão e exclusão dos doentes e à própria adesão dos doentes ao protocolo do estudo, podendo a situação clínica não ser facilmente reproduzível fora do contexto de um ensaio clínico. Existem ainda dois aspectos igualmente importantes a considerar ao interpretar os resul-

comparison due to the lack of parallel clinical trials. The model only considers the presupposition that the effects in survival are identical among active treatments; b) *Utility* – There is a limitation in the published data meaning it is possible to reliably attribute utility values to the health stages considered in the model. In this case, we used a sample of healthy subjects from the UK. While the utilities attributed to a healthy population are suitable, it would be preferable to have obtained the utilities from a population of patients with advanced or metastatic NSCLC. Another limitation is connected to the consumption of resources having been mainly estimated based on a panel of experts, which could equal an uncertainty factor.

Conservative presuppositions were considered in an attempt to minimise the model's limitations, and deterministic sensitivity and probabilistic analyses which confirmed the data's robustness were performed. The

Table VIII – Analysis of the impact of replacing docetaxel/pemetrexed with erlotinib (considering 1000 NSCLC patients)

% of replacement	No. of patients being treated with erlotinib	Saving obtained by replacing docetaxel with erlotinib	Saving obtained by replacing pemetrexed with erlotinib
5%	50	-€ 135,046	-€ 291,801
10%	100	-€ 270,093	-€ 583,601
15%	150	-€ 405,139	-€ 875,402
20%	200	-€ 540,185	-€ 1,167,203
25%	250	-€ 675,232	-€ 1,459,004
30%	300	-€ 810,278	-€ 1,750,804
35%	350	-€ 945,324	-€ 2,042,605
40%	400	-€ 1,080,371	-€ 2,334,406
45%	450	-€ 1,215,417	-€ 2,626,200
50%	500	-€ 1,350,463	-€ 2,918,007
55%	550	-€ 1,485,509	-€ 3,209,808
60%	600	-€ 1,620,556	-€ 3,501,608
65%	650	-€1,755,602	-€ 3,793,409

tados obtidos: a) *Eficácia* – A comparação dos dados clínicos de erlotinib *versus* comparadores activos baseia-se numa comparação indirecta, devido à falta de ensaios clínicos em paralelo. Neste modelo, apenas se considerou o pressuposto de que os efeitos na sobrevivência são idênticos entre terapêuticas activas; b) *Utilidades* – Existe uma limitação relativamente aos dados publicados a partir dos quais é possível atribuir, de forma fidedigna, valores de utilidade para os estados de saúde considerados no modelo. Neste caso, recorreu-se a uma amostra de pessoas saudáveis no Reino Unido. Embora as utilidades atribuídas por uma população saudável sejam adequadas, seria preferível ter-se obtido utilidades a partir de uma população de doentes com CPNPC avançado ou metastizado. Outra limitação prende-se com o facto de o consumo de recursos ter sido maioritariamente estimado com base num painel de peritos, o que poderá constituir um factor de incerteza.

No sentido de minimizar as limitações do modelo, consideraram-se pressupostos conservadores, tendo-se ainda efectuado análises de sensibilidade determinísticas e probabilísticas que confirmaram a robustez dos dados. Os resultados do modelo foram examinados de forma a assegurar que estes reflectiam os dados de sobrevivência dos ensaios e que o número de ciclos de medicação coincidiam com os resultados dos ensaios clínicos principais – sendo este o caso do erlotinib, docetaxel e pemetrexedo.

Conclusões

A substituição de docetaxel ou pemetrexedo por erlotinib poderia contribuir para uma redução considerável dos gastos do SNS na aquisição de medicamentos antineoplásicos para tratamento dos doentes com CPNPC avançada.

model's results were scrutinised to guarantee they reflected the clinical trial survival data and that the number of cycles of medication were the same as the main clinical trial results. This was true for erlotinib, docetaxel and pemetrexed.

Conclusions

The use of erlotinib instead of docetaxel or pemetrexed could contribute to annual savings for the NHS (substitution rates: 5%-65%) ranging from € 135,046 – € 1,755.602 (docetaxel replacement) and € 291,801 – € 3,793,409 (pemetrexed replacement), with a gain in terms of QALYs.

Second or 3rd line treatment with docetaxel and pemetrexed is respectively € 2,784 and €6,284 more costly (at two years) than treatment with erlotinib.

The sensitivity analyses results corroborate the base-case analysis results, demonstrating that erlotinib a possibly cost-saving alternative to docetaxel or pemetrexed.

The results of this pharmacoeconomic analysis should be confirmed through random parallel clinical trials which gather direct data on efficacy, utility, toxicity and use of healthcare resources for all the treatments dealt with here. No such clinical trial has been performed yet, meaning that our results should be considered as estimates for a patient with advanced or metastatic NSCLC, and can be used as a reliable tool for clinical decision making.

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AVALIAÇÃO ECONÓMICA DO ERLOTINIB, DOCETAXEL, PEMETREXEDO E TRATAMENTO DE SUPORTE NO TRATAMENTO DE SEGUNDA OU TERCEIRA LINHAS DE DOENTES COM CANCRO DO PULMÃO DE NÃO PEQUENAS CÉLULAS

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do ou metastizado, estimando-se uma poupança anual, com taxas de substituição de 5% a 65%, que variaria entre 135 046€-1 755 602€ e entre 291 801€-3 793 409€, respectivamente, com um ganho em termos de QALY.

Comparativamente ao tratamento com erlotinib, o custo total de tratar um doente em segunda ou terceira linhas com docetaxel e pemetrexedo é, respectivamente, 2784€ e 6284€ mais elevado (aos dois anos).

Os resultados das análises de sensibilidade corroboram os resultados da análise-base, demonstrando que o erlotinib é uma alternativa possivelmente *cost-saving*, comparativamente ao docetaxel ou ao pemetrexedo.

Os resultados desta análise fármaco-económica deveriam ser confirmados através de ensaios clínicos aleatorizados e em paralelo, onde se recolhessem dados directos de eficácia, utilidade, toxicidade e utilização de recursos em saúde para todas as alternativas terapêuticas aqui abordadas. Dado que até ao momento não foi realizado nenhum ensaio clínico com estas características, considera-se que os resultados aqui apresentados deverão ser considerados como estimativas para um doente tipo com CPNPC avançado ou metastizado, podendo ser utilizados como uma ferramenta fiável para a tomada de decisões clínicas.

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Resposta ao Editor

Reply to the Editor

Araújo A, et al. Avaliação económica do erlotinib, docetaxel, pemetrexedo e tratamento de suporte no tratamento de segunda ou terceira linhas de doentes com cancro do pulmão de não pequenas células
Rev Port Pneumol 2008; 14(6):803-827¹

Araújo A, et al. An economic analysis of erlotinib, docetaxel, pemetrexed and best supportive care as second or third line treatment of non-small cell lung cancer
Rev Port Pneumol 2008; 14(6):803-827¹

Resposta/*In reply*

As actuais recomendações de tratamento, nomeadamente as elaboradas pelo *National Comprehensive Cancer Network*², recomendam a utilização de erlotinib, pemetrexedo ou docetaxel em doentes com carcinoma do pulmão de não pequenas células (CPNPC) avançado ou metastizado com falência a, pelo menos, um regime de quimioterapia, independentemente do tipo de histologia. Pode, portanto, inferir-se que estas recomendações reconhecem eficácia semelhante entre as três opções terapêuticas mencionadas no tratamento de uma população de doentes com CPNPC avançado ou metastizado, que representa a população-alvo do erlotinib, do pemetrexedo e do docetaxel. Nesta medida, entende-se que a população considerada na nossa análise¹, e que representa a população incluída nos ensaios clínicos principais realizados com cada medicamento, representa os doentes elegíveis, na prática clínica, para tratamento com os medicamentos citados. A informação obtida através da realização de ensaios clínicos aleatorizados, comparativos e controlados, é o método mais fiável

Current practice guidelines, particularly those of the National Comprehensive Cancer Network², recommend the use of erlotinib, pemetrexedo or docetaxel in patients with advanced or metastised non-small cell lung cancer (NSCLC) with at least one failed chemotherapy regime, independent of the histology type. It can thus be inferred that these recommendations recognise a similar level of efficacy among these three therapeutic options for treating a population of patients with advanced or metastised NSCLC, the target population of erlotinib, pemetrexed and docetaxel. This is the thus the population taken for our analysis¹, one which represents the population included in the main clinical trials held for each drug, meaning the patients eligible in clinical practice for treatment with the abovementioned drugs.

Informed gleaned from randomised, comparative and controlled clinical trials is the most reliable method for demonstrating evidence of possible differences in health results obtained from different therapeutic

para a demonstração de evidência de possíveis diferenças dos resultados em saúde, obtidos com diferentes intervenções terapêuticas. Na ausência de ensaios clínicos em paralelo, a comparação indirecta é adequada e recomendada por organizações como o *National Institute for Health and Clinical Excellence* (NICE)³.

Na nossa análise¹, a população considerada corresponde a uma coorte hipotética de doentes portugueses com CPNPC avançado ou metastizado em que se observou falência a, pelo menos, um regime de quimioterapia, e que são tratados com erlotinib, pemetrexedo, docetaxel ou tratamento de suporte.

Considerando que não existem ensaios clínicos que comparem directamente as três opções de tratamento activo referidas, a informação utilizada no nosso modelo baseia-se em dados clínicos obtidos a partir de ensaios clínicos principais de fase III e aleatorizados: o BR.21 (erlotinib *vs* tratamento de suporte)⁴; Shepherd FA *et al.*, que comparou docetaxel *vs* tratamento de suporte⁵, e Hanna N *et al.*, que comparou pemetrexedo *vs* docetaxel⁶. As características dos doentes incluídos nos ensaios clínicos de erlotinib⁴ e de pemetrexedo *vs* docetaxel⁶ eram semelhantes, nomeadamente em termos demográficos, terapêutica prévia e histologia do tumor⁷, Quadro I.

Um pressuposto do modelo consiste em assumir que as sobrevivências livre de progressão e global são idênticas entre os braços erlotinib, docetaxel e pemetrexedo. Este pressuposto baseia-se nos dados dos ensaios clínicos com erlotinib, docetaxel e pemetrexedo mencionados. Os resultados destes ensaios clínicos indicam que o erlotinib e o docetaxel apresentam vantagens em termos de sobrevivência em relação ao tratamento

interventions. In the absence of parallel clinical trials, indirect comparison is suitable and recommended by bodies such as the National Institute for Health and Clinical Excellence (NICE)³.

The population considered in our analysis¹ is a hypothetical cohort of Portuguese patients with advanced or metastised NSCLC who have had at least one failed chemotherapy regime and who receive erlotinib, pemetrexed, docetaxel or support treatment.

As there are no clinical trials directly comparing the three abovementioned active treatment options, the information used in our model was based on clinical data obtained from leading phase III and randomised clinical trials: BR.21 (erlotinib *vs* support treatment)⁴; Shepherd FA *et al.* comparing docetaxel *vs* support treatment⁵ and Hanna N *et al.* comparing pemetrexed *vs* docetaxel⁶. The characteristics of patients enrolled on the erlotinib⁴ and pemetrexed *vs* docetaxel⁶ clinical trials were similar, particularly in terms of demographics, prior treatment and tumour histology⁷, Table I.

One supposition of the model was assuming that free of progression and overall survival were identical in the erlotinib, docetaxel and pemetrexed arms. This presupposition was based on data from the abovementioned erlotinib, docetaxel and pemetrexed clinical trials. The results of these clinical trials indicated that erlotinib and docetaxel presented advantages in terms of survival over support treatment, while there was no statistically significant difference between pemetrexed and docetaxel¹, Table I just as NICE stated in 2007⁸, pag. 7.

Median global survival among the patients treated with docetaxel and pemetrexed⁶ was higher than in patients treated with erlo-

de suporte, enquanto não há diferença estatisticamente significativa entre pemetrexedo e docetaxel^{1, Quadro I}, como, aliás, é referido pelo NICE em 2007^{8, pag. 7}.

A sobrevivência global mediana entre os doentes tratados com docetaxel e pemetrexedo⁶ é superior à dos doentes tratados com erlotinib no ensaio clínico BR.21^{1, Quadro I}. No entanto, esta diferença na sobrevivência global mediana pode ser explicada pelo facto dos doentes tratados com erlotinib no ensaio BR.21 apresentarem um *eastern cooperative oncology group performance status* (ECOG PS) superior aos doentes tratados com docetaxel ou pemetrexedo. No ensaio clínico BR.21 existe uma proporção superior de doentes com ECOG PS 2-3, particularmente com ECOG PS 3 (cerca de 9%)^{1, Quadro I}. De acordo com Socinski MA *et al.*⁹, o factor mais importante com impacto na sobrevivência de doentes com CPNPC é o PS.

Adicionalmente, os doentes do ensaio com erlotinib receberam mais terapêuticas prévias para o CPNPC avançado do que os doentes incluídos nos outros ensaios. Globalmente, isto demonstra que os doentes envolvidos no ensaio com erlotinib encontravam-se numa pior situação clínica comparativamente aos incluídos nos ensaios clínicos com docetaxel e pemetrexedo.

Este é um resultado importante, mas é necessário demonstrar que a sobrevivência global é influenciada pelo ECOG PS. Esta relação foi analisada e a avaliação ECOG mostrou uma relação estatisticamente significativa com a sobrevivência global, conforme indicado no Quadro I. Foram efectuados três testes estatísticos: para testar se a correlação entre a sobrevivência global e o ECOG PS é nula, para testar se a sobrevi-

tinib in clinical trial BR.21^{1, Table I}. This difference in median global survival could be explained by the fact that the patients treated with erlotinib in trial BR.21 had a higher Eastern Cooperative Oncology Group Performance Status (ECOG PS) than the patients treated with docetaxel or pemetrexedo. There was a higher proportion of ECOG PS 2-3 patients in the BR.21 clinical trial, particularly patients with ECOG PS 3 (around 9%)^{1, Table I}. Socinski MA *et al.*⁹ consider PS the factor with the most bearing on NSCLC patient survival.

Further, the erlotinib clinical trial patients had received more prior treatment for NSCLC than the patients in the other trials. Overall, this shows the erlotinib clinical trial patients were in a worse clinical situation than the docetaxel and pemetrexed clinical trial patients.

This is a significant result but it is necessary to show that global survival is influenced by ECOG PS. This relationship was analysed and the ECOG evaluation revealed a statistically significant relationship with global survival, as Table I shows. Three statistical tests were performed; to test if the correlation between global survival and ECOG PS was null; to test if global survival did not differ in patients with different ECOG PS and to test if there was an association between global survival and ECOG PS. Each test had an alternative hypothesis, shown in Table I. The *p* value indicates in each case if the hypothesis being tested is very improbable in the light of the data gleaned.

The key result shown in Table I refers to the second test (ANOVA). The results of this test indicated that median global survival is different in patients with different ECOG PS. This seems to indicate that the

Quadro I – Estatística de Cochran-Mantel-Haenszel

Estatística	Hipótese alternativa	Graus de liberdade	Valor	Valor p
1	Correlação diferente de zero	1	22,8156	<0,0001
2	Diferença entre médias	1	22,8156	<0,0001
3	Associação geral	1	22,8156	<0,0001

Table I – Cochran-Mantel-Haenszel statistics

Statistics	Alternative hypothesis	Degress of freedom	Value	p value
1	Correlation different from zero	1	22.8156	<0.0001
2	Difference between means	1	22.8156	<0.0001
3	General association	1	22.8156	<0.0001

vência global não difere em doentes com diferentes ECOG PS e para testar se não existe uma associação entre a sobrevivência global e o ECOG PS. Cada teste tem uma hipótese alternativa, apresentada no Quadro I. O valor p indica, em cada caso, se a hipótese a ser testada é muito improvável tendo em consideração os dados obtidos.

O resultado-chave apresentado no Quadro I é referente ao segundo teste (ANOVA). Os resultados deste teste indicam que a sobrevivência global mediana é diferente em doentes com diferentes ECOG PS. Isto parece indicar que a diferença encontrada na sobrevivência global entre o erlotinib e o docetaxel poderá ser explicada pela diferença encontrada no ECOG PS dos doentes incluídos nos ensaios clínicos principais. Ou seja, é possível que o facto de a sobrevivência mediana ser inferior nos doentes tratados com erlotinib se deva a uma população com um *status* clínico mais crítico e não esteja associada a diferenças na eficácia (embo-

difference found in global survival between erlotinib and docetaxel could be explained by the difference found in ECOG PS in the patients enrolled in the principle clinical trials. Put another way, it is possible that median survival being lower in patients treated with erlotinib is due to a population with a more critical clinical status and not associated to differences in efficacy, although in the absence of data from other trials it is difficult to specify if erlotinib would maintain a lower median survival and if this difference would attain statistical significance.

Accordingly, given the improbability of difference in median global survival between erlotinib, docetaxel and pemetrexed attaining statistical significance, while a tighter pairing of trial populations would reduce this difference, it is assumed that global survival in the docetaxel and pemetrexed arms is equivalent to the erlotinib arm.

ra sem dados de outros ensaios seja difícil especificar se erlotinib se manteria com uma sobrevivência mediana inferior e se esta diferença seria estatisticamente significativa).

Assim, dada a improbabilidade da diferença da sobrevivência global mediana entre o erlotinib, docetaxel e pemetrexedo ser estatisticamente significativa, sendo que um melhor emparelhamento das populações entre ensaios reduziria esta diferença, assume-se que a sobrevivência global para os braços do docetaxel e pemetrexedo é equivalente à do erlotinib. Desta forma, o modelo utiliza as curvas de sobrevivência do erlotinib para representar a sobrevivência nestes braços.

Adicionalmente, a sobrevivência a um ano e as taxas de resposta globais obtidas nos ensaios clínicos de erlotinib¹ e pemetrexedo *vs* docetaxel⁶ foram igualmente comparáveis. Não existe evidência publicada que sugira diferença significativa em termos de eficácia entre docetaxel, pemetrexedo e erlotinib. Adicionalmente, e para além do já referido reconhecimento nas actuais recomendações de tratamento de que erlotinib, docetaxel e pemetrexedo têm eficácias semelhantes, publicações recentes referem-se igualmente a *outcomes* semelhantes em termos de actividade antitumoral e eficácia entre eles^{10,11}.

Esta eficácia comparável entre as diferentes opções terapêuticas justifica a utilização da análise de minimização de custos, que aliás tem sido utilizada em diversas avaliações económicas de erlotinib *vs* docetaxel e/ou pemetrexedo^{12,17}.

Em conclusão, consideramos que a população incluída na nossa análise (que representa a população incluída nos ensaios clínicos principais de cada medicamento) reflecte a população elegível para o tratamento com as opções terapêuticas consideradas na prática clínica.

Thus, the model used the erlotinib survival curves to represent the survival of these arms.

Additionally, survival at one year and the global response rates obtained in the erlotinib¹ and pemetrexed *vs* docetaxel⁶ clinical trials were equally comparable.

There is no published evidence suggesting significant difference in efficacy between docetaxel, pemetrexed and erlotinib. In addition, and beyond the abovementioned recognition of the current therapeutic guidelines in which erlotinib, docetaxel and pemetrexed have similar efficacy, recent publications also cite similar outcomes in compared anti-tumoural activity and efficacy^{10,11}.

This comparable efficacy between the different therapeutic options justifies the use of a minimised cost analysis, as has already been used in several economic evaluations of erlotinib *vs* docetaxel and/or pemetrexed^{12,17}.

In conclusion, we consider that the population in our analysis, one which represents the population enrolled in the main clinical trials of each drug, reflects the eligible population for treatment with the therapeutic choices considered in clinical practice.

The rationale presented supports the methodology used in that there are as yet no clinical trials with parallel arms which gather direct information on the efficacy, utility, toxicity and use of health resources for the therapeutic choices compared. We add that to minimise the model's limitations, we performed deterministic and probabilistic sensitivity analyses which confirmed the results' robustness.

The results gleaned in our analysis should thus be considered as estimated costs to the

O racional apresentado suporta a metodologia utilizada, uma vez que até ao momento não existem ensaios clínicos com braços em paralelo que reúnam informação directa sobre eficácia, utilidades, toxicidade e utilização de recursos de saúde para as opções terapêuticas comparadas. Acresce que, no sentido de minimizar as limitações do modelo, efectuaram-se análises de sensibilidade determinísticas e probabilísticas, que confirmaram a robustez dos resultados.

Os resultados obtidos na nossa análise devem, portanto, ser considerados como estimativas de custos para o sistema de saúde português no que diz respeito ao tratamento de um doente com CPNPC avançado ou metastizado, podendo ser utilizados como uma ferramenta para a tomada de decisões clínicas.

Portuguese health service for treating a patient with advanced or metastised NSCLC and can be used as a tool for making clinical decisions.

António Araújo

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CUSTO DO TRATAMENTO DO CANCRO EM PORTUGAL

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RESUMO

Introdução: O cancro é a segunda maior causa de morte em Portugal, logo a seguir às doenças cardiovasculares (DCV), e o seu peso percentual no total de mortes revela um aumento constante e progressivo. Em Portugal, tal como na generalidade dos países, o orçamento para a saúde sofre constantes pressões de contenção. Neste contexto, é necessário verificar se estão a ser afectados os recursos necessários para a doença em termos de despesas de saúde.

O principal objectivo deste estudo é o de realizar uma estimativa do custo do tratamento do cancro em Portugal e compará-lo aos valores dedicados a este fim na Europa e Estados Unidos da América (EUA) e aos valores dedicados ao tratamento das DCV. Como objectivo secundário pretende-se avaliar o custo dos medicamentos utilizados no tratamento do cancro em Portugal, relativamente ao gasto total em medicamentos e a outras áreas de despesa em saúde.

Métodos: Este estudo recorreu a três principais fontes de informação: revisão da literatura pertinente, fontes primárias e secundárias, e um Painel Delphi modificado, que foi usado para preencher as lacunas de informação identificadas nos dados e na revisão da literatura. O indicador utilizado para determinar a carga da doença (*Burden of Disease-BoD*) foi o *Disability-adjusted life-year* (DALY) e, para se determinar os custos do tratamento do cancro, recorreu-se a informação detalhada relativa a 2006 sobre custos de consultas médicas e episódios de internamento com base nos *Grupos de Diagnósticos Homogêneos (GDHs)*. Para estimar o custo total do cancro, utilizou-se uma combinação de metodologias *top down* (com base em dados referentes à despesa total, repartidos entre níveis específicos) e *bottom up* (com base na soma de diferentes componentes de despesa). Resultados: Baseado em dados de 2006 constatou-se que foram gastos 565 milhões de € em termos de gastos directos com o tratamento do cancro em Portugal e 1.320 milhões de € nas DCV o que representa 3,91% e 9,14% dos gastos totais na saúde, respectivamente. Ao dividirmos os gastos totais em medicamentos por área terapêutica, os medicamentos para as DCV representaram cerca de 21,6% dos gastos totais em medicamentos e para o cancro cerca de 5,6%. Os medicamentos oncológicos representaram 32% dos gastos totais relativos ao cancro, enquanto que os das DCV 54% do gasto total em DCV. Em comparação, no que toca às BoD em Portugal, 18,6% dos DALYs foram associados às DCV e 15,3% ao cancro.

Conclusão: Considerando a BoD entre as DCV e o cancro em Portugal, pode-se afirmar que os gastos com o tratamento do cancro em Portugal ficam aquém do que seria esperado. Usando o critério de despesa de acordo com as necessidades verificámos um diferencial entre despesa/BoD no cancro, dando a entender que o tratamento do cancro parece estar sub-financiado em Portugal. Embora este não deva ser o único critério a determinar o volume de despesa em determinada área terapêutica, o diferencial identificado neste estudo é suficientemente grande para merecer a atenção dos decisores.

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SUMMARY

COST OF CANCER CARE IN PORTUGAL

Introduction: Cancer is the second most important cause of death in Portugal, following cardiovascular diseases (CVD), and shows a constant progressive increase in the proportional share of total deaths. In Portugal, as in most countries, the health care budget is under constant cost-containment pressures. In this context it is necessary to verify if enough resources have been allocated to the disease in terms of health care expenditure.

The main objective of this study is to estimate the cost of cancer care in Portugal and to compare it to similar data in Europe and the United States of America (USA), to the cost of CVD. The secondary objective is to evaluate the cost of pharmaceuticals used in the treatment of cancer in Portugal, both in relation to total pharmaceutical expenditure and to other therapeutic areas.

Methods: Three main sources of information were used: comprehensive literature review, primary and secondary data sources, and a modified Delphi Panel, which was used to fill in gaps in the information derived from the data sources and the literature review. The burden of cancer was measured through the *Disability-adjusted life-year* (DALY) and, in order to determine the costs of cancer, detailed information on the costs of medical visits and of inpatient episodes based on Diagnosis Related Groups (DRG), in 2006, was used. To estimate the total cost of cancer, we used a combination of top down (breaking global expenditure data to specific levels) and bottom up methodology (based on the sum of different components).

Results: Based on 2006 data on direct medical care expenditures in Portugal, we found that 565 million € were spent on cancer in comparison to 1 320 million on CVD representing 3.91% and 9.14% of total cost on health respectively. When we break down total expenditure on drugs by therapeutic area we find that CVD drugs represent about 21.6% of total drug costs in Portugal and cancer drugs represent about 5.6% of the total. Oncology drugs represent 32% of the total expenditure on cancer, while CVD drugs represent 54% of the total expenditure on CVD. In comparison, in terms of BoD in Portugal, 18.6% of DALY's were associated with CVD and 15.3% with cancer.

Conclusion: Considering the burden of disease (BoD) of CVD and cancer in Portugal, we can state that the expenditure allocated to cancer is significantly lower than expected. Using the criterion of expenditure according to need, we observed that there is an imbalance of expense/BoD in oncology indicating that cancer seems to be underfunded in Portugal. Even considering that this shouldn't be the only criterion to determine the volume of expense in a certain therapeutic area, the differential observed in this study is sufficiently high to deserve attention from the decision-makers.

INTRODUÇÃO

Durante o século XX, a esperança média de vida à nascença, em Portugal, praticamente duplicou, tanto nas mulheres (40,0 anos em 1920, 79,7 anos em 2000) como nos homens (35,8 anos em 1920, 72,6 anos em 2000). Esta tendência continuou a desenvolver-se a partir de meados dos anos 80, fazendo com que a esperança média de vida portuguesa convergisse com a média da UE. Em 2005, a esperança média de vida em Portugal à nascença era de 78,2 anos, enquanto na Europa dos 15 era de 78,8 anos¹. As melhorias no estado de saúde da população portuguesa parecem estar ligadas ao aumento de recursos humanos,

materiais e financeiros dedicados aos cuidados de saúde, assim como à melhoria generalizada das condições socioeconómicas da população¹. Em Portugal, tal como noutros países europeus, o orçamento do sector público em geral – incluindo o orçamento para a saúde – está sujeito a contenção. Neste momento existem várias alterações no sector da saúde em Portugal, com grande incidência no sector do medicamento, como por exemplo, redimensionamento das embalagens de medicamentos, redução de preço dos medicamentos, alterações nos direitos de propriedade farmacêutica, legislação aprovada para a comercialização de produtos farmacêuticos sem prescrição fora das farmácias, prescrições de acordo com a DCI/INN, preços de refe-

rência, alterações na gestão das infra-estruturas de saúde pública, incentivos aos genéricos, alterações dos níveis de participações do estado e por diante, restrição do acesso aos médicos pela indústria farmacêutica para fins promocionais. A situação causada pelas alterações demográficas e a elevada prevalência de determinadas patologias, associadas ao acréscimo na utilização de novas tecnologias e medicamentos, coloca os *decisores* numa posição onde é necessário definir prioridades.

Na actualidade, o cancro é a segunda maior causa de morte em Portugal, logo a seguir às doenças cardiovasculares (DCV), e o seu peso percentual no total de mortes revela um aumento constante e progressivo². De acordo com dados do Instituto Nacional de Estatística (INE), pode-se dizer que a mortalidade por cancro em Portugal estabilizou em 2,1% por mil habitantes. Na última década, as duas principais causas de morte demonstraram tendências divergentes: enquanto as mortes por cancro têm vindo a aumentar, as mortes causadas por DCV diminuíram.

O Ministério da Saúde invoca a ideia – no *Plano Nacional de Saúde 2004-2010* (PNS-2004-10) – que se os indicadores de saúde Portugueses forem comparados com os *melhores* países da UE, é possível reduzir a mortalidade prematura masculina em 38% e a feminina em 10%². O mesmo documento também considerou o cancro como uma das principais prioridades na saúde.

Em 2006, estimou-se existirem na Europa 3.191.600 casos de cancro diagnosticados (excluindo o cancro de pele não-melanoma) e 1.703.000 mortes atribuíveis à doença³. Os tipos mais comuns de cancro foram o cancro da mama (13,5%), o cancro colorectal (12,9%) e o cancro do pulmão (12,1%). Entre as causas de morte oncológicas, a causa mais comum foi o cancro de pulmão, seguida do cancro colorectal e do cancro do estômago³. Verificou-se também um aumento significativo da incidência global de cancro. Como exemplo, durante o período de 1963-1997 houve um aumento na ordem de 50% (excluindo o cancro de pele não-melanoma)⁷. Estes dados colocam o cancro como um importante problema de saúde pública na Europa. Mais ainda, numa população europeia em envelhecimento, muito provavelmente haverá um aumento destes números^{3,4}.

A carga da doença oncológica entre os diferentes países está ligada à incidência, à prevalência e à mortalidade de indivíduos com cancro⁴. Em Portugal, a taxa de mortalidade estabilizou em cerca de 10 mortes/10³. Em 2005, foram registadas 107.839 mortes na população residente, sendo 23.232 associadas ao cancro (21,5%)⁵. Em termos comparativos, é interessante referir que, no mesmo ano, as mortes derivadas de acidentes de viação foram cerca

de 1.100; e que o cancro foi apenas suplantado pelas DCV (34%) como a maior causa de morte em Portugal.

Relativamente à incidência de cancro, de acordo com dados recentemente publicados, a taxa de incidência padronizada pela idade em Portugal é de 428:100.000 nos homens e 289:100.000 nas mulheres³.

Dada a importância atribuída à área oncológica no PNS 2004-10, é necessário verificar se têm sido afectados ao tratamento do cancro recursos financeiros que estejam em sintonia com o peso da doença. No contexto actual, onde os gastos nos medicamentos continuam a aumentar e os recursos disponíveis para financiar novas terapias são limitados, existe uma necessidade de se realizar um estudo no contexto português acerca dos custos do tratamento do cancro e, especificamente, do custo dos medicamentos usados para tratar a doença. Tal estudo é crucial para a tomada de decisão informada e fundamentada no que toca à afectação de fundos do orçamento da saúde para a área de oncologia.

De acordo com os dados do IMS de 2006, foram gastos 3.284 milhões de € em medicamentos (mercado hospitalar e ambulatorio) representando cerca de 22,7% da despesa total em saúde (14.450 milhões de € – 9,7% PIB).

O objectivo deste estudo é o de estimar o custo do tratamento do cancro em Portugal e compará-lo, por um lado, aos valores dedicados a este fim na Europa e Estados Unidos da América (EUA) e, por outro lado, aos valores dedicados ao tratamento das DCV. O objectivo secundário do estudo é avaliar o custo dos medicamentos utilizados no tratamento do cancro em Portugal, tanto em relação ao gasto total em medicamentos como em relação a outras áreas de despesa em saúde.

MATERIALE MÉTODOS

Este estudo centra-se nos custos directos associados ao tratamento do cancro, onde os custos directos se referem aos recursos destinados à prevenção, detecção, tratamento, etc.

Pretendemos obter o custo do cancro repartindo-o pelas seguintes componentes: hospitalização, cuidados ambulatorios e tratamento farmacológico. Para além dos dados epidemiológicos sobre incidência e prevalência, os indicadores da carga da doença são um importante complemento para os *decisores* na área da saúde⁴. Assim, e para contextualizar as estimativas, também medimos a carga da doença oncológica através de um dos indicadores de carga de doença mais habitualmente utilizados – o *Disability-adjusted life-year* (DALY), desenvolvido pelo Banco Mundial e pela Organização Mundial de Saúde

(OMS)⁴. O DALY e os seus componentes, os anos de vida perdidos devido a mortalidade prematura e o número de anos vividos com incapacidade, são instrumentos de avaliação do impacto da doença na saúde do indivíduo. É considerado como um instrumento de avaliação sumário, que combina a avaliação do impacto da enfermidade, a incapacidade e a mortalidade sobre uma determinada população, assim como a sua prevalência.

Para estimar o custo total do cancro, utilizamos uma combinação de metodologias *top down* e *bottom up*. A metodologia *top down* baseia-se em dados referentes à despesa total, repartidos entre níveis específicos e a *bottom up* baseia-se na soma de diferentes componentes de despesa de forma a estimar-se um valor total.

Em Portugal, existem poucos dados disponíveis sobre custos para determinar o custo real do cancro, portanto, utilizámos três principais fontes de informação: a) fontes primárias e secundárias, tais como a base de dados Grupos de Diagnóstico Homogêneos (GDH) e bases de dados IMS, b) uma revisão da literatura pertinente e c) um Painel Delphi modificado que foi usado para preencher algumas lacunas de informação identificadas nos dados primários e secundários e na revisão da literatura.

Revisão da Literatura

De forma a determinar a carga da doença oncológica em Portugal, foi desenvolvida uma exaustiva revisão da literatura relativamente à mortalidade, DALYs e custos associados ao cancro.

Relativamente aos custos do cancro, recorreu-se a informação detalhada relativa a 2006 sobre custos de consultas médicas e episódios de internamento com base nos GDH. Os custos associados às DCV em Portugal foram também determinados com recurso aos GDHs, consultas médicas e consumo de medicamentos (Dados da IMS).

A revisão da literatura incluiu também uma pesquisa em bases de dados disponíveis tais como: Administração Central do Sistema de Saúde (ACSS), INFARMED, Organização Mundial de Saúde, INE, Observatório Nacional dos Sistemas de Saúde (ONSA), Direcção Geral de Saúde, Organização para a Cooperação e o Desenvolvimento Económico (OCDE), Direcção Geral de Viação (DGV), Globocan 2002, MedLine. Para além das bases de dados externas mencionadas, várias bases internas da IMS foram também analisadas, nomeadamente: IMS LifeCycle, IMS MIDAS, IMS Knowledge Link.

Foi dada prioridade aos dados oficiais portugueses. Quando não existiam dados oficiais portugueses disponíveis, recorreu-se a dados internacionais da OMS e OCDE. Os dados utilizados foram sempre os publicados mais recentemente.

Método Delphi

Quando não existiam dados disponíveis referentes à despesa com o cancro, e à sua distribuição entre vários níveis (hospitalizações, cuidados ambulatoriais, medicamentos oncológicos e medicamentos para cuidados paliativos), recorreu-se ao método Delphi. Este método foi utilizado para: potenciar a informação a partir da revisão da literatura e análises a bases de dados já realizadas; adequar todos os argumentos para maximizar o alcance dos objectivos previamente definidos e sublinhar importantes questões e temas não respondidos pela revisão efectuada previamente.

O método Delphi baseia-se num processo estruturado para reunir e apurar conhecimentos a partir de um grupo de peritos através de um série de questionários. Quando combinado com o *feedback* de opinião controlada permite um consenso objectivo das avaliações dos peritos sobre o objecto do estudo. Este método tem sido utilizado com sucesso para avaliar e combinar as opiniões dos peritos e é considerado como um meio eficaz para reunir e analisar grupos de consenso em cuidados de saúde.

No nosso estudo os indivíduos envolvidos foram nove oncologistas, seis farmacêuticos hospitalares e quatro administradores hospitalares. Em termos geográficos, os oncologistas representam as principais zonas do país e a maior parte dos grandes centros hospitalares onde é feito o tratamento da doença oncológica. Os farmacêuticos hospitalares representam principalmente a região Centro de Portugal e são oriundos de quatro hospitais diferentes, desenvolvendo todos eles actividades na área oncológica. Relativamente aos administradores hospitalares, dois dos peritos pertencem ao maior hospital do país e os outros dois estão afectos a uma Administração Regional de Saúde com trabalho já desenvolvido em hospitais de tratamento do cancro.

As sessões Delphi foram desenvolvidas em encontros *head-to-head* com duas rondas, com base num questionário e com discussão de resultados, sempre que os peritos considerassem necessário. Este método é por vezes referido como Painel Delphi modificado. Os oncologistas estiveram todos presentes numa sessão e os farmacêuticos e administradores hospitalares foram entrevistados em 6 sessões separadas.

RESULTADOS

Carga da doença (BoD)

No quadro 1 podemos observar o número e a proporção de DALYs perdidos pelos maiores grupos de doença na UE25, UE15 e EUA/Canadá⁴. Como podemos observar

Quadro 1 – Cinco maiores grupos de doenças em termos de BoD na UE25, UE15 e EUA/Canadá

	UE 25		UE 15		Estados Unidos e Canadá	
	Total DALYs	%	Total DALYs	%	Total DALYs	%
Todos os grupos de doença	58 807 846	100,0	47 092 868	100,0	45 213 504	100,0
Doença Mental	14 857 720	25,3	12 379 282	26,3	13 484 719	29,8
Doença Cardiovascular	10 088 093	17,1	7 637 493	16,2	6 616 765	14,6
Cancro	9 839 035	16,7	7 989 864	16,9	5 658 112	12,5
Traumatismos	5 099 011	8,7	3 644 620	7,7	4 338 436	9,6
Doença Respiratória	3 523 243	5,9	3 167 675	6,7	3 167 067	7,0

Fonte: JONSSON B., WILKING N.: The burden and cost of cancer; Annals of Oncology 18: Supplement 3: ii8-ii22, 2007

na tabela, o cancro é a terceira causa de DALYs perdidos na UE25 (segunda causa se considerarmos a UE15) e nos EUA/Canadá, sendo apenas suplantado pelas doenças mentais e DCV.

Quando analisamos os dados específicos referentes a Portugal, a distribuição de DALYs perdidos devido às DCV, doenças mentais e cancro são os apresentados no quadro 2. Os acidentes de viação foram incluídos na análise porque foram considerados um importante comparador fora da área dos cuidados de saúde. O número de DALYs perdidos devido a tais acidentes perfaz cerca de 20% daqueles que são perdidos devido ao cancro.

Como complemento à informação apresentada no Quadro 2 existem dados do PNS 2004-10 relativamente aos *anos de vida potencial perdida* (AVPP) (Quadro 3). A partir destes dados podemos verificar que na projecção desenvolvida pelo Ministério da Saúde, a taxa de AVPP devido ao cancro irá aumentar em 2010, o que contrasta com as estimativas relativas às DCV, o mesmo se passando relativamente ao total de AVPP. Assim, o cancro representou em 2002 cerca de 23% do total de AVPP em Portugal, enquanto que as DCV representaram 14%. As projecções para 2010 demonstraram que os AVPP associados ao cancro iriam representar o dobro dos AVPP perdidos devido às DCV. O total de AVPP previstos para 2010 irá decair 3%,

enquanto os AVPP associados às DCV irão decair 8%, considerando os valores de base apresentados para 2002. Por outro lado, os valores projectados para o cancro representam um aumento em cerca de 3% na sua carga (em termos absolutos e relativos).

Devemos também referir que os AVPP são uma componente dos DALYs, sendo também um importante indicador de caracterização de doenças. Podemos então dizer que em 2010, por cada AVPP associado às DCV, o Ministério da Saúde estima que 1.82 AVPP serão perdidos devido ao cancro.

Custo dos Cuidados de Saúde

Os custos com os cuidados de saúde são uma grande preocupação em praticamente todos os países. Aqui iremos comparar as diferentes despesas com o tratamento do cancro nos EUA, Europa e Portugal.

De acordo com o recente estudo Karolinska¹, contemplando os 19 países europeus presentes na OCDE, a despesa total em saúde calculada através das paridades do poder de compra foi de 844.800 milhões de €, ou de 1.872,1 € *per capita*. De acordo com os últimos dados da OCDE, nos países considerados (excepto a Hungria e Holanda porque não existiam dados disponíveis), a despesa de saúde foi, em média, 9,1% do PIB e a despesa média em saúde

Quadro 2 – DALYs perdidos em Portugal e nos EUA (Estimativas para 2002, calculadas a partir das bases de dados da OMS)

	DALYs perdidos (estimativas 2002)*					% DCV	% Cancro	População
	Mental	DCV	Cancro	Acidentes de Viação	Total			
Portugal	339 913,7	277 392,8	228 123,3	45 667,0	1 492 496,2	18,6	15,3	10 595 600,0
EUA	12 287 960	6 156 359	5 175 399	1 243 153	41 520 900	14,8	12,5	291 037 900,0

* Dados retirados da base de dados da OMS (adaptado)

Quadro 3 – Anos de vida potencial perdida em 2002 e projecção para 2010 para Portugal

Anos de vida potencial perdida (AVPP)*						
Idade	2002			Projecção 2010		
	DCV	Cancro	Todas as causas	DCV	Cancro	Todas as causas
<1	1.320,5	278,0	39.684,0	834,0	347,5	35.862,0
1-4	134,0	1.273,0	11.122,0	335,0	1.139,0	10.988,0
5-9	187,5	1.562,5	7.375,0	312,5	1.500,0	7.000,0
10-14	402,5	1.207,5	8.337,5	287,5	1.150,0	8.280,0
15-19	577,5	2.415,0	21.472,5	525,0	2.257,5	20.947,5
20-24	1.187,5	2.185,0	33.772,5	1.187,5	2.042,5	33.582,5
25-44	18.630,0	28.510,0	179.670,0	20.600,0	30.275,0	173.565,0
45-64	42.352,5	71.947,5	194.137,5	35.325,0	72.800,0	190.275,0
65 +	6.622,5	7.105,0	21.510,0	6.320,0	8.062,5	20.687,5
Total	71.414,5	116.483,5	517.081,5	65.726,5	119.574,0	501.187,5
%	13,81	22,53	100,0	13,11	23,86	100,0
Evolução 2002/2010				-7,96	2,65	-3,07

Plano Nacional de Saúde 2004-2010

per capita utilizando paridades do poder de compra foi de US\$ 2.839,9.

Nos EUA, a despesa total em saúde (2004) foi de 1.792 biliões \$ (15,3% do PIB), atingindo uma despesa *per capita* de 6.156,9 dólares².

Utilizando dados referentes a 2004, a despesa total em saúde em Portugal foi de 9,5% do PIB (13.591,4 milhões de €). A despesa *per capita* foi de 1.303,29 €. A despesa pública em saúde remontou a 73,2% do total da despesa em saúde (9.948,9 milhões de €), sendo 58,2% (7.911,7 milhões de €) financiada pelo Serviço Nacional de Saúde e o restante através de subsistemas públicos e deduções de impostos em despesas de saúde privadas. As despesas directas das famílias totalizaram 20,6% do total das despesas em saúde³.

Com as recentes medidas de contenção de despesa tem havido uma redução da taxa de crescimento do volume de despesa pública em 2003 e 2004, respectivamente de 6,6% e 6,0%. Por outro lado, em 2004, a despesa privada em saúde cresceu 7,9%⁹.

Os dados preliminares para 2005, que são os dados disponíveis mais recentes, sugerem que a despesa total em saúde foi de 9,7% do PIB (14.449,9 milhões de €). A despesa *per capita* foi de 1.369,74 €, 72% da qual foi referente a despesa pública⁴. De acordo com os últimos dados

da OCDE, a despesa total em saúde *per capita* em paridade do poder de compra é de US\$ 2.041.

Custos do Tratamento do Cancro

Alguns estudos disponíveis demonstram que os custos indirectos podem representar cerca de 70%-85% dos custos totais do cancro. Entretanto, espera-se que o montante atribuído aos custos directos do cancro possa aumentar dentro de um determinado tempo, à medida que as opções terapêuticas evoluem⁴.

Através duma pesquisa bibliográfica exaustiva encontramos vários estudos sobre custos ligados ao tratamento do cancro em diferentes países. No quadro 4 podemos observar os resultados obtidos através dos vários estudos publicados com base nos dados da OCDE para os custos do tratamento do cancro, utilizando paridades do poder de compra ajustadas aos preços de 2004⁸.

Nos EUA (2004), 4,7% do total dos custos médicos são com o cancro e a despesa em custos médicos directos do cancro foi de 69,4 biliões de dólares. Para destacar a tendência de crescimento no investimento no cancro nos EUA, estima-se que a despesa atribuída a custos oncológicos directos em 2006 seja de 78,2 biliões de dólares¹¹.

Ao analisar os dados presentes no Quadro 4, deve-se ter em conta que alguns dos estudos utilizaram dados

Quadro 4 – Custo do Tratamento do Cancro, PPC, 2004⁸

	Custo directo em cancro (milhões €)	Custo directo em cancro <i>per capita</i>	Custo do cancro em % relativa aos custos da saúde	Custo Total da saúde (milhões €)	População (2004)
Holanda ¹⁶	1 502	92	4,1	36 643	16 275 000
EUA ¹⁵	62 321	212	4,7	1 325 988	293 655 000
Hungria ¹⁶	495	49	5,0	9 897	10 107 000
Polónia ¹⁶	1 138	30	5,0	22 758	38 180 000
República Checa ¹⁶	514	50	5,0	10 287	10 211 000
Austrália ²¹	2 199	109	5,2	42 298	20 111 000
França ¹⁸	7 458	124	5,3	140 714	60 200 000
Alemanha ¹⁹	12 108	147	6,6	183 455	82 491 000
Canadá ²⁰	5 013	157	6,7	74 818	31 946 000
Suécia ²¹⁻²³	1 316	146	7,0	18 802	8 994 000
Japão ²⁴	19 750	155	9,3	212 370	127 687 000
Reino Unido ^{7,24}	10 823	182	10,6	102 100	59 554 000

Quadro 5 – Custo do Tratamento do Cancro em Portugal

	Custo directo em cancro (milhões €)	Custo directo em cancro <i>per capita</i>	Custo do cancro em % relativa aos custos da saúde	Custo Total da saúde (milhões €)	População (2007)
Portugal	565,03*	53,33	3,91	14 500**	10 595 600

* Dados de 2006 relativos a GDH's de internamento, quimioterapia, radioterapia e medicamentos

** Dados de 2005

antigos e isso numa área terapêutica como a oncologia, onde o número de procedimentos e medicamentos inovadores está constantemente a aumentar, e onde o aumento da prevalência é também um factor, é altamente recomendado que se utilizem dados mais actualizados por forma a obter uma visão mais precisa das tendências actuais.

Em Portugal, existem poucos dados disponíveis para determinar o custo real do cancro. Tendo isto em mente utilizou-se o número de episódios de internamento (tal como referenciado pelos respectivos GDHs) e o número de consultas médicas para determinar o custo do cancro. Em acréscimo, também foi considerado o custo dos medicamentos (fora dos hospitais).

Tendo em conta os dados disponíveis, podemos observar no Quadro 5 a distribuição do custo do tratamento do cancro em Portugal. A partir deste quadro podemos constatar que o custo directo do tratamento do cancro representa 3,91% da despesa total em saúde e que isso representa cerca de 53 € *per capita*.

Estes valores provêm dos dados e fontes apresentados no Quadro 6. Estes dados representam a soma da despesa oncológica de GDHs em 2006, despesas em Quimioterapia e Radioterapia em 2006, e a despesa em medicamentos oncológicos fora do ambiente hospitalar (medicamentos comprados em farmácias) assim como as despesas em consultas médicas.

Custo das Doenças Cardiovasculares

As doenças cardiovasculares são vistas com a maior causa de incapacidade e morbilidade e a maior causa de morte e morte prematura para os cidadãos da UE¹². Num recente estudo que englobou a Europa dos 25 (dados de 2003), estimou-se que os custos directos de cuidados de saúde associados às doenças cardiovasculares atingissem 104.780 milhões de €, perfazendo cerca de 12% do total da despesa em saúde na Europa dos 25¹².

No estudo mencionado, 8% de toda a despesa de saúde portuguesa recaiu sobre doenças cardiovascu-

Quadro 6 – Custo do Tratamento do Cancro em Portugal (dados e fontes)

Preço de GDH oncológicos (2006)*	313 792 774 €
Custo de Quimioterapia (doente internado) (2006)*	17 365 170 €
Custo da radioterapia (2006)	75 034 009 €
Preço de hospital de dia quimioterapia (2006)*	125 882 086 €
Consultas médicas **	29 460 463 €
Custo de medicamentos oncológicos – farmácia de oficina (2006)	3 500 000 €
Total	565 034 503 €
% relativo ao custo total da saúde	3.91 %

Fontes: Dados da ACSS 2006²⁵; IMS Health, 2006²⁶; Estatísticas do Movimento Assistencial do SNS, 2005²⁷; Relatório de Retorno Nacional, 2006²⁸; Portaria nº 110A/2007

* Despesa em medicamentos está incluída nestes GDHs

** Custo de consultas retirado da Contabilidade Analítica dos Hospitais SNS, 2006; 123,74 € para oncologia e 51,93 € para radioterapia

lares. Este valor está em concordância com as nossas estimativas (no Quadro 7), baseadas na ACSS (Administração Central do Sistema de Saúde) onde os GDHs (2006) para as DCV contabilizaram 442 milhões de €, o custo de consultas médicas remontou a 190 milhões de € e o custo de medicamentos no mercado ambulatorio perfiz 690 milhões de €.

Quadro 7 – Custo do Tratamento das DCV em Portugal (dados e fontes)

Preço de GDH DCV (2006)*	441 646 454 €
Custo de medicamentos para DCV – ambulatorio (2006)	688 087 851 €
Consultas médicas – Públicas**	156 672 596 €
Consultas médicas – Privadas***	33 908 273 €
Total	1 320 315 173 €
% relativo ao custo total da saúde	9.14 %

Fonte: Dados da ACSS 2006²⁵; IMS Health 2006²⁶; Relatório de Retorno Nacional, 2006²⁸; Portaria nº 110A/2007

* Despesa em medicamentos está incluída nestes GDHs

** Custo de consultas retirado da Contabilidade Analítica dos Hospitais SNS, 2006; valor ponderado, 76,84 €

*** Consultas médicas retiradas do Relatório da Comissão de Sustentabilidade do SNS²⁹; preço por consulta utilizado 65 €

Nos EUA, de acordo com as *Heart disease and stroke statistics – 2007 update*¹³, as estimativas relativas aos custos directos das DCV para 2007 são na ordem dos 283.200 milhões \$, o que equivale a 973 \$ *per capita*.

Custo dos Medicamentos

Quando se calculam os custos totais em medicamentos por área terapêutica verifica-se que os medicamentos para doenças cardiovasculares representam cerca de 21,6% do custo total de medicamentos e que os medicamentos para o cancro representam cerca de 5,6% da despesa total de medicamentos de 2006 (Dados do IMS referentes a 2006).

Considerando o custo total do cancro, podemos dizer que os medicamentos para o cancro representam 32% da despesa total do tratamento do cancro; por outro lado, os medicamentos para as DCV representam 54% da despesa total do tratamento das DCV. Na Europa, em 2004, estimou-se que a despesa total em medicamentos oncológicos representava cerca de 5% da despesa total em medicamentos⁴.

Convém salientar que a despesa *per capita* em medicamentos para o cancro em Portugal é inferior à observada na UE.

Os resultados provenientes do Painel Delphi relativamente ao custo dos medicamentos são semelhantes aos mencionados previamente: 38% para medicamentos oncológicos e 52% para medicamentos de DCV. Para além disso, os peritos consideraram que 26% da despesa total em medicamentos para o tratamento do cancro recaiu sobre medicamentos para cuidados paliativos ou de suporte.

Custo das Hospitalizações de Cancro e tratamento Ambulatorio

Existem duas grandes áreas de custos de tratamento de cancro: os associados às hospitalizações e os associados ao tratamento ambulatorio. De acordo com dados referentes ao custo do cancro podemos estimar que quase 60% dos custos recaem sobre as hospitalizações, sendo que 37% são atribuídos ao tratamento ambulatorio.

DISCUSSÃO

Apesar de tanto na Europa como em Portugal o cancro ser uma forte preocupação em termos de mortalidade e morbilidade, os resultados do nosso estudo indicam que a proporção da despesa de saúde com o tratamento do cancro é inferior à proporção da respectiva carga da doença. Este estudo revelou ainda que a despesa com as DCV é duas vezes superior à do cancro numa situação em que a carga da doença é semelhante.

Para além o montante dispendido no cancro (como % do custo da saúde) em Portugal é muito inferior ao que podemos encontrar noutros países da UE. O custo do tratamento do cancro atingiu 565 milhões € (custos médicos directos), que correspondem a 53,33 € *per capita*. Os valores *per capita* para Portugal são apenas comparáveis aos dos países recém integrados na UE como é o caso da República Checa, Hungria e Polónia.

Apesar dos medicamentos serem um dos principais custos directos na saúde em Portugal, os resultados obtidos demonstram que na despesa total em medicamentos, os medicamentos específicos para o cancro não são a principal razão destes custos. Ao realizar-se a repartição dos custos totais dos medicamentos por área terapêutica, constatamos que os medicamentos para as DCV representam cerca de 21,6% da despesa total em medicamentos, enquanto que os medicamentos para o cancro apenas representaram 5,6%.

Para além disso, se compararmos a proporção dispendida com os medicamentos oncológicos e das DCV em relação ao custo total das respectivas doenças, verificamos que, embora os medicamentos oncológicos representem uma parte importante dos custos do cancro, o seu peso não ultrapassa os 34% dos custos totais da doença, enquanto que os medicamentos para as DCV representam 60% da despesa total das DCV. O Painel Delphi obteve resultados semelhantes; realizaram-se estimativas dos custos do cancro divididas entre medicamentos, hospitalizações e tratamento ambulatorio, verificando-se que os maiores custos são referentes aos medicamentos específicos para o cancro, seguidos das hospitalizações, dos medicamentos para cuidados paliativos e, finalmente, o tratamento ambulatorio.

Todos os indicadores de carga da doença (BoD) apresentados, DALY e AVPP, demonstram que, na actualidade, a carga do cancro é semelhante à carga das DCV e que, no futuro, o cancro tenderá a ter uma carga de doença superior às DCV. Ao considerarmos os anos de vida potencial perdida (AVPP) podemos verificar que, de acordo com os dados do Ministério da Saúde, o cancro representou em 2002 cerca de 23% do total de AVPP em Portugal, enquanto as DCV representaram 14%. As projecções para 2010 demonstraram que os AVPP associados ao cancro iriam representar o dobro dos AVPP perdidos devido às DCV.

Um outro factor que poderá parecer surpreendente é que na UE-15 e em grande parte dos países desenvolvidos, os DALYs perdidos devido ao cancro são superiores aos DALYs perdidos devido às DCV, enquanto nos países recém integrados na UE (países da Europa de leste), os DALYs das DCV são ainda superiores aos do cancro. Isto

pode ser explicado pelo baixo investimento na saúde nestes países durante vários anos, sem campanhas de prevenção adequadas para as DCV, e também por uma possível falta de registo das ocorrências de cancro.

Considerando a carga das DCV e do cancro em Portugal, e o impacto dos custos médicos directos dos dois grupos de patologias, e tendo em conta que a despesa alocada ao cancro é significativamente mais baixa que a carga da doença oncológica, parece razoável sugerir que o cancro em Portugal parece não ser suficientemente financiado. Tendo em consciência que os critérios de distribuição de recursos não correspondem na totalidade à carga da doença, é razoável sugerir, de acordo com a situação já descrita, que o cancro não recebe o financiamento adequado em Portugal. Embora este não deva ser o único critério a determinar o volume de despesa em determinada área terapêutica, o diferencial identificado neste estudo é suficientemente grande para merecer a atenção dos decisores.

Enquanto que os tratamentos e procedimentos para as DCV estão actualmente desenvolvidos, e não existirem grandes inovações em termos terapêuticos para esta área, no que concerne ao cancro o paradigma é totalmente diferente, visto que novos procedimentos de diagnóstico e tratamento ainda estão a ser implementados, regimes inovadores estão a ser desenvolvidos e onde ainda existem muitas necessidades médicas por cobrir.

De acordo com os dados disponíveis, quando comparamos a carga de doença oncológica e outras áreas fora da área dos cuidados de saúde como os acidentes de viação, também verificamos que existem grandes diferenças em termos de DALYs perdidos e recursos que são atribuídos a cada área. Tal como mencionámos anteriormente, os DALYs perdidos devido a acidentes de viação representam cerca de 20% dos que estão associados ao cancro.

Entre das limitações do estudo, devemos mencionar que alguns dos estudos desenvolvidos noutros países da UE utilizaram dados mais antigos, sendo portanto difícil fazer uma comparação entre países numa área terapêutica como a oncologia, em que o número de novos procedimentos e medicamentos está a aumentar e em que o aumento da prevalência é também um factor, recomenda-se uma análise mais actualizada de maneira a obter uma imagem mais precisa das tendências actuais.

Devemos também mencionar que a quantificação dos custos através dos GDHs utilizados neste estudo, apresentam algumas limitações porque em alguns casos estes não são ajustados à realidade e procedimentos actuais. Na definição de GDHs podemos constatar que cada GDH possui

um *preço* total por cada procedimento, incluindo uma diversidade de custos associados (incluindo medicação) sem considerar o consumo específico do doente durante o seu internamento. Não obstante, os GDHs são os únicos dados disponíveis em Portugal relativamente à utilização de procedimentos hospitalares específicos.

Os dados referentes aos consumos para cada GDH relativos ao cancro e às DCV foram obtidos através da ACSS logo, podemos inferir que os consumos relativos aos cuidados prestados em hospitais fora do SNS não estarão contabilizados. Tal facto poderá sobrevalorizar o impacto do cancro face às DCV na medida em que se considera que os recursos gastos para o cancro são na sua grande maioria efectuados no Sistema Nacional de Saúde (SNS), enquanto que relativamente às DCV tal poderá não acontecer, existindo uma maior solicitação do sector privado.

Relativamente ao número de DALYs perdidos (carga da doença) em Portugal, conseguimos verificar que 18,6% dos DALYs foram associados às DCV e 15,3% foram atribuídos ao cancro. Estes valores alteraram-se certamente nos últimos anos e isto pode ser considerado como uma limitação ao estudo, subestimando a carga da doença oncológica. Ao analisar DALYs devemos considerar que as bases de dados disponíveis e consultadas são as estimativas para 2002. Desde então, a mortalidade derivada das DCV em Portugal diminuiu e a mortalidade derivada do cancro aumentou, alterando os cenários actuais em termos de carga da doença. Este factor associado ao aumento da prevalência do cancro e ao envelhecimento da população irá determinar um aumento em DALYs para o cancro comparativamente às DCV.

CONCLUSÃO

No contexto actual em que a despesa em medicamentos continua a aumentar e os recursos disponíveis para financiar novas terapias são limitados, é crucial tomar decisões fundamentadas acerca do valor real dos tratamentos oncológicos em termos de benefícios para a saúde e custos e poupanças para o SNS. Para este fim, será eventualmente necessário realizar outros estudos, focados nos custos directos actuais do cancro no Sistema de Saúde Português.

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6. Discussion

Portugal does not have a reliable cancer registry and this makes it is very difficult to know the Portuguese reality about cancer care. The NSCLC annual incidence in this country is roughly estimated in about 3400 new cases (34/100.000 inhabitants), 28/100.000 new cases in men and 6/100.000 in women (Bento, M.J. 2008).

In 1988, the Regional Oncologic Registry was created by the Decree of the Government 35/88 of 16 January. It is headquartered at the three Portuguese Institutes of Oncology (Oporto, Coimbra and Lisbon). The National Cancer Registry is the sum of all data collected by the regional registries. The last Portuguese National Cancer Registry dates back from 2001 and it has many flaws on the registration. The registry of the death certificates also has many faults, especially because medical doctors do not fulfill correctly the cause of the dead. These facts create great difficulties to acknowledge the true rate of incidence of the NSCLC and consequently the current clinical practice in terms of its treatment.

The 2001 National Cancer Registry registered 33.052 new cases of cancer, 3054 of which were new cases of lung cancer, with an incidence rate of 22,7 for the north region, 16,0 for the center and 28,5 /100.000 inhabitants for the south region. Lung cancer was the fourth cancer in the country, the second in men and the tenth in women (Bento, M.J. 2008).

The Oncologic Pulmonology Committee of the Portuguese Society of Pulmonology tried to know better the Portuguese reality and has launched for over a decade a hospital based registry. Between 2000 and 2002, the 22 participants' hospital registered 4396 new cases of lung cancer (Parente, B. et al. 2007). This registry was also far from being the ideal one because it was only a hospital based registry, depending solely on the participant physicians, without any support structure, with little registration from the south of the country, and had already several years.

In a study published by Ferlay and co-workers, with the estimates of the cancer incidence and mortality in Europe in 2006, the authors estimate that Portugal registered an age-standardised incidence rate of lung cancer of 44,5 /100.000 inhabitants for men and 11,7 /100.000 inhabitants for women and an age-standardised mortality rate of 43,3 /100.000 and 7,9 /100,000 inhabitants for men and women, respectively. Lung cancer was the forth on the rank in incidence among cancers in Portugal. The incidence and the mortality for lung cancer were about half that estimated for Europe and for the EU (EU25) and Portugal was the second country with lower incidence (Ferlay, J. et al. 2007). This numbers reflect the fact that Portugal had one of the lowest

rates of cigarette consumption in Europe (WHO 2002). In Portugal, it is estimated that there were 1.664.073 current smokers in 2006, 1.428.487 ex-smokers and 6.154.423 never-smokers (INE 2008b).

Non-small-cell lung cancer (NSCLC) accounts for 75%-85% of all histotypes of lung cancer. Adenocarcinoma is the most common histologic subtype of lung cancer in several countries. The proportion of the two principal histological sub-types of NSCLC differs by sex: squamous cell carcinomas comprise 44% of lung cancers in men and 25% in women, while adenocarcinomas comprise 28% cases in men and 42% in women. But the incidence of adenocarcinomas has raised, mainly due to an ever-increasing proportion of ex-smokers in the population (the declining in risk of lung cancer on smoking cessation is faster for squamous cell tumors than for adenocarcinomas) and changes in cigarette composition (low tar, low nicotine, filtered cigarettes resulted in addicted smokers in more puffs and deeper inhalation) (Wynder, E.L. et al. 1995; Stellman, S.D. et al. 1997; Khuder, S.A. 2001; Janssen-Heijnen, M.L. et al. 2003; Patel, J.D. 2005; B'Chir, F. et al. 2007).

The stage of the disease is important for prognosis and treatment planning and, unfortunately, in the daily clinical practice most patients present at late stages of their disease.

In Portugal, little is known about the global characteristics of the lung cancer patients in the current clinic practice. In Parente *et al.* registry, adenocarcinoma was the most frequent histologic sub-type with 37,5%, squamous cell accounted for 30,5% and small cell lung cancer represented 12,5% of all lung cancers. Only 8,9% of the patients presented at stage I, 5,3% at stage II, 30,0% presented at stage III and 46,9% at stage IV (Parente, B. et al. 2007). This means that 76,9% of the reported cases were advanced or metastatic lung cancer. For this reason 20,3% of the patients only had best supportive care and 43,7% have done only chemotherapy. There was no collection of information regarding second and third-line chemotherapy and there are no data in Portugal about this issue.

Since in virtually all patients with advanced disease initial therapy will ultimately fail, second-line therapy will often be necessary. The clinical improvements provided by first- and second-line treatment in NSCLC have led a higher proportion of patients to be considered for third-line treatment, rising from 6% in 1990s (Massarelli, E. et al. 2003) to 26% after 2000 (Murillo, J.R., Jr. et al. 2006). It was calculated that for every 100 patients subjected to first-line chemotherapy with a doublet platin-based, only 75% of

these will have clinic benefit (stable disease/partial response/complete response), and only 38 patients will receive second-line chemotherapy (Stinchcombe, T.E. et al. 2009).

For second-line treatment, three agents have been approved so far – docetaxel, pemetrexed, and erlotinib. These drugs, although providing a modest 1-year survival benefit (ranging from 6 to 10%), significantly improve quality of life and cancer-related symptoms (Shepherd, F.A. et al. 2000; Hanna, N. et al. 2004; Shepherd, F.A. et al. 2005).

In Portugal, from 2000 to 2004, docetaxel was the standard for second line treatment of NSCLC. With the introduction of pemetrexed, at the end of 2004, with a better tolerability profile over docetaxel, it rapidly became the standard for this setting.

Portuguese Lung Cancer Study Group (GECP) decided to conduct a study evaluating the efficacy and safety of pemetrexed as second-line treatment for advanced or metastatic NSCLC patients in the current clinical practice. 244 patients from 19 Portuguese centers treated with pemetrexed in second-line for NSCLC between October 2004 and December 2006 outside clinical trials were retrospectively evaluated. The results in this unselected population were very similar to those published by others, in terms of efficacy and safety. Moreover, a statistically significant difference was observed in time to progression between the histology squamous versus adenocarcinoma / large cell carcinoma but not in overall survival (Araújo, A. et al. 2008). The Portuguese population with advanced or metastatic NSCLC responds, in terms of efficacy and safety, in the same manner to the second and third-line treatment as the European population.

The main challenge in lung cancer treatment is the ability to identify in advance the subpopulation of patients most likely to respond to a particular therapy, an accomplishment that would not only increase the likelihood of response, but would also avoid needlessly treating those patients who have little probability of benefiting from treatment. This is the quest to identify predictive factors and to personalize cancer therapy.

There are two fundamental principles that underlie the concept of personalized cancer therapy: significant genomic heterogeneity exists among tumors, even those derived from the same tissue of origin, and these differences can play an important role in determining the likelihood of a clinical response to treatment with particular agents. Such genomic heterogeneity can involve differences in the spectrum of coding sequence mutations, as well as focal gene amplifications, deletions, or translocations. It might also involve epigenetic changes in the expression profile of a tumor cell,

although the sources of epigenetic variation among tumors remain poorly understood (McDermott, U. et al. 2009).

Pharmacogenetics and pharmacogenomics are emerging areas that will be crucial for personalized medicine. With the establishment of a relationship between genotype (i.e., polymorphisms and genetic mutations), gene expression profiles (i.e., level of gene expression of all or of target genes in the genome), and phenotype, drug prescription will be based on the patient's individual genetic and molecular profile. But lung cancer has genetic complexities that exceed those of almost any other solid tumor (Greenman, C. et al. 2007).

In 2008, the histology emerged as a strong prognostic and predictive factor for NSCLC, but major attention has been derived to molecular markers, such as the epidermal growth factor receptor (*EGFR*), the excision repair cross-complementing 1 (*ERCC1*), the ribonucleotide reductase subunit M1 (*RRM1*), the breast cancer susceptibility gene1 (*BRCA1*) and *KRAS* mutation.

EGFR mutations, gene copy number or overexpression, for instance, identify patients likely to respond to EGFR-TKIs. In early 2000s, with the appearance of the EGFR-TKIs, like gefitinib and erlotinib, for the treatment of chemotherapy-refractory locally advanced or metastatic NSCLC, *EGFR* took a major importance.

Overexpression of EGFR was associated with a more aggressive phenotype, worse clinical prognosis, and chemo- and radioresistance in different solid tumors (Sozzi, G. et al. 1991; Nomura, M. et al. 2007). But *EGFR* mutation status positive could also predict better response to EGFR-TKIs (Uramoto, H. et al. 2007).

Recent clinical studies in which EGFR-TKIs were administered as first-line treatment to patients with NSCLC preselected on the basis of *EGFR* mutation–positive tumors yielded impressive response rates (>50%) and significantly increased overall survival (Sequist, L.V. et al. 2007; Inoue, A. et al. 2009). Although the link between *EGFR* mutations and response to TKI therapy in NSCLC has had an important impact on clinical management of this disease, it is also clear that *EGFR* activating mutations are not the sole determinants of clinical response. The correlation between *EGFR* mutations and clinical response is not 100%, and thus several additional genomic biomarkers have been linked to TKI sensitivity and resistance, including amplification of wild-type *EGFR*, *K-Ras* mutation, *PTEN* disruption, and *HER2* mutations (Pao, W. et al. 2005; Buckingham, L.E. et al. 2007; Varella-Garcia, M. et al. 2009).

Patients carrying different functional polymorphic alleles from *EGFR* and *EGF* genes may potentially respond differently to EGFR-TKIs, although this remains an

unanswered question. It has been proposed that the abnormal interaction between EGF and its receptor may be a susceptibility and/or prognosis factor in various tumors, such as malignant melanoma, glioblastoma multiforme, gastric cancer, or non-small cell lung cancer (NSCLC) (Araujo, A. et al. 2007). Furthermore, there is scant information regarding the influence of genetic polymorphism on EGFR and EGF expression levels in peripheral blood and tumor tissue, and further research to understand the field of *EGF* and its receptor remains a priority (Araujo, A. et al. 2007).

As already shown *in-vitro*, the *EGF+61A/G* polymorphism, that consist in a substitution of guanine (G) for adenine (A) located in the 5'-untranslated region of the *EGF* gene, and it was identified 61 bp downstream of the *EGF* promoter, significantly correlates with production of EGF. EGF production from AA homozygous individuals is significantly inferior to that from G carrier individuals (Shahbazi, M. et al. 2002). To the best of our knowledge, *EGF+61A/G* polymorphism is the only known functional polymorphism which leads to increased EGF expression. EGF, as a growth factor, plays an important role in carcinogenesis, activating multiple signalling pathways by binding to its receptor (EGFR), leading to proliferation, differentiation and tumorigenesis of epithelial tissues (Bhowmick, D.A. et al. 2004; Hamai, Y. et al. 2005). An EGF vaccine is already in development and tested in phase II clinical trials for advanced NSCLC patients (Neninger Vinageras, E. et al. 2008). A direct correlation between anti-EGF antibody titers and survival was demonstrated in vaccinated patients, whereas an inverse association between EGF expression reduction and patient's survival was also found (Ramos, T.C. et al. 2006).

The influence of the *EGF+61A/G* polymorphism in lung cancer prognostic was prospectively evaluated in 306 NSCLC Caucasian patients from the north region of Portugal, with histologically or cytologically confirmed disease recruited since July 2006 at the Portuguese Institute of Oncology – Oporto Centre (unpublished data). The demographic characteristics of NSCLC patients included in this study are summarized on Table 3.

Table 3 – Characteristics of NSCLC patients

Cases (n=306)					
Age (years)			Stage	N	%
Mean / Median	62,4 / 64,0		I	37	12,1
Gender			II	29	9,5
	N	%			
Male	244	79,7	III	136	44,4
Female	62	20,3	IV	104	34,0
Smoking status			1 st line CT	N	%
	N	%			
Never	78	25,5	Platin	249	81,6
Former smoker	64	20,9	Paclitaxel	192	63,0
Smoker	164	53,6	Gemcitabine	45	14,8
Histopathologic type			2 nd line CT	N	%
	N	%			
Squamous cell	116	37,9	Docetaxel	38	12,5
Adenocarcinoma	145	47,4	Pemetrexed	42	13,8
Large-cell			2 nd and 3 rd lines CT	N	%
	N	%			
NSCLC	34	11,1	Erlotinib	31	10,2

CT - Chemotherapy

The study was previously approved by Portuguese Institute of Oncology of Porto (IPO-Porto) Ethics Committee and after obtained the signed informed consent of patients, according to the Helsinki Declaration, venous blood samples for genotyping and patient and demographic information (including age, gender, and smoking status) were collected at the time of recruitment. Follow-up data was collected at July 2008. A modified standardized American Thoracic Society respiratory questionnaire was used to collect smoking information (Ferris, B.G. 1978), with never smokers being defined as those who smoked 100 cigarettes or fewer over a lifetime, former smokers being defined as those who quit at least 1 year before diagnosis, and current smokers being defined as those who were smoking within a year of diagnosis. The date of first

pathologic diagnosis of malignancy was used as date of diagnosis. All patients were followed at IPO-Porto at regular intervals (every 2 to 6 months) with standard radiographs and/or computed tomography of the chest and imaging studies of all metastatic lesions. The first date of unequivocal clinical evidence of disease or histological confirmation, in questionable cases, was recorded as recurrence date. The clinical response and progression of disease were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST).

Genomic DNA was extracted from the white blood cell fraction of each study subject by a commercial “QIAmp® DNA Blood Mini Kit”. The purified DNA was used to determine the genotypes of the *EGF+61A/G* polymorphism, using PCR-RFLP technique as previously described (Randerson-Moor, J.A. et al. 2004). Briefly, the *EGF* region from nucleotide positions -78 to +164 was amplified by PCR, producing a 242-bp fragment, followed by Alul digestion (Fermentas, Ontario, Canada). The 61 G alleles were distinguished from 61 A alleles by visualization of a single 193-bp fragment instead of 91 and 102 bp fragments on a 2% agarose gel, stained in ethidium bromide and photographed under UV illumination.

Analysis of data was performed using the computer software Statistical Package for Social Sciences (SPSS) for Windows (version 15.0). Differences in proportions were evaluated by the χ^2 test. The probabilities of survival were calculated, and the means and life tables were computed using the product limit estimate of Kaplan and Meier. The curves were analyzed by the Breslow (generalized Wilcoxon) test, a statistical test for equality of survival distributions. A level of $P < 0.05$ was considered statistically significant. Time to progression (TTP) was defined as the time from the first day of drug administration to the date of the first observation of progression or death due to the disease. Overall survival (OS) was defined as the date of diagnosis until date of death. Patients not presenting the event of interest were considered censored at the last known follow up time. TTP and OS were analysed by the Kaplan-Meier product-limit method. The response rate was defined as the percentage of patients with a complete or partial response among all patients. Response rate to treatment was estimated with corresponding two-sided 95% confidence intervals (CI). A $P \leq 0.05$ was considered statistically significant.

The *EGF+61A/G* genotype frequencies in NSCLC patients are shown in Table 4.

Table 4 – *EGF+61A/G* genotype frequencies in NSCLC patients

EGF Polymorphism	Patients (n=306)	
Genotypes	n	%
AA	123	40,2
AG	122	39,9
GG	61	19,9
Recessive model		
AA	123	40,2
G Carrier	183	59,8

The *EGF+61A/G* genotype frequencies observed were 40,2% for homozygous genotype AA, 39,9% for heterozygous genotype AG and 19,9% for homozygous genotype GG.

Concerning the overall survival (OS) rates found using Kaplan-Meier methodology, no statistically significant differences were observed for the mean survival rates according to patient's genotypes (AA genotype versus G carrier genotypes – AG and GG genotypes) ($P=0,948$) (Figure 15).

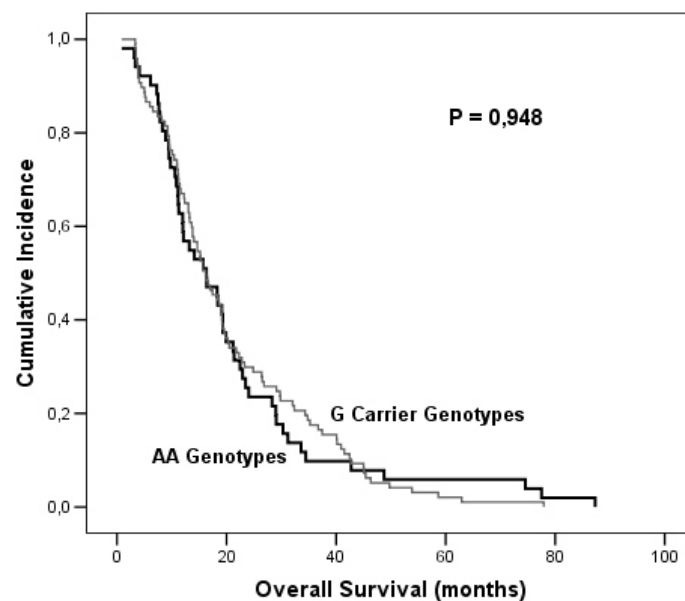


Figure 15 – Association of *EGF+61A/G* genotype with overall survival by Kaplan-Meier curves.

Moreover, no statistically significant association was found between *EGF+61A/G* polymorphism genotypes and time to progression of the disease after 1st and 2nd lines of chemotherapy ($P=0,12$ and $0,19$, respectively) (Figure 16).

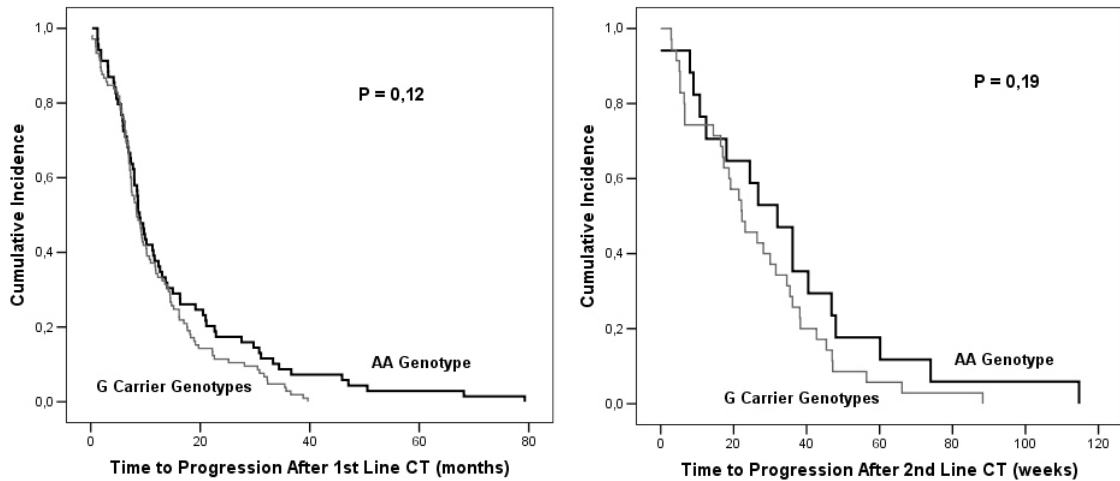


Figure 16 – TTP after 1st and 2nd line CT for all the NSCLC cases.

Stratifying NSCLC cases according to histological type (squamous type versus non squamous type), a statistically significant difference was found regarding time to progression after first line CT within the non-squamous NSCLC group, between individuals with G carrier genotypes and homozygous AA individuals (Log Rank (Mantel-Cox) test, $P=0,044$) (Figure 17). Thus, individuals with AA genotype showed a time to progression after 1st line CT of 16,2 months whereas this interval of time was only 11,4 months for individuals with G carrier genotypes.

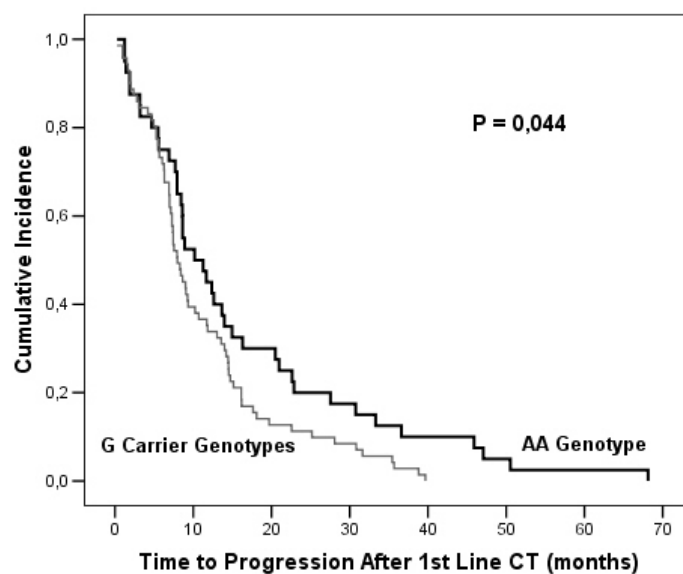


Figure 17 – Time to progression after first line CT in non-squamous NSCLC.

In summary, the only statistically significant association found in this study was a shorter time to progression after first line CT in non-squamous NSCLC patients with G carrier genotypes (data not published).

Additional studies with a larger sample size and for different ethnic populations will be needed to confirm these findings.

The combination of pemetrexed and bevacizumab for second-line of non-squamous NSCLC seems promising (Adjei, A.A. et al. 2010). In the future, it will be useful to perform a phase III trial with this combination treatment versus the standard arm of pemetrexed alone for non-squamous NSCLC but including the evaluation of the polymorphisms of some genes linked to pemetrexed activity, like *SLC19A1* which encodes a protein responsible for the transport, *FPGS* that encodes a protein linked to activation, and *GGH* which encodes a protein important for inactivation. It would be another step in the treatment of second-line, because until now none of two drugs combination assayed showed better results in this setting versus the standard “one drug treatment”. It would also be another step on the knowledge of the role of these genes directly linked to pemetrexed activity (Araujo, A.M. 2010).

NSCLC is associated with high economic costs. Indirect costs account for a large part of the total costs (Molinier, L. et al. 2006; Bradley, C.J. et al. 2008; Yabroff, K.R. et al. 2008). When the intrinsic value-of-life lost plus loss-of-productivity costs from cancer deaths were taken into account using a willingness-to-pay approach, lung cancer was estimated to represent > 25% (433.4 billion US dollars) of the total 1472.5 billion US dollars value-of-life lost in the US in 2020 (Yabroff, K.R. et al. 2008). When only direct costs are considered, hospitalization and drug treatments account for the majority of costs (Dedes, K.J. et al. 2004; Ramsey, S.D. et al. 2008; Pompen, M. et al. 2009). *Per capita* direct costs of NSCLC ranged from 4262 to 30424 euro (year of valuation 1988-2001) in a methodological review of studies of the cost of lung cancer in Canada, the UK and France (Molinier, L. et al. 2006) and a study in Switzerland (Dedes, K.J. et al. 2004). And direct costs are even higher for patients who receive additional treatment regimens after the first-line chemotherapy (Ramsey, S.D. et al. 2008).

Before a new drug is introduced in the market, it should prove its added therapeutical value, which means that its cost-effectiveness should also be calculated.

The new drugs are expensive and generally are only effective for a relatively small subset of treated patients. This is the reason why, for a society to consider spending its money in these new drugs for a group of patients, they must be effective for a certain patient and cost-effective for a society.

The predictive factors are an important piece because they can select the right characteristic of a certain disease permitting to achieve the best result with a drug.

With this on mind and because erlotinib was the last new drug introduced in Portugal for the second and third-line treatment of advanced or metastatic NSCLC, a cost-minimization and cost-utility analysis was carried out to compare the costs and clinical benefits of erlotinib for this indication with those of the three possible clinical care alternatives - docetaxel, pemetrexed and best supportive care, considering a Kaplan-Meier survival curve of two years (Araujo, A. et al. 2008). Among the several limitations of this study, it is worth to underline that this type of study is normally undertaken using a theoretical model which tries to mimic reality as simplistic as possible; the several sources of data used have some limitations from an economic evaluation perspective; the information contained in the literature does not necessarily represent normal clinical practice, because is based on data from clinical trials; the clinical situation may not be easy to reproduce outside a clinical trial context. At two years, the QALY (Quality Adjusted Life Year) per patient observed was higher with erlotinib (0.250) than with best supportive care (0.186), docetaxel (0.225) or pemetrexed (0.241). The total cost per patient was lower with erlotinib (€26 478) than with docetaxel (€29 262) or with pemetrexed (€32 762) and higher than with best supportive care (€16 112). For most simulations in the probabilistic analysis, the ICER (Incremental Cost-Effectiveness Ratio) between erlotinib and supportive care was above the 30.000 euro / QALY “willing to pay” threshold, both for the analysis of YLG (Year of Life Gained – cost-effectiveness) and the QALY (cost-utility). The model shows that second or third line treatment of NSCLC with erlotinib could add a benefit in terms of QALY when compared with docetaxel, pemetrexed or best supportive care, and a lower cost than that for the active treatments. And the study concluded also for the need of a prospective randomized phase III trial, comparing all the active treatments in terms of efficacy, utility, toxicity and use of healthcare resources.

This results are on line with several other published studies from Turkey (Batigun, O. et al. 2007), UK (Lewis, G. et al. 2006), Poland (Orlewska E, S.A., Szkultecka-Debck M. 2006), Spain (Terrés, C.R. et al. 2006), Taiwan (Hsia, T. et al. 2007) and USA (Carlson, J.J. et al. 2008).

This study received some criticisms such as differences in studied populations which makes them not comparable, after the change in the drug label of pemetrexed any conclusions on effectiveness in the second-line treatment of NSCLC are misleading, and that differences between the trials can result in bias and the direction of this bias is unknown, which means uncertainty of the results (Bartmiski, W. 2009).

The analysis is also limited to direct medical costs from a healthcare payer perspective. However, from a patient perspective, other direct costs, such as travel costs associated with intravenous administration, may also incur by the patient and their families or caregivers. From a society perspective, the improvement in disease-free survival would be expected to have only minimal effects on patient-related loss-of-productivity costs, as many of these patients would no longer be expected to be part of the work force. However, there may be costs to society related to loss-of-productivity of family and caregivers (e.g. time away from their jobs to take patients to outpatient clinics or hospitals, especially for intravenous drug administration or management of adverse events).

For these critics several counterparts need to be considered. All current practice guidelines, at that time, recommend the use of erlotinib, pemetrexed or docetaxel in patients with advanced or metastatic NSCLC with at least one failed chemotherapy regimen, independently of the histology type, inferring that these recommendations recognize a similar level of efficacy among these three therapeutic options for treating this type of population. This population is also that one represented in the main clinical trials held for each drug. The information obtained from randomized, comparative and controlled clinical trials is the most reliable method for demonstrating evidence of possible differences in health results with the use of different therapeutic interventions (Araujo, A. 2009).

Obviously, it is well known that there is a clear need for well designed head-to-head trials comparing the efficacy of erlotinib with that of docetaxel and pemetrexed, alongside prospective cost-utility analyses.

The Portuguese National Health Plan of 2004-2010 gives a great importance to the oncologic diseases, setting them as a priority. But until now no studies were performed in order to clearly elucidate the financial resources allocated to cancer disease considering his social burden. Such study was crucial so that decision makers could take informed and reasoned decisions regarding the allocation of funds from the national health budget for the area of oncology.

In the aim of the present work, a study was conducted in order to estimate the costs of cancer treatment in Portugal, its comparison to the amounts spent in Europe

and in United States of America, and also to the values spent with the cardio-vascular diseases in Portugal. Moreover, it also evaluated the cost with cancer treatment drugs in Portugal, and compared it with the total spending and with other areas of health expenditures (Araujo, A. et al. 2009).

Like every other country, Portugal has a limited annual budget. The amount of it spent on health is below the average of the EU, in percentage of Portuguese GDP, and because this is also smaller than the *per capita*, spend was also inferior to the mean of the EU. Nevertheless, the social burden of the cancer and the cardio-vascular diseases are almost the same in Portugal and in the EU. And it is important to be aware of the fact that the social burden with cancer has increased in the last decade and is going to increase on the next one in opposition to the cardio-vascular diseases. The percentage spent with cancer from the total of the health budget was a little more than half and *per capita* was below half of the mean on EU. If these values are compared to the total spend with cardio-vascular diseases and with cancer in Portugal, it is possible to verify that the first is more than twice the second.

Personalized cancer medicine has the potential to save costs to the insurance industry and to governments. The ability to use genomic information to exclude large numbers of patients from treatment consideration with particular agents to which they are unlikely to benefit from not only spares patients needless treatment, but also could have a substantial impact on the reimbursement costs associated with these relatively expensive therapies.

In face of the price of the new drugs, it is also urgent to define healthcare and drug policies and strategies for its use that will allow a rational utilization of available resources to obtain an optimal cost/benefit ratio. Formal pharmacoeconomic analyses provide greater insights into the true value of treatments. Studies which permit this evaluation are thus a precious tool for decision makers, especially when it comes to making decisions over diseases such as lung cancer which have a great impact on patient quality of life. There is the need to struggle for policies promoting an expansion of the therapeutic rationality, equitable access to drugs and facilitation of the access to innovative medicines. It is important to emphasize that the equity access to drugs for the patients should be vertical (in one hospital all the patients with the same disease should have access to the same treatment) and horizontal (in every hospital in the

country, a patient should have access to the best and the same treatment for his disease).

Portugal is a poor country with limited amount of resources. The expenditure with drugs should be rational and equal for every patient, cost-effective, and enabling financial sustainability of the National Health System and of Portuguese society. But it should also enable the right patient to get the right (and the best) treatment at the right time.

7. Conclusions

The work presented in this thesis shows that:

1. Knowledge of the incidence of lung cancer and its characteristics in Portugal is crucial, especially for calculating costs and allocating the necessary funds.
2. In Portugal, second and third-lines treatment for NSCLC are according the international guide-lines and its effectiveness compared with what is published.
3. *EGF*, *EGFR* and other polymorphisms are not yet reliable tools as prognostic or predictive factors in non-small-cell cancer outcomes but some biomarkers are already established as prognostic factors and a few as predictive ones.
4. Knowledge of the costs of cancer treatment in Portugal is fundamental and it is possible to develop studies on this field that could guide decision makers on their policies.
5. The cost-effectiveness studies of the new drugs are important tools for evaluating the value of the new drugs, namely for second and third-lines for NSCLC treatment.
6. Knowledge about the incidence of lung cancer, the role of prognostic and predictive biomarkers in selecting the most appropriate therapy, the amount spend with cancer each year and the pharmaco-economic studies about new drugs, are all essential tools for a rational Portuguese National Health Plan, in general, and a Drug National Policy, in particular.

In this way, the questions placed at the beginning of this assignment were successfully answered, demonstrating that studies allowing better knowledge about the lung cancer Portuguese reality and the potential value of a new drug may be extremely useful for our decision makers, allowing an adequate drug policy and contributing to a better health care service.

8. Future Studies

1. Proceed with two projects, in collaboration with other institutions:
 - a) Started a decade ago, to registry all the lung cancer cases treated on the Portuguese hospitals, to better determine the characteristics of NSCLC patients and its outcomes;
 - b) Started this year, to determine the frequency of the *EGFR* mutation in the Portuguese population in general, and in some sub-groups in particular, and to evaluate the outcomes for the *EGFR*-mutated positive NSCLC patients.
2. Initiate a cost-effectiveness analysis for gefitinib in *EGFR*-mutated positive NSCLC and for pemetrexed in non-squamous NSCLC, in order to elucidate the pharmaco-economic value of these options.

Such studies are expected to bring more scientific information about the value of new drugs for NSCLC patients and about their economic weight to Portuguese society, permitting a more objective public discussion and politic decision about these issues.

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