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Infection risk for chemotherapy-induced neutropenia in Hodgkin Lymphoma and in Acute Myeloid Leukemia

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Infection risk for chemotherapy-induced neutropenia in Hodgkin Lymphoma and in Acute Myeloid Leukemia

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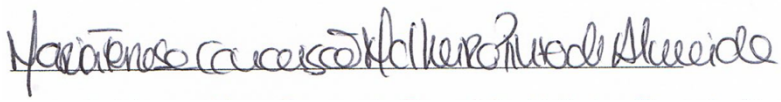

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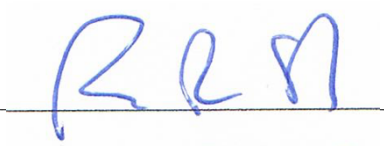

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“I hear and I Forget.

I see and I remember.

I do and I understand.”

Confucius

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TABLE OF CONTENTS

ABSTRACT iii

RESUMO iv

ABBREVIATIONS v

1. INTRODUCTION 1

2. METHODS 2

3. FEBRILE NEUTROPENIA 2

3.1. Febrile neutropenic syndromes 3

3.2. Risk Stratification 4

3.3. Epidemiology 5

3.4. Prophylaxis and Treatment 7

3.4.1 Chemoprophylaxis 7

3.4.2. Prophylaxis with Granulocyte Colony-Stimulating Factor 7

3.4.3. Treatment 8

4. MALIGNANT HEMATOLOGICAL DISEASES 9

4.1. Hodgkin Lymphoma 9

4.1.1. Diagnosis and Staging 10

4.2. Acute Myeloid Leukemia 11

4.2.1. Diagnosis and Risk Stratification 11

5. FEBRILE NEUTROPENIA IN HODGKIN LYMPHOMA COMPARED WITH ACUTE MYELOID LEUKEMIA 12

5.1. Neutropenia and Neutropenic Complications during Chemotherapy for Hodgkin Lymphoma 12

5.2. Neutropenia and Neutropenic Complications in Acute Myeloid Leukemia Treatment 16

5.2.1. Invasive Fungal Disease 19

5.3. Final Considerations 20

6. CONCLUSIONS 21

7. REFERENCES 23

ABSTRACT

Febrile neutropenia is a serious and potentially fatal complication in oncology patients treated with chemotherapy, with a mortality rate of 5-20%. The severity and the duration of neutropenia depend on type of malignancy, as well as the chemotherapy schema. Treatment with aggressive chemotherapy regimens has an increased risk of neutropenia associated with consequent bacterial or fungal infections. Fever in neutropenic patients is usually associated with bacterial infections, while fungal infections occur more frequently in a severe and prolonged neutropenia context with a mortality rate of 55%.

In hematological malignancies, neutropenia induced by the myelosuppressive effect of chemotherapy has not been associated with the same infectious risk, varying with neutropenia progression and type of treatment. In Hodgkin Lymphoma, an indolent type of pathology, treatment with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) chemotherapy has been associated with significant neutropenia although with frail association with infection when compared with other therapeutic regimens. In Acute Myeloid Leukemia, neutropenia caused by induction chemotherapy with cytarabine and idarubicin is significant, with high bacterial infection risk. It is not so well understood in what it concerns fungal infections.

Considering the high mortality risk in patients with febrile neutropenia, prompt prophylactic or acute treatment has been shown critical in mortality reduction. However, there has been an increased mortality in neutropenic patients caused by infections with drug resistant microorganisms. Differences described in the infectious profile of neutropenia in hematological diseases raise the question of whether an aggressive antimicrobial therapeutic approach is needed for all hematological malignancies. The potential risk of developing microbe resistant strains in subsequent infection in these patients, and true cost-benefit of center specific antimicrobial therapeutic protocols, should lead to a more individualized and efficient medical approach.

The objective of this bibliographic review is to analyze the different studies regarding neutropenia in hematological malignancies, having as paradigms: ABVD-treated Hodgkin Lymphoma, whose neutropenia is frequent and severe but seems to be rarely associated with infection and Acute Myeloid Leukemia in remission induction chemotherapy, usually associated with infections in the context of prolonged neutropenia.

A reflection about the true infectious risk and the use of wide-spectrum antibiotics should be brought up by this literature review.

Keywords: neutropenia, chemotherapy, febrile neutropenia, prophylaxis, infection, hematological malignancies, Hodgkin Lymphoma, Acute Myeloid Leukemia.

RESUMO

A neutropenia febril é uma complicação grave e potencialmente fatal em doentes oncológicos tratados com quimioterapia, com uma taxa de mortalidade de 5-20%. O grau e duração de uma neutropenia dependem do tipo de neoplasia e da quimioterapia utilizada. O tratamento com quimioterapia agressiva associa-se a um risco de neutropenia com potencial desenvolvimento de infeções bacterianas e fúngicas. O desenvolvimento de febre nos doentes neutropénicos está normalmente associada a infeções bacterianas, enquanto as infeções fúngicas ocorrem mais frequentemente no contexto de uma neutropenia grave e prolongada com uma mortalidade até 55%. Nas neoplasias hematológicas, as neutropenias induzidas pelo efeito mielossupressor da quimioterapia não têm mostrado o mesmo risco infecioso, variando com a patologia, com a evolução da neutropenia e com o tipo de tratamento. No Linfoma de Hodgkin o tratamento com ABVD (adriamicina, bleomicina, vimblastina e dexametasona) tem sido associado a neutropenia importante, mas com fraca associação a infeção, quando comparado com outros esquemas terapêuticos. Na Leucemia Mieloide Aguda, as neutropenias que se desenvolvem com a quimioterapia de indução com idarrubicina e citarabina são significativas e com elevado risco infecioso bacteriano. Não é, contudo, tão claro no que diz respeito às infeções fúngicas.

Considerando a mortalidade significativa nos doentes com neutropenia febril, a instituição da profilaxia ou tratamento emergente tem-se mostrado crítica na redução da mortalidade. Contudo, verifica-se um aumento da mortalidade em doentes neutropénicos causada por infeções com micro-organismos resistentes. As diferenças que têm sido descritas no perfil infecioso das neutropenias nas diversas patologias hematológicas levam a questionar a verdadeira necessidade de uma abordagem terapêutica antimicrobiana agressiva para todas as neoplasias hematológicas.

Os potenciais riscos de desenvolvimento de resistências microbianas em infeções subsequentes nestes doentes, e a relação custo-benefício das terapêuticas antimicrobianas protocoladas nos hospitais, devem fazer pensar numa abordagem médica mais individualizada e eficiente.

O objetivo desta revisão bibliográfica é analisar os estudos existentes sobre as neutropenias nas neoplasias hematológicas, tendo como paradigmas: o Linfoma de Hodgkin tratado com ABVD, cuja neutropenia associada é frequente e profunda, mas raramente associada a infeção; e a Leucemia Mieloide Aguda em tratamento de indução, habitualmente associada a infeções no contexto de neutropenia prolongada. Pretende-se ainda, uma reflexão acerca do risco infecioso nas neutropenias e uso de antibioterapia de largo espetro.

Palavras-chave: neutropenia, quimioterapia, neutropenia febril, profilaxia, infeção, neoplasias hematológicas, Linfoma de Hodgkin, Leucemia Mieloide Aguda.

ABBREVIATIONS

A+AVD - Brentuximab-vedotin plus Doxorubicin (Adriamycin), Vinblastine and Dacarbazine
ABVD - Doxorubicin (Adriamycin), Bleomycin, Vinblastine and Dacarbazine
AML - Acute Myeloid Leukemia
ANC - Absolut Neutrophil Count
ARF - Acute Respiratory Failure
ASCO - American Society of Clinical Oncology
ASH - American Society of Hematology
ASXL1 - Additional Sex Combs-Like 1
BEACOPP - Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine and Prednisone
CD30 - Lymphoid transmembrane receptor of the tumor necrosis factor receptor superfamily
CHOP - Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone
CIN - Chemotherapy-induced neutropenia
CISNE - Clinical Index of Stable Febrile Neutropenia
COPD - Chronic Obstructive Pulmonary Disease
CT - Chemotherapy
DNA - Deoxyribonucleic Acid
EBV - Epstein-Barr Virus
ECIL - European Conference on Infections in Leukemia
EORTC - European Organization for Research and Treatment of Cancer
ESBL - Extended spectrum β-lactamase
ESMO - European Society for Medical Oncology
FDA - United States Food and Drug Administration
FDG-PET - Fluoro-deoxyglucose positive emission tomography
FLT3 - FMS-like tyrosine kinase 3
FN - Febrile Neutropenia
G-CSF - Granulocyte Colony-stimulating Factor
HMA - Hypomethylating Agents
HSCT - Hematopoietic Stem Cell Transplantation
HiDAC - High Dose Cytarabine
HIV - Human Immunodeficiency Virus
HL - Hodgkin Lymphoma
HLA - Human Leukocyte Antigen
IDSA - Infectious Diseases Society of America
IFD - Invasive Fungal Disease
IIHS - International Immunocompromised Host Society
Non-HL - Non-Hodgkin Lymphoma
LDH - Lactate Dehydrogenase
MASCC - Multinational Association for Supportive Care in Cancer
MRSA - Methicillin-resistant *Staphylococcus aureus*
NCCN - National Comprehensive Cancer Network
TP53 - Tumor suppressor Protein p53
USA - Unites States of America
VRE - Vancomycin-resistant enterococci

1. INTRODUCTION

Over the last decades the overall survival of oncologic patients has suffered a remarkable progress. This relates in particular with increased development of both diagnostic and therapeutic options offered to these patients. Regardless of the important breakthrough in the field of biological treatments, chemotherapy (CT) continues to play a central role in neo-adjuvant, adjuvant and palliative care in oncology [1]. However, the majority of CT protocols induces suppression of both innate and adaptive immunity, neutropenia being an important deleterious consequence of this treatment and constituting a risk factor for infection in oncologic patients [2]. In 1966, Bodey and coworkers have shown that adults with a reduction in numbers of neutrophils (neutropenia) following cytotoxic CT were in direct risk of serious infection, and that early aggressive treatment with broad spectrum antibiotics could contribute to a decrease in mortality rates [3,4]. This clinical manifestation of neutropenia with fever was then on known as 'febrile neutropenia' (FN). Marked differences between cancer patients have been documented in their response to infection [5,6].

The pathophysiology of infection following the administration of CT is complex. Deficiencies occur in both innate and adaptive immunity, with changes in cellular and non-cellular elements of the defense mechanisms against infection [7]. Anatomical barriers are also compromised by the effects of chemo- and radiotherapy with disruption of the gut mucous membranes and the skin integrity with resultant mucositis and dermatitis, respectively. This, in turn, enables local tissue infection and colonization or bacteria dissemination into the blood stream [8].

Although CT treatments have improved the overall survival in oncologic patients, it has been done at the expense of neutropenia development, with increased risk factor for susceptibility to bacterial/fungal infections.

The objective of this study is to present a literature review about the subject neutropenia and infection in hematological malignancies, having as paradigms: ABVD-treated Hodgkin lymphoma (HL), whose neutropenia is frequent and severe but rarely associated with infection and Acute Myeloid Leukemia (AML) in remission induction CT, usually associated with infections in the context of prolonged neutropenia. With this revision, a reflection about the true infection risk in CT-induced neutropenia (CIN), the routine use of wide-spectrum antibiotics and potential treatment compromise, should be carried out.

2. METHODS

In our research strategy and selection criteria for a systematic literature search, we used the Medline database (via PubMed) to search for English-language articles published in the last 15 years (from January 2004 until June 2019). Some articles published before were also included because they were considered relevant to this subject. Keywords used in this search were, neutropenia, chemotherapy, febrile neutropenia, prophylaxis, infection, Hodgkin Lymphoma, Acute Myeloid Leukemia and hematological malignancies, using the following search strategies: 1. ("neutropenia"[All Fields] OR "febrile neutropenia"[All Fields] OR “infection” [All Fields]) AND ("Hodgkin lymphoma"[All Fields] OR "Acute Myeloid Leukemia"[All Fields] or "Hematological malignancies"[All Fields]); 2. ("chemotherapy"[All Fields] OR "prophylaxis"[All Fields]) AND ("neutropenia"[All Fields] OR "febrile neutropenia"[All Fields] OR “infection”[All Fields]) AND ("Hodgkin lymphoma"[All Fields] OR "Acute Myeloid Leukemia"[All Fields] OR "Hematological malignancies"[All Fields]). We reviewed all retrieved titles and abstracts for relevance, and further assessed full papers that we judged appropriate for inclusion in this work. From different keyword combination strategies, in total, 221 articles were used for this review. Case reports, low quality studies and conference meeting abstracts were excluded.

3. FEBRILE NEUTROPENIA

Febrile neutropenia (FN) is one of the most serious problems in patients with cancer who receive myelosuppressive CT, increasing infection risk that frequently requires hospitalization and treatment with broad-spectrum antibiotics [9-11]. Patients who develop FN during CT treatment not only have increased rates of morbidity and mortality [10,12] and higher health care costs [13,14], but are also more likely to require reduction in chemotherapy dose intensity, or experience treatment delay or even treatment discontinuation, all of which can lead to reduced treatment response and lower survival [15-18].

FN may represent the only sign of severe infection in cancer patients, since symptoms and signs of inflammation are typically attenuated due to a reduced absolute neutrophil count (ANC) [19,20]. The frequent need for indwelling central venous catheters in association with damage of the gastrointestinal mucosa caused by anticancer agents provides a portal of entry for pathogenic bacteria, predisposing patients to bacteremia [21]. This fact, in association with an impaired host response to infection due to neutropenia and decreased cellular immunity secondary to intensive CT, leads to increased risk for severe infections in cancer patients. Despite recent improvements in managing FN, infections in the context of neutropenia continue to be associated with substantial mortality, which may reach values of approximately 10% in specialized centers [12,16]. In patients who

develop septic shock, pneumonia or documented bacteremia, mortality exceeds 50% [22], despite prompt antibiotic initiation.

Both fever and neutropenia definitions have not been consensual. Average normal body temperature of 37ºC has been proposed by Carl-Wunderlich in 1868, which considered values above 38ºC as fever [23]. The *Infectious Diseases Society of America (IDSA)*, *American Society of Clinical Oncology (ASCO)*, *American Society of Hematology (ASH)* and *National Comprehensive Cancer Network (NCCN)* define fever in a neutropenic patient as one individual temperature measurement ≥38.3 ºC or 38ºC for more than one hour [21]. The *European Society for Medical Oncology (ESMO)* defines FN as an oral temperature of >38.3°C or two consecutive readings of >38.0°C for 2 hours and an ANC of <500 cells/μL or expected to fall below 500 cells/μL [24]. Neutropenia definition varies from institution to institution, but is usually defined as an ANC of <1500 or 1000 cells/μL. Severe neutropenia is usually defined as an ANC <500 cells/μL or an ANC that is expected to decrease to <500 cells/μL over the next 48 hours [24]. Profound neutropenia is defined by an ANC <100 cells/μL. The risk of clinically important infection rises exponentially as the neutrophil count falls below 500 cells/μL and is higher in those with a prolonged duration of neutropenia (more than 7 days) [21].

The severity of neutropenia, which directly influences the frequency of FN, is related to different CT characteristics, the intensity, the number of agents and respective doses, as well as the myelotoxic potential of each component. Nevertheless, the correlation between the type of CT and the risk of FN is far from being optimal because they do not take into account the factors linked to the type of malignancy and respective co-morbidities, which can influence the risk of developing FN despite the use of the same type of CT, as well as the risk of complications and death during an episode of FN [25]. Different models tried to classify the common CT regimens according to the risk of FN as being low (<10%), intermediate (10%-20%) or high (>20%), but their predictive values are not very strong [15,26,27].

3.1. Febrile neutropenic syndromes

Studies involving patients with different tumors (lymphoma, breast, colon, lung, ovary and others) have shown that the risk of developing FN is maximal during the first cycle of CT, diminishing afterwards [28]. In hematologic malignancies involving the bone marrow, recovery of normal hematopoiesis is slower after first cycle of treatment and hence neutropenia is more prolonged, and the risk of FN is more pronounced.

A number of neutropenic fever syndromes have been described [29]. Similar to the immune reconstitution inflammatory syndrome, that can follow the initiation of antiretroviral therapy in

patients with Human immunodeficiency virus (HIV) infection, the myeloid reconstitution syndrome is a neutropenic syndrome defined by fever and a new inflammatory focus or progression of a preexisting inflammatory focus in temporal relationship to neutrophil recovery from aplasia.

The International Immunocompromised Host Society (IIHS) has classified initial neutropenic fever syndromes into the following three categories [30]:

1) Microbiologically documented infection – Neutropenic fever with a clinical focus of infection and an associated pathogen;

2) Clinically documented infection – Neutropenic fever with a clinical focus (*e.g.*, cellulitis, pneumonia) but without the isolation of an associated pathogen;

3) Unexplained fever – Neutropenic fever with neither a clinical focus of infection nor an identified pathogen.

3.2. Risk Stratification

Risk stratification allows for a guided orientation of both medical and therapeutic approach febrile neutropenic patients. Clinical evaluation focuses on assessing the risk of serious complications, including the need for hospital admission, intravenous antibiotics, and prolonged hospitalization [21,24,31].

Risk factors predictive for developing FN can be divided in three categories: *patient-related* (history of prior FN, age >65 years, female gender, obesity, cardiovascular disease, poor performance and nutritional status), *disease-related* (high levels of lactate-dehydrogenase [LDH] in lymphoproliferative disease, bone marrow failure due to tumor invasion and advanced stage of oncologic disease) and *treatment-related* (mucositis, high-dose CT regimens without leucocyte growth factor administration, no use of antibiotic prophylaxis or granulocyte colony-stimulating factor [G-CSF]) [32-34].

Overall, the risk of serious medical complications in febrile neutropenic patients with one or more co-morbidities is significantly increased, which in turn will contribute in deciding whether a CT-treated patient should receive primary antibiotic prophylaxis to decrease the potential risk of FN [24].

Considering the different risk stratification systems, several international organizations (ASCO, IDSA, NCCN and ESMO) developed specific guidelines for FN [21,24,31,35]. Validated scoring systems used to estimate the risk for medical complications include the Talcott rules, the Multinational Association for Supportive Care in Cancer (MASCC) score, and the Clinical Index of Stable Febrile Neutropenia (CISNE) score [36-38]. Generally, a low-risk patient for serious complications is defined as a neutropenic patient whose neutropenia (ANC <500 cells/µL) is expected to last less than 7 days and that does not have any active co-morbidities, or evidence of significant hepatic or

renal dysfunction and have an MASCC score ≥21 or a CISNE score of 0 at the time of assessment. Most patients receiving CT for solid tumors are considered to be of low risk for complications requiring hospitalization. This group of patients has been target at randomized studies which demonstrated their low risk for serious medical complications [21,24,31,39]. High-risk for serious complications is considered in neutropenic patients whose neutropenia (ANC <500 cells/µL) is expected to last for more than 7 days, present ongoing co-morbidities, liver or renal dysfunction, and have a MASCC score <21 or a CISNE score of ≥2 at the time of assessment [37,38,40] requiring immediate hospitalization and urgent evaluation.

Risk stratification in a febrile neutropenic patient depends significantly on the underlying malignancy. The majority of hematological malignancies automatically characterize a high-risk patient [29,41]. Patients receiving CT for solid tumors will generally have neutropenia that lasts less than 7 days, and only 5% to 30% will have FN, with the highest rates occurring during the first cycle of treatment. Conversely, patients undergoing hematopoietic stem-cell transplantation (HSCT) with conditioning therapy or receiving CT for hematologic malignancies may have neutropenia lasting longer than 14 days. Consequently, more than 80% of patients receiving CT for leukemia or undergoing allogeneic HSCT will experience at least one episode of FN [15,21,42,43].

Some experts have defined high-risk patients as those expected to have profound prolonged neutropenia (ANC ≤100 cells/µL for more than 7 days) based on experience that such patients are most likely to have life-threatening complications, tending to occur in the pre-engraftment phase of HSCT (particularly allogeneic) and in patients undergoing induction CT for acute leukemia [21,35]. However, formal studies that clearly differentiate between patients with an ANC <500 cells/µL of patients with ANC ≤100 cells/µL are lacking [44].

3.3. Epidemiology

The type of underlying neoplasia, hematological malignancy or solid tumor, does not significantly influence the incidence of complications or deaths in FN [25]. However, the presence of bacteremia notably increases morbidity and mortality. Bacteremia is not easy to predict on a clinical basis at the time of onset of fever, although manifestations such as high temperature, hypotension and thrombocytopenia are possible clues for it. The presence of a focal infection and specific local complications (*e.g.*, pneumonia or cellulitis) increases the risk of dying during an episode of FN; probably as a substitute of bacteremia [45].

The Gram-negative Enterobacteriaceae (*Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp) and *Pseudomonas aeruginosa*, are the most common pathogens causing bloodstream infections in neutropenic patients with cancer. Lately, Gram-positive bacteria have become more prevalent, such as coagulase-negative staphylococci and viridans group streptococci. Nevertheless, due to the

high morbidity and mortality associated with Gram-negative sepsis, empiric therapy for FN should target these organisms specifically. An increase in antibiotic-resistant strains has been described, such as extended spectrum β-lactamase (ESBL)-producing Gram-negative bacteria, vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) [46]. The presence of Gram-negative bacteremia has a high mortality rate (70%) in neutropenic patients who did not receive empiric antibiotics [47,48]. In contrast, the overall mortality rate in patients with FN treated with empiric antibiotics is just 4% to 20%. Increased mortality was seen in patients presenting co-morbidities, documented Gram-negative rod bacteremia, and/or tissue-invasive infections such as pneumonia [12]. Throughout decades the optimal treatment for FN was based in the prompt administration of broad-spectrum antibiotics to all neutropenic patients with fever, although with time, patients with FN start constituting a heterogeneous population and usually only a minority develops major serious complications [49].

Candida spp and *Aspergillus* spp account for most invasive fungal infections during neutropenia. The former is acquired through gastrointestinal tract colonization and translocation across damaged intestinal epithelial surface. The latter are acquired by inhalation of airborne spores into the upper and lower respiratory tract followed by germination and invasive hyphal growth [25]. Increasing numbers of infections with fluconazole-resistant *Candida* strains (e.g., *Candida krusei* and *Candida glabrata*) have also been reported [50]. Fungal infections are common in high-risk patients with FN but are uncommon in low-risk patients. The risk for invasive fungal infections increases with the duration and severity of neutropenia, prolonged antibiotic use, and number of CT cycles. Fungi are rarely the cause of the first febrile episode in neutropenic patients. Invasive fungal infections are usually identified as a cause of persistent or recurrent fever beyond the first week of neutropenia. However, fungal infections can occasionally present early or even prior to initial CT [51]. In an autopsy study of patients who died after prolonged FN between 1966 and 1975, 69% of patients had evidence of invasive fungal infections [52]. It is important to note that this study was done before either antifungal prophylaxis or early diagnosis and treatment of invasive fungal infections was routine.

The underlying malignancy and the cumulative treatment also influence the risk and spectrum of infection. Patients with refractory disease who have received multiple lines of CT and more prolonged neutropenia are typically at higher risk for infectious complications compared with patients at earlier stages of their treatment course [46].

3.4. Prophylaxis and Treatment

3.4.1 Chemoprophylaxis

Antibiotics have been used for the prevention of episodes of FN in CT treated patients. A Cochrane meta-analysis published in 2005 recommended the use of ciprofloxacin or levofloxacin in cancer patients undergoing intensive CT [53]. This approach has been successful but resistant strains started to emerge, limiting its efficacy. Since the 1990s, fluoroquinolones have been used extensively for chemoprophylaxis. Several studies have shown that fluoroquinolones reduce the incidence of infection and the infection-related mortality. However, with the emergence of quinolone-resistant strains, prophylaxis is rendered useless. Additionally, these strains compromised the use of fluoroquinolones as a therapeutic option in low-risk patients. Recent guidelines from the European Organisation for Research and Treatment of Cancer (EORTC) and American Society of Clinical Oncology (ASCO) recommend that clinicians limit the use of antibiotic prophylaxis to patients at high risk for FN [24].

3.4.2. Prophylaxis with Granulocyte Colony-Stimulating Factor

Primary prophylaxis with G-CSF, i.e. G-CSF administered immediately after cycle 1 of CT, reduces the risk of FN by at least 50% in patients with solid tumors without significantly affecting tumor response or overall survival [28,45,54].

Prophylactic G-CSF is recommended to be administered when the risk of FN is >20% for all cycles of treatment [55]. For patients with an intermediate risk (10%–20%), it is important to assess clinical factors that increase the frequency or risk of FN, such as patient age co-morbidities and CT regimen [34,55,56]. G-CSF can also be considered in patients with reduced bone marrow reserve due to extensive radiotherapy or neutropenia in the context of HIV infection [24]. Recent studies confirmed a significant success in FN chemoprevention when using primary prophylaxis with filgrastim or pegfilgrastim [57,58].

In most CT regimens used for common tumors, the risk of FN is maximal during the first course. Therefore, it is reasonable to recommend primary prophylaxis for the patients at risk rather than to use secondary prophylaxis as an alternative. Secondary prophylaxis (i.e. G-CSF given for a course of CT following a course with FN) is indicated if a significant dose reduction or delay of CT will compromise the treatment with a curative intent. There are few complications associated with G-CSF administration, the most common adverse effect is minor or moderate bone pain that can usually be handled with standard analgesics [24].

3.4.3. Treatment

The management of FN requires urgent evaluation and medical attention with prompt administration of antibiotics. Empiric antibiotics are standard of care and significantly reduce morbidity and mortality in patients with cancer with FN [16].

Patients with a high MASCC score and thus considered to be low risk, which are planned to be treated as outpatients, are usually given a dose of intravenous antibiotics after blood cultures were obtained. Then they may be treated with oral antibiotics [35,59]. However, patients who are already receiving an oral fluoroquinolone as prophylaxis are not candidates for treatment with oral agents [31].

Patients with fever and neutropenia who do not meet the low-risk MASCC criteria (score <21) are considered to be at high risk for complications during their course of neutropenia [31]. Although duration of neutropenia is not included as a risk factor in the MASCC scoring system, it is of practice to admit all patients who are receiving CT, especially for acute myelogenous leukemia, or HSCT, and are expected to have more than a week of low ANC (<500 cells/μL). High-risk patients should be admitted to the hospital for evaluation and treatment of potential infection with a broad-spectrum parenteral antibiotic with antipseudomonal activity [60].

The following two management strategies have been outlined for the treatment of these patients: escalation and de-escalation [61]. The de-escalation approach includes initial multiagent therapy that includes coverage for multidrug-resistant Gram-negative and Gram-positive bacteria (*e.g.*, carbapenem in combination with an aminoglycoside and glycopeptide). Once the patient is stable or a bacterial pathogen is identified, treatment can be de-escalated to a narrower targeted therapy. Alternatively, patients with FN who are stable at presentation are typically treated with the escalation approach with ß-lactam monotherapy initially with addition of agents if indicated on the basis of culture data or clinical deterioration [61].

The choice of monotherapy should be guided by previous infections and susceptibility patterns as well as institutional antibiograms [21,35]. Patients with abdominal symptoms such as abdominal pain or diarrhea may also need anaerobic coverage with the preferential use of piperacillin-tazobactam as initial empiric therapy or the addition of metronidazole to cefepime.

Although the antipseudomonal carbapenems have excellent anti-anaerobic activity, they are best reserved for use in treating complicated infections with drug-resistant organisms. Depending on site antibiogram profiles showing carbapenem coverage of most Gram-negative pathogens, carbapenems may be a good choice for neutropenic patients presenting with sepsis. Carbapenems are not recommended for routine coverage in uncomplicated, stable patients.

Although Gram-positive bacteremia have become more common in the past 30 years, they rarely cause mortality in patients with FN, with the exception of viridans group streptococci.

Therefore, for stable patients without sepsis, pneumonia, mucositis, or evidence of line infection, there is no benefit of empirically adding vancomycin to the initial empiric regimen used for management of neutropenic fever [62,63]. Several clinical practice guidelines exist to help with management of FN [21,24,64].

Patients with neutropenic fever should be examined daily with attention to fever curve and new signs or symptoms. Therapy should be broadened to include coverage against resistant Gram-negative, Gram-positive bacteria, anaerobes as well as the *Candida* fungus if the patient is septic.

In patients who are stable but have ongoing fever despite more than 3-4 days of treatment with broad-spectrum antibiotics without an identified source, there is no need to broaden antibiotic therapy. Fever alone in an otherwise stable patient is not an indication to add or change antimicrobials. However, additional work-up may be indicated in patients with new or persistent fever during neutropenia.

High-risk patients with hematologic malignancies who are anticipated to have neutropenia for more than 7 days should be closely evaluated for invasive fungal disease (IFD). Fungal markers including galactomannan and 1,3-ß-D-glucan can be sent for evaluation, but sensitivities of these two tests are only 49% to 80% and 40% to 90%, respectively [65-67]. Both markers are usually negative in the setting of mucormycosis. Therefore, empiric antifungal therapy should also be a consideration, especially in patients with acute leukemia, patients receiving allogeneic HSCT, or patients receiving high-dose corticosteroids who are at high risk for mold infections.

Practices vary among centers and in the guidelines if no infectious etiology is identified. The European Conference on Infections in Leukemia (ECIL) guidelines suggests stopping broad-spectrum antibiotic therapy and/or resuming prophylaxis. Conversely, the IDSA and NCCN favor the continuation of broad-spectrum therapy until recovery of neutrophils. However, in a recent multicenter study, patients with hematologic malignancies with FN and negative blood cultures were randomly assigned to either continuation of empiric antibiotics or cessation of antibiotics after being afebrile for 72 hours. Cumulative days of antibiotic therapy were lower in the group with early de-escalation, and adverse events, including recurrent fevers and infection, were similar between the two groups [39], suggesting that cessation of antibiotics before neutrophil recovery in stable afebrile patients without an identified infection may be a reasonable approach.

4. MALIGNANT HEMATOLOGICAL DISEASES

4.1. Hodgkin Lymphoma

Hodgkin lymphoma (HL) incidence in Europe is 2.3 cases per 100 000 inhabitants per year [68]. The disease has a bimodal distribution with an increased incidence in young adults as well as in patients

with 55 years and older [69]. Factors shown to be associated with HL include familial factors, viral exposures, and immune suppression [69].

While familial factors may suggest a genetic cause for this disease, research also suggests that immune response to infection may play a role in the pathogenesis of HL [70-72]. It is known that after an episode of infectious mononucleosis, although small, there is a significantly increased risk of developing Epstein-Barr virus (EBV)-positive HL [70,73]. HIV infected patients also have a significantly increased risk of HL when compared to the general population [72]. In general, HL in immunocompromised patients, including those who are HIV positive, is associated with advanced stage HL at presentation, unusual sites of disease, and a poorer outcome after initial therapy [74,75]. However, some childhood infections, such as, chickenpox, measles, mumps, rubella, and pertussis, are in turn, possibly protective and negatively associated with the risk of HL [71].

Over the last decades, advances in radiation therapy and the addition of combination CT, have significantly increased the cure rate of HL patients, about 80% of all newly diagnosed patients younger than 60 years are likely to be cured of their disease [76].

4.1.1. Diagnosis and Staging

At the time of diagnosis, the majority of patients with HL present with supradiaphragmatic lymphadenopathy, commonly cervical, anterior mediastinal, supraclavicular, and axillary lymph node involvement [77,78]. Approximately 30% of patients with advanced disease present systemic symptoms like fever, night sweats, and weight loss [79].

The diagnosis of HL should be confirmed histologically. An excisional biopsy of the involved lymph node is preferred to establish a definitive diagnosis since the architecture of the lymph node is extremely important for an accurate diagnosis [80]. HL is a unique malignancy in that the tumor cells constitute the minority of the cellular population and an inadequate biopsy may fail to include characteristic malignant Reed-Sternberg cells, which are of follicular B-cell origin, within the appropriate cellular environment of normal reactive lymphocytes, eosinophils, and histiocytes [81,82].

HL is composed of two distinct disease entities; the more commonly diagnosed classical HL and the rare nodular lymphocyte predominant HL [83].

Staging is carried out according to the Ann Arbor classification in consideration of defined clinical risk factors. After completion of staging, patients are allocated to one of three categories (limited, intermediate and advanced stages) critical for the selection of the appropriate therapy [68].

Fluoro-deoxyglucose positive emission tomography (FDG-PET) scanning has emerged as an important tool in the staging of patients with HL in that it significantly adds to the information obtained using other standard radiographic methods [84-86].

4.2. Acute Myeloid Leukemia

AML is the most common acute type of leukemia in adults, with an European incidence of 5 to 8 cases per 100 000 individuals per year, increasing with age reaching 15 to 25 case per 100 000 inhabitants per year in the population aged over 70 years, with a median age at diagnosis of 68 years [87,88]. Several genetic and environmental risk factors have been identified that predispose individuals to the development of AML [89]. History of antecedent hematological disorders, including the myelodysplastic syndromes or myeloproliferative neoplasms, is also associated with a substantially increased likelihood of progression of AML [90,91].

AML is a malignant disorder of haemopoietic stem cells characterized by clonal expansion of abnormally differentiated blasts of myeloid lineage. Proliferation of the immature myeloid cells leads to accumulation of immature progenitors (blasts) with impairment of normal hematopoiesis, leading to severe infections, anemia, and hemorrhage [89].

Prompt diagnosis and initiation of AML directed therapy is imperative, especially when rapid proliferation of malignant blasts is accompanied by tumor lysis syndrome or disseminated intravascular coagulation, both of which can be rapidly fatal without aggressive supportive management and treatment of the underlying AML [92].

AML is characterized by several recurrent mutations that affect disease biology and phenotype, response to therapy, and risk of subsequent relapse [93]. Advances have been made in understanding the genomic diversity of AML and how these various mutations interact to affect disease phenotype, prognosis and serve as potential targets for AML directed therapies [94-96].

4.2.1. Diagnosis and Risk Stratification

A diagnosis of AML requires identification of 20% or more myeloid blasts with morphological assessment of the peripheral blood or bone marrow [97]. In addition, immunophenotyping by flow cytometry is used at the time of diagnosis to confirm the blast lineage and to help in further categorization of AML subtype [98]. The 2016 WHO update recognized AML subgroups defined by the presence of recurrent genetic alterations, including balanced translocations, gene fusions, or single molecular mutations [97]. Additional genomic testing for FMS-like tyrosine kinase 3 (FLT3), TP53, and additional Sex Combs-Like 1 (ASXL1) should also be done, considering their prognostic importance [99].

The outcome of AML is heterogeneous, with both patient-related and disease-related factors contributing to an individual probability of achieving response to therapy and overall survival [89].

5. FEBRILE NEUTROPENIA IN HODGKIN LYMPHOMA COMPARED WITH ACUTE MYELOID LEUKEMIA

The prevalence of hematologic malignancies has been increasing in developed countries, due to earlier diagnosis and improved treatment efficacy and patient care [100,101]. The treatment of hematologic malignancies is based on a wide range of therapeutic options: CT, small molecules, or antibodies, which are often associated with toxic side effects ranging from nausea and vomiting to diarrhea and mucositis and to life-threatening myelosuppression [102].

FN represents a life-threatening complication in hematological malignancies. Although its etiology is most often due to infections, FN of other origins, such as tumor-related fever and non-infectious inflammation, should be excluded [103]. CT-induced leukopenia stimulates endogenous cytokines, including interleukin-6 and tumor necrosis factor which can result in fever, even in the absence of infection [9].

Tumor-associated fever is common in both hematological and solid-tumor malignancies, including HL and non-HL, AML, soft-tissue sarcoma, and renal cell carcinoma [104,105].

Pel-Ebstein fever, is a non-infectious fever associated with HL and presents a cyclical pattern of several days of fever followed by afebrile episodes of 1 to 2 weeks [106]. Moreover, in presence of neutropenia, tumor-associated fever is commonly found in acute leukemias attributed to the general hypermetabolic condition caused by the disease [107]. No clinical features are consistently present to distinguish different causes of fever and therefore, tumor-associated fever is a diagnosis of exclusion [108-110].

The central concern in a patient with FN is the risk of infection [12] and the incidence of infections appears to be dependent on the type of hematological malignancy and on the employed CT regimen [111]. Congenital neutropenia studies also relate the duration and degree of neutropenia with the infection risk in patients with severe chronic neutropenia [112].

5.1. Neutropenia and Neutropenic Complications during Chemotherapy for Hodgkin Lymphoma

The introduction of multi-agent CT regimens have changed the outcome of HL. The BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) dose-intensive regimen, developed by the German Hodgkin's Lymphoma Study Group (GHSG), is used in some countries for advanced-stage HL [113-115]. Although having high efficacy, BEACOPP is a highly myelotoxic regimen, with a FN incidence of >20% and is associated with greater risk of development of secondary malignancies [116-121]. Therefore, it is reserved to young patients with a good performance status [122].

Combination therapy with doxorubicin (adriamycin), bleomycin, vinblastine and dacarbazine (ABVD) is, however, the standard CT regimen for patients with HL [123-125]. HL is exquisitely responsive to ABVD CT, which results in a high cure rate. In order to achieve maximum benefit from this CT, it is important to maintain optimal dose intensity. Severe neutropenia is a well-recognized complication of this regimen, which in theory could lead to an increased risk of morbidity and mortality from infectious complications [126]. For HL, retrospective data suggested that the incidence of FN with neutropenic sepsis, and death in patients receiving ABVD CT is low (<1%), although the proportion of patients with HL in these retrospective studies is small, and full details of the delivered CT were not described [126-129].

Available evidence suggested that, although severe neutropenia is a common occurrence with ABVD therapy, FN and other related infectious complications are rare in this context [118,120,123,130,131].

Myelosuppression, in particular neutropenia, is common during ABVD treatment [124] and the effect of ABVD-related neutropenia and neutropenic complications on CT delivery in patients with HL, are poorly documented [124,126].

In 2010, Schwenkglenks and colleagues presented a subgroup analysis of HL patients, to assess the effects of neutropenic complications on the delivery of ABVD CT. Infection was considered as FN when ANC was <1000 cells/μL in combination with fever above 38°C. The authors also characterized the incidence of CIN and FN in patients with HL undergoing ABVD. The results showed that CIN was substantial, with an incidence of 32% and 43% for an ANC <1000 cells/μL and <500 cells/μL, respectively. FN incidence in this small sample size was 11%, with 9% of HL patients experiencing FN in the first cycle of ABVD CT. Despite the low rate of FN, treatment dose delays and dose reductions were frequent, resulting in suboptimal delivery of CT in approximately one fifth of patients with afebrile CIN. Use of primary G-CSF prophylaxis appeared to reduce CT-induced neutropenia rates [132].

In several randomized controlled trials including HL patients treated with ABVD and BEACOPP, the incidence of severe neutropenic events, including overall risk of FN has been assessed [117,118,120,133-135]. Overall, these studies show a high rate of severe neutropenia (35%) induced by ABVD regimens with a FN median incidence of only 7%. This data suggests a low correlation between the level of neutropenia and the risk of infection in ABVD treated patients.

Patients can safely proceed with ABVD CT in the presence of severe neutropenia, without other therapeutic interventions. Several ongoing multicenter and international trials in HL currently utilize full-dose ABVD without modifications for neutropenia. These prospective trials should confirm or refute the findings of the retrospective analyses described above [126,127,129].

In order to balance conflicting priorities of maintaining dose intensity while preventing neutropenia-related complications, physicians use different strategies, such as dose modifications, G-CSF support and antibiotic prophylaxis [136].

Some of the greatest evidence of antimicrobial prophylaxis for lymphoma patients was the SIGNIFICANT trial, reported in 2005, on the use of levofloxacin in patients receiving CT [137]. In 1565 patients included in the study, the risk of fever, probable infections, the incidence of severe infections and hospitalization were all reduced in group treated with levofloxacin compared to one with placebo. However, there was no difference in infection-related deaths between the two groups [137].

In 2012, a meta-analysis including trials which assessed patients with solid cancer or lymphoma, reported that quinolone antibiotics prophylaxis resulted in a significant decrease in febrile episodes, clinically documented infection, microbiologically documented infection, bacteremia and mortality rates. However, most trials in this meta-analysis included mainly high-risk hematological patients, with a smaller group of patients with lymphoma [138].

In a recent retrospective analysis including exclusively lymphoma patients, there was no significant difference in the total incidence of infection episodes, FN or clinically documented infection, with antibiotic prophylaxis compared to patients without prophylaxis [139]. The same result was found in the two subtypes of lymphoma of non-HL and HL. To our knowledge, this was the first study addressing only lymphoma patients on this topic. Altogether, it is assumed that there is no role for routine administration of prophylactic antibiotics with ABVD CT, and this recent study results support this conviction [136,139].

Recently, an editorial in the New England Journal of Medicine, by Longo and colleagues, brings to discussion the progress in the treatment of HL in what it concerns the value of bleomycin as a component of ABVD regimen [140]. The authors argue, based on several clinical studies, that bleomycin acute and chronic pulmonary toxicity may be the culprit for persistent decreased in overall survival in patients with HL that were not cured with the primary treatment approach [133,141-144]. It is also discussed how the incorporation of new active agents into frontline therapy, such as the anti-CD30 immunotoxin brentuximab-vedotin or the programmed death 1–inhibitor nivolumab, may be promising in the treatment for advanced stage HL [141,144]. Other investigators randomly assigned patients to receive ABVD and patients to receive AVD plus brentuximab-vedotin (A+AVD) and found that progression-free survival rate was significantly increased in the A+AVD group [133]. Neutropenia was higher in the A+AVD group, but successfully addressed by incorporating prophylaxis with G-CSF between doses. Mortality in the A+AVD group was attributed to treatment myelotoxicity, as compared ABVD group, which was associated with pulmonary toxicity. In ABVD treatment although neutropenia is frequent (38%), FN rate is only of 8% and does not justify

treatment alterations [133]. In A+AVD, by probable contribution of brentuximab-vedotin, there are higher rates of both neutropenia and FN, which justifies prophylatic G-CSF [140]. It would be interesting to further investigate why ABVD-induced neutropenia is less susceptible to infection than A+AVD. Moreover, the perception that neutropenia justifies ABVD treatment modifications, such as dose reductions or treatment delays, is not demonstrated in current literature.

Despite treatment advances in younger patients with HL, the treatment of elderly HL patients , which constitute 20-30% of all patients diagnosed with HL, remains challenging [145].

Improvement in outcomes in elderly patients have not occurred at the same rate as in younger patients [146]. It is known that elderly HL patients have a biologically more aggressive disease that might not respond well to treatment [147]. Unlike younger patients, elderly HL patients experience higher rates of treatment toxicity and more frequently have early relapses [148]. The inferior outcome in this older-aged group depends on the presence of co-morbidities, which decrease tolerance to CT and predispose to serious toxicity [149]. In addition, myelosuppression increases with age and risk of neutropenia is increased in elderly patients receiving CT which may cause physicians to abstain from treatment and thus preclude the possibility of cure [150].

The substantial contribution of age to therapeutic outcomes is such that several studies have investigated the effects of CT in the elderly population with HL [122,151]. Management of neutropenia have specific recommendations regarding the elderly population [35,150].

The CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) regimen was applied in advanced stage elderly patients, and although found to be effective in a small number of patients, FN was the most common toxicity (31%), but only limited conclusions on efficacy and toxicity can be drawn because of the small number of patients in this trial [148].

In a study comparing efficacy and tolerability of ABVD and Stanford V in older HL patients, the rate of severe neutropenia in patients treated with ABVD or the Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone) was 64% in those older than 60 years and 38% in younger patients [152]. No other significant differences in hematological or non-hematological adverse events were seen between the two CT regimens for older HL patients.

The trial combining A+AVD in patients with advanced stage HL [133] included elderly patients up to 83 years of age and A+AVD resulted in more hospitalizations and higher toxicity compared with ABVD. Older patients were particularly prone to FN (37%), in line with previous reports suggesting that increased treatment intensity results in increased toxicity in older patients. In addition to the risk of infection and fever in elderly HL patients, neutropenia can also increase the risk for hospitalizations and contribute to nosocomial infection-associated mortality [13].

Importantly, most of the studies mentioned above are do not mention consistently how infection documentation was performed, if there was isolation of any infectious-agent in microbiology specimens and even if there has been any imagological documentation for pneumonia or infection.

5.2. Neutropenia and Neutropenic Complications in Acute Myeloid Leukemia Treatment

Bacterial and fungal infections are one of the major causes of morbidity and mortality in patients with AML during induction CT [153]. They may cause not only an increased risk of death, but also an increased risk of leukemia relapse due to CT delays [154].

Treatment for AML is classically divided into remission induction and post-remission consolidation therapy. Standard remission induction regimens include 3 days of infusional anthracycline and 7 days of cytarabine, commonly known as the "3+7" regimen [88]. This therapeutic strategy for AML treatment has not changed significantly in more than 30 years [155,156]. The question of whether intensification of the anthracycline dose, for remission induction therapy, might improve survival in patients with AML was addressed by a phase 3 randomized study conducted by Eastern Cooperative Oncology Group (ECOG) [157]. Standard anthracycline dose (45 mg/m^2 of body-surface area) was compared with two times the same dose (90 mg/m^2 of body-surface area), resulting in a higher rate of complete remission and improved overall survival in the high-dose anthracycline treated group. The rate of serious adverse events was similar between the two groups, namely, neutropenia, infection and FN [157].

Hematopoietic growth factors are an optional adjunct to intensive induction therapy [88]. However, evidence on their role in reducing the incidence or severity of infectious complications during bone marrow aplasia, and on their benefit through priming of leukemic cells to increase sensitivity to cytostatic agents, is not consensual [155,158-163].

Remission induction regimen is an intensive cytotoxic therapy that can cause severe, prolonged or profound neutropenia with serious life-threatening infections, requiring the use of prophylactic antibacterial, antiviral, and antifungal agents in high-risk AML patients [21,164,165]. Antimicrobial prophylaxis during remission induction CT in AML is a recommended starting point for managing these patients and relies on risk stratification according to clinical signs and symptoms, anticipated duration of neutropenia, and comorbidities [21,166,167]. Whether this approach should be applied to all leukemic patients who receive induction CT has been a subject of controversy. Several clinical trials have shown that fluoroquinolone prophylaxis decreases infection-related all-cause mortality and morbidity and reduces the risk for all-cause clinically

documented and microbiologically documented bacterial infections in adult patients with AML who receive remission induction CT [31,138,166,168,169]. However, the emergence of antimicrobial resistance associated with continuous use of fluoroquinolone prophylaxis, reduces both prophylaxis and treatment efficacy in neutropenic patients [21,170]. Considering the risks and benefits, international guidelines suggest consideration of fluoroquinolone prophylaxis for neutropenic patients receiving induction CT for AML at high risk for profound prolonged neutropenia [24,35,171]. Very high-risk AML patients are those with refractory or relapsed disease, previously submitted to several CT regimens and HSCT recipients [21,88].

In order to reduce selective pressure for antimicrobial resistance and drug-drug interactions with antineoplastic agents, it has been recommended initiating prophylaxis after completion of CT, although, the optimal timing for initiating and discontinuing antibacterial prophylaxis as the duration of appropriate prophylactic treatment, have not been determined [171].

Once hematological remission has been achieved, further consolidation therapy in AML treatment is required to prevent relapse. Options include repeated courses of consolidation CT followed by allogeneic HSCT for patients with intermediate and high-risk disease [88,172]. Although HSCT is the only curative treatment for high-risk AML, the lack of an appropriate Human Leukocyte Antigen (HLA) donor and advanced age and comorbidities turn many patients ineligible for this strategy [173,174].

Recent concerns regarding antimicrobial prophylaxis include increased risk of *Clostridium difficile* colitis, antimicrobial toxicities, and the potential for fostering multidrug-resistant pathogens. These emerging concerns coupled with the relatively shorter duration of neutropenia for AML patients with consolidative CT raise the question whether antimicrobial prophylaxis in this setting is necessary. A retrospective study was performed in patients who received high dose cytarabine consolidation therapy (HiDAC) [175]. The primary endpoint of this study was the incidence of FN, while secondary endpoints consisted of hospitalizations for any cause as well as incidence of bacteremia, invasive fungal infection, *Clostridium difficile* colitis, and death from infection. Antimicrobial prophylaxis during consolidation CT with HiDAC did not reduce the incidence of FN frequency or hospitalizations. Additionally, there was no difference in the rates of bacteremia, *Clostridium difficile* colitis, or invasive fungal infections between the two groups. AML prophylactic antimicrobials may not be necessary for all patients consolidated with HiDAC due to a potentially shorter course of neutropenia when compared to patients with AML undergoing induction CT, especially younger AML patients [175].

Development of immunotherapeutic agents and molecular targeted therapies have changed the antineoplastic therapy in hematology, with impact on both innate and adaptive immunity. Recent efforts have focused on adding therapies targeting molecular mutations to

traditional induction therapy, such as FLT3 inhibitors, kinase inhibitors, and agents blocking overexpressing multidrug resistance genes [172,176]. Combination of intensively pretreated patients with different treatment modalities may be associated with potentially serious infections [177].

As autoimmune inflammatory reactions are typical adverse events occurring in several of these patients, immunosuppressive treatment will often be required, that can cause secondary infections. Therefore, differential diagnostic efforts are important to distinguish inflammatory reactions from infections and recommendations for routine antimicrobial prophylaxis should be avoided [178-182].

Abnormal DNA methylation plays a critical role in the impairment of differentiation of myeloid cells in AML [183,184]. With the breakthrough of molecular biology research on the characteristics and pathogenesis of AML, hypomethylating agents (HMA) have become beneficial for its treatment. Two HMA, azacitidine and decitabine, have been approved by the USA Food and Drug Administration (FDA) for treating AML, and previous clinical trials have shown that the efficacy of demethylation therapy is superior to conventional care regimens [185-191]. Decitabine as a reduced-intensity therapy for older or unfit patients with AML, has few precise data available on the incidence and characteristics of bacterial, fungal, and viral infections in AML [41,192]. The risk of infection with decitabine treatment was addressed in a recent retrospective study, where infection-related serious adverse events were identified in AML [193]. In patients receiving 10-day cycles of decitabine infectious complications were common (30%) and may occur during any cycle of therapy. Although frequently culture-negative, febrile events in decitabine treatment are more often associated with infections caused by Gram-positive bacteria, while those caused by Gram-negative bacteria represent a significant risk of mortality [193]. High concentrations of decitabine inhibit DNA synthesis and induce cell death, and their clinical application is largely limited by its inherent cytotoxicity. Nevertheless, low-dose of decitabine has the demethylation effect rather than cytotoxic effect, which makes it feasible to reduce myelosuppression by decreasing the dosage [194,195]. Kantarjian and colleagues found that serious adverse events were experienced by nearly 70% of decitabine patients due to myelosuppression-related side effects [187]. Similarly, another study showed that FN was present in 25% of patients receiving decitabine compared with 7% of patients receiving best supportive care [189].

In clinical practice, bone marrow suppression is the most common adverse reaction in demethylation therapy and the main reason for the dose-reduction or discontinuations of this therapeutic regimen. Therefore, the purpose of a recent meta-analysis was to fully assess the incidence and relative risk of the hematologic toxicity effects associated with HMA [196]. For the analysis of high-grade hematologic toxicity effects, the incidence of anemia, neutropenia, thrombocytopenia, and FN was 27%, 45%, 38%, and 25%, respectively. This meta-analysis also

demonstrated that the relative risk of high-grade anemia, leukopenia, and FN in comparison with conventional care regimens did not significantly increase among patients receiving HMA [196]. These findings can provide strong evidence for clinicians when assessing the risk-benefit balance of HMA in clinical practice.

5.2.1. Invasive Fungal Disease

Patients with AML treated with myelosuppressive CT, like cytarabine and anthracycline, are in risk for developing IFD, namely due to prolonged and profound neutropenia and monocytopenia, use of purine analogues (fludarabine), the presence of indwelling intravenous catheters, gastrointestinal mucositis and individual genetic predispositions [197]. Additionally, pre-admission factors in AML patients may increase IFD risk, like Chronic Obstructive Pulmonary Disease (COPD), professional exposure to fungal pathogens, influenza H1N1 infection and a lack of response to remission induction CT [198,199]. Fungal infections occur in 5% to 40% of patients with hematologic malignancies and are most common in AML [200].

With the increasing use of intensive immunosuppressive cancer therapies, IFD became more frequent and is a leading cause of morbidity and mortality, also attributed to the diagnostic difficulties of fungal infection and delayed treatment initiation. Limited activity of antifungal agents, their side effects, and increasing use of corticosteroids, further facilitates fungal dissemination [201].

Aspergillus and *Candida* species (spp) currently account for 95% of all cases, but the epidemiological characteristics of IFD evolve under the selection pressure of antimicrobials and other factors [202,203]. *Aspergillus* has become the dominant species in Europe with the incidence of invasive aspergillosis in AML ranging from 5% to 24%, while rates of candidaemia are 2% [204]. In a multicenter study, the overall rate of proven and probable aspergillosis in patients with AML receiving remission induction CT was 8.1% [205]. Although significant variation in the incidence rate was noted between participating centers, preventative measures such as a primary antifungal chemoprophylaxis has been recommended, but not all treating centers adopt it [205-208]. Epidemiological surveys have reported much lower incidences (0%–5%) of IFD during consolidation CT than has been reported during the remission induction phase, though the intensity of consolidation regimen may impact on this risk [209]. In general, primary antifungal prophylaxis is not recommended beyond remission induction CT, unless patients are to undergo re-induction CT or intensified consolidation therapy [206].

Diagnosis of IFD is challenging and hampered by the relatively low sensitivity and specificity of the standard diagnostic procedures, as well as a low yield of the microbiological and histopathological tests [210-212]. In the absence of a known pathogen, surrogate markers for IFD such

as persistent fever, computed tomography, fungal polymerase chain reaction, or serological assays, and local epidemiological data should guide treatment decisions [213].

The most frequent mortality etiologies of acute respiratory failure (ARF) in hematological malignancies are bacterial infections, viral or opportunistic infections, followed by disease-related infiltrates and cardiogenic pulmonary edema [214]. Regarding AML, recent studies described autopsy findings concerning the cause of death and lung pathology in patients with ARF between 2003 and 2018 [215]. The study showed that in more than 50% of cases, major clinical diagnoses were missed. Lung malignant infiltration was frequently found (20%) accounting for most of the causes of death. Bacterial pneumonias and less often fungal pneumonias (10%) were also observed, proven to be less frequent than what has been previously described (24%) [204]. However in about a third of cases of ARF without identified cause, pulmonary edema or alveolar damage were the only findings. Fungal infections reported in this study have shown that patients with ARF and fungal pneumonia were not receiving antifungals at the time of death [215].

Primary antifungal prophylaxis during curative-intent therapy for AML has been continuously reviewed. Considering that no single agent will prevent all IFD, careful monitoring during the period of risk is essential with treatment of emergent fungal infections. Although prevention of IFD during neutropenia in AML induction therapy reduces morbidity and mortality, and shortens hospital stay, special considerations should be taken like considering drug toxicities, selection for resistant pathogens, adverse drug-drug interactions, and costs [200,203,206,216-218].

Despite recent advances in the field of hematologic malignancies, such as non-invasive bio-markers for early diagnosis, radiographic screening and the widespread use of novel antifungal drugs, IFD remains a major cause of morbidity and mortality in patients with AML [219].

5.3. Final Considerations

AML is an acute, rapidly evolving, and potentially fatal disease, whose prompt treatment with standard “3+7” CT regimen (anthracycline, cytarabine), is the only option to offer to these patients in the hope to achieve remission. This treatment has a well-recognized associated toxicity, with high incidence of FN. The potential risk of fatal infection associated with AML induction CT is, however, justified given the high risk of mortality associated with loss of disease control. Having AML as the FN paradigm, HL appears in this review as an example of a more indolent disease, presenting mostly in young patients, with a high cure rate when treated with ABVD combination CT. As mentioned above, ABVD is associated with high rates of severe neutropenia, but with a less clear subsequent associated infectious risk. The high neutropenia risk associated with ABVD may be related with both treatment delay and dose reduction which can compromise treatment efficacy in a disease with high curative intent. Some relevant aspects for the understanding of infection risk

in HL patients treated with ABVD, such as grade of neutropenia, duration of severe neutropenia and patient's age, are not well characterized in the literature. In fact, data from HL clinical studies demonstrate the difficulties in obtaining a thorough evaluation of neutropenia risk in some CT regimens, due to inconsistencies in reporting and documenting severe neutropenia, FN and febrile infection (neutropenic or non-neutropenic) [117,121,220]. This lack of uniform information is particularly important in ABVD CT regimens considering the urgent need to withdraw conclusions in how to weight the timing of a high-curative CT regiment and its proven infection risk in HL.

With this study we want to emphasize and bring to reflection the hypothesis of how HL patients may be having an overdefensive clinical approach, with CT dose reductions and delays in the presence of neutropenia, that in turn can compromise the cure of HL. Having AML CT-induced neutropenia and infectious risk as paradigm, and yet, not so solid and robust evidence for HL treatment-induced FN, the risk of infection in ABVD CT may be clinically overestimated.

6. CONCLUSIONS

FN is a medical emergency with high mortality without an appropriate treatment. It is imperative to assess the risk for serious complications in neutropenic patients to decide the use of prophylaxis and an antimicrobial therapy and the need for inpatient admission. High-risk patients with FN are those who are expected to be neutropenic (ANC <500 cells/µL) for more than 7 days and those with comorbidities. Those patients should be admitted.

An important advance in the management of FN has been the stratification of the patients with FN for the risk of complications and death, using validated predictive instruments, such as the MASCC score to identify low-risk patients who can benefit from simplified and less expensive therapeutic approaches. Although the MASCC scoring index has been widely accepted, there is still room for improving its effectiveness, especially for FN in patients with hematological malignancies [25].

AML is an acute disease with a high mortality rate. Although its treatment is associated with severe risk of FN and infections, the risk and benefit evaluation favor a prompt initiation of the CT treatment and FN prophylaxis for a better survival of these patients. Moreover, since AML-treated patients are expected to have prolonged severe neutropenia, in this context, IFD should be prevented with antifungal prophylaxis in remission induction CT. Early diagnosis and appropriate treatment of serious infections in neutropenic patients is important, although lack of accurate clinical and microbiological data in these patients constitute major problems in the diagnostic approach.

HL is a more indolent disease and commonly treated with neutropenia inducingCT regimens, such as ABVD, with a curative rate >80%. Therefore, therapeutic intervention with CT should not be compromised with dose delays or dose reductions in ABVD treatment. Although there are no well-designed studies addressing the risk of infection in CIN in HL, the studies demonstrate that CT dose delays or dose reductions with ABVD are not recommended only on a basis of ANC, contrarily to the majority of CT treatment regimens. Treatment modification are required in A+AVD, considering its high FN association and G-CSF prophylaxis, and in bleomycin containing regimens, especially due to its acute and sometimes lethal, pulmonary toxicity, and not due to infection in particular.

Although not universally used, it appears that the greatest benefit of BEACOPP CT in the progression-free survival is among the highest-risk patients. However, this comes at the cost of increased toxicity with no clear improvement in patients overall-survival when compared with ABVD alone. Moreover, BEACOPP is associated with significantly more severe hematologic toxicity, infections, and occurrence of myelodysplastic syndrome and AML [120,121].

Prophylactic measures have been shown to be effective in CT-induced FN. Unfortunately, the balance between their cost and wide benefit in FN management led to restrictive algorithms and guidelines for their use. It is highly desirable that future research focuses on the definition of subset of patients who could benefit from FN prophylaxis, taking into account the type of CT regimen, patient clinical and laboratorial stability and also comorbid conditions [25].

Efforts in developing a more accurate and individualized approach in FN diagnosis and treatment should upraise against the development of microbial resistance, secondary infections, increased toxicity and hospitalization costs. To this end, each center should closely monitor its own causes of infection, antibiotic protocols and disease-specific CIN risk of infection [221]. Susceptibility to infection in CIN could also profit on better understanding neutropenia daily evolution and characterizing, both morphological and functionally, the remaining neutrophils in these patients.

As ECIL recently reviewed, a good balance between scientific rigor and clinical pragmatism reflects that guidelines are intended to deal with commonly anticipated risks to patient populations rather than being a recipe suited to each individual case [206].

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