Artigo tipo “Case Report”

MYELODYSPLASTIC SYNDROMES - THERAPEUTIC OPTIONS IN HIGH-RISK PATIENTS

Diogo Alcino de Abreu Ribeiro Carvalho Machado

Orientadora: Maria Alexandra dos Santos Mota da Silva

Mestrado Integrado em Medicina

Instituto de Ciências Biomédicas de Abel Salazar – Universidade do Porto

2009 / 2010

SÍNDROMES MIELODISPLÁSICOS – OPÇÕES TERAPÊUTICAS EM DOENTES DE ALTO RISCO

Diogo Machado

Serviço de Hematologia Clínica do Hospital de Santo António – Centro Hospitalar do Porto, Portugal

RESUMO ALARGADO

Introdução

Os Síndromes Mielodisplásicos consistem num grupo heterogéneo de distúrbios clonais das células hematopoiéticas, caracterizados por citopenias periféricas e por um risco variável de progressão para leucemia mielóide aguda. Apesar da leucemia mielóide aguda ser a causa de morte mais importante, muitos doentes acabam por falecer devido a complicações das citopenias, em especial por hemorragia ou infecção. Os Síndromes Mielodisplásicos afectam sobretudo a população acima dos 70 anos. Nos últimos tempos observaram-se grandes avanços na caracterização da natureza da doença, considerando aspectos clínicos, biológicos e genéticos. O tratamento desta doença evoluiu nos últimos anos com o uso generalizado dos factores de crescimento e com o aparecimento de novos fármacos (imunomoduladores e agentes hipometilantes). No entanto, o transplante alogénico de células progenitoras hematopoiéticas continua a representar a única hipótese de cura.

Descrição do caso

É apresentado o caso de um doente de 48 anos que recorreu ao Serviço de Hematologia com sintomas de anemia. Foi feito o diagnóstico de Síndrome Mielodisplásico classificado como anemia refractária com excesso de blastos tipo 2, de alto risco segundo o International Prognostic Scoring System. O transplante alogénico de células progenitoras hematopoiéticas foi proposto, no entanto não foi atingida a remissão, acabando o doente por falecer como resultado da progressão da doença apesar dos diferentes tratamentos com quimioterapia e suporte.

Discussão e conclusão

A descrição deste caso permite uma abordagem global dos Síndromes Mielodisplásticos, permitindo a compreensão da evolução da doença e das diferentes hipóteses de tratamento, sobretudo nos pacientes de alto risco, não esquecendo os recentes avanços e perspectivas futuras em relação a esta doença, à qual há cerca de dez anos pouco se teria a oferecer além de suporte transfusional.

MYELODYSPLASTIC SYNDROMES - THERAPEUTIC OPTIONS IN HIGH-RISK PATIENTS

Diogo Machado

Serviço de Hematologia Clínica do Hospital de Santo António – Centro Hospitalar do Porto, Portugal

Myelodysplastic Syndromes are a heterogeneous clonal stem cell disorders, characterized by ineffective hematopoiesis and a tendency to progress to acute myeloid leukemia. This case describes a patient who came to our Department of Hematology with symptoms of anemia and as result of our study we diagnosed a Myelodysplastic Syndrome, classified as refractory anemia with excess of blasts-2, high-risk according to International Prognostic Score System. While describing the case, different treatment options were approached.

Key words: Myelodysplastic Syndromes, anemia, blasts, cytogenetics, high-risk, IPSS, treatment

Introduction

Myelodysplastic Syndromes (MDS) are a heterogeneous clonal stem cell disorders, characterized by ineffective hematopoiesis and a tendency to progress to acute myeloid leukemia (AML).[1, 2] Although AML is the most important cause of death, several die from complications of cytopenias, especially hemorrhage or infection.

The median age of diagnosis is 70-75 years old. In a study involving the population of Dusseldorf (Germany),[3] the annual incidence was 4.9 per 100 000 (5.52 in males and 4.36 in females). Age specific incidence was 8.7, 24.5, and 31.3 per 100 000 for the age groups 60-70, 71-80, and 80-90 years, respectively. Incidence of MDS in the age group older than 70 years was significantly higher among males (42.3 per 100 000) than among females (19.0 per 100 000). There was no evidence that age-adjusted incidence of MDS was rising.[3] A study in Orense (Spain) showed similar results.[4] Data from Surveillance, Epidemiology, and End Results, and North American Association of Cancer Registries show that the annual incidence of MDS increases with age (p<0.05) from 0.14 per 100 000 in patients less than 40 years old to 34.49 per 100 000 in patients more than 80 years old, and age-adjusted incidence of MDS was significantly higher among males (4.4 per 100 000) than females (2.5 per 100 000; p <0.05), with no significant differences observed by race.[5]

For the great majority of patients with MDS, no causative factor can be identified.[6] Several etiologies have been proposed, including bone marrow aging process, based on the fact that the median age of presentation is more than 70 years old. Genetic factors have also been included in the possible etiologies. Several occupational factors and substances that might be risk factors for MDS have been studied. Secondary MDS is a term used to emphasize that MDS results from exposure to mutagens,[7] which can be a consequence of therapy (therapy related MDS (t-MDS)). There is a well-recognized association between cytotoxic drug therapy or radiotherapy and t-MDS and t-AML. Prior chemotherapy exposure is associated with at least 100-fold increased risk for developing MDS[8] and has been described following therapy of malignancies (e.g.

Hodgkin's disease, non-Hodgkin lymphomas, multiple myeloma), including autologous transplantation.[9-11]

The latency of onset of *de novo* MDS is unknown,[6] however investigations of *de novo* MDS cases show that in the 2-3 years prior to the diagnosis there is a probable acceleration in the rate of decrease in blood count.[12] In the MDS exposure related cases, the latency period ranges 1-10 years when the exposure is to alkylator cytotoxic drugs, and 1-41 years if it's radiation exposure.

The diagnosis of MDS is based on the presence of dysplasia within single or multiple lineages.[13] Therefore, the definitive diagnosis is made from morphologic features in peripheral blood and bone marrow. The progressive hematopoietic failure leading to anemia, thrombocytopenia, and leucopenia, either alone or in any combination, is the dominant finding in MDS. Anemia is the most frequent peripheral blood abnormality[6] and more than 80% of patients present with a hemoglobin concentration below 10 g/dl[7] with a low reticulocyte count. Peripheral blood leukocyte count is low in about 25-30% of individuals with MDS.[7] Significant neutropenia (<1.5x10^9 cells/L) is evident at presentation in less than 50% of patients.[6] Neutrophils are often morphologically dysplastic, with nuclear hypolobulation and hyposegmentation. Thrombocytopenia is another common peripheral blood abnormality. Blast cells are often identified in peripheral blood, especially in more advanced MDS. Recurrent infections occur in one third of the individuals, as a result of not only the neutropenia but also from the defects in neutrophil function. Less than 10% of patients will present initially with serious bleeding.

In 1982, the French-American-British Cooperative Group (FAB) classified five subentities of MDS[14](Table 1): refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess of blasts (RAEB), refractory anemia with excess of blasts in transformation (RAEB-t), and chronic myelomonocytic leukemia (CMML). This classification was based on the proportion of myeloblasts and the degree of dysplasia, was easy to apply, and had good reliability between investigators.[15] The five different subentities had also prognostic significance, with a median survival of 50 months in the more favorable RA and RARS subentities compared with less than 12 months in the other FAB subentities.

Later, in 2001, this morphologic classification was revised, resulting in the World Health Organization (WHO) classification.[16] There are a number of key differences to the FAB system. The eight subtypes of WHO classification were: refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory cytopenia with multilineage dysplasia

Table 1. FAB Classification of the MDS.

FAB subtype	% of Peripheral blasts	% of Bone marrow blasts
RA	< 1	<5
RARS	< 1	<5
RAEB	< 5	5 – 20
RAEB-t	≥ 5	21 – 30
CMML (>1x10^9/L monocytes in blood)	< 5	5 – 20

Adapted from Bennett et al., 1982[14]

(RCMD), refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD/RS), refractory anemia with excess of blasts-1 (RAEB-I), refractory anemia with excess of blasts-2 (RAEB-II), MDS unclassified (MDS-U), and MDS associated with isolated del(5q). The key differences were the introduction of cytogenetics as an important prognostic and diagnostic marker; previous RA with dysplasia in at least two cell lines belonged to the new RCMD; RAEB was split in two subtypes based on marrow blast count, as this has been shown to have prognostic significance; RAEB-t subentity was abolished; del(5q) was defined as a distinct entity; CMML moved to the MDS/myeloproliferative syndromes group; AML was diagnosed when bone marrow blast count was higher than 20%; and all the patients with unilineage dysplasia who did not fit into the other subtypes were MDS-U.[6] In 2008, the WHO classification was revised (Table 2).[17] Several changes were made, including the diagnosis of Presumptive MDS when persistent clinical cytopenias without dysplasia are present with certain cytogenetic abnormalities. The refractory cytopenia with unilineage dysplasia (RCUD) includes cases where dysplasia is demonstrated in 10% of one cell line. Refractory anemia, refractory neutropenia (RN) and refractory thrombocytopenia (RT) are included in this category. RAEB-I includes 5-9% bone marrow blasts and <5% peripheral blood blasts with no Auer rods present, while RAEB-II includes 10-19% bone marrow blasts and 5-19% peripheral blood blasts with or without Auer rods presence. Patients with unilineage erythroid dysplasia, isolated del(5q), and less than 5% blasts are now in the category of MDS associated with del(5q). The MDS-U includes patients with pancytopenia and unilineage dysplasia; patients with no overt dysplasia but cytogenetic evidence of MDS; and RCUD and RCMD where bone marrow blasts are less than 5%.

Although the FAB classification provided some prognostic guidance, there was a needed for more refined tools. So, after years of different proposals, in the mild 1990s an international group was convinced to attempt to amalgamate the data from seven working groups. The fruit of their labor is the International Prognostic Scoring System (IPSS) (Table 3), [18] which remains the most widely accepted prognostic system currently available. The prognosis is

Table 2. 2008 WHO classification of MDS

Subtype	Blood	Bone marrow
RCUD	Single or bicytopenia	Dysplasia in ≥ 10% of one cell line, <5% blasts
RARS	Anemia, no blasts	≥ 15% of erythroid precursors with ringed sideroblasts, erythroid dysplasia only, <5% blasts
RCMD	Cytopenia(s), < $1x10^9$/L monocytes	Dysplasia in ≥ 10% of cells in ≥2 hematopoietic lineages, ±15% ringed sideroblasts
RAEB-I	Cytopenia(s), ≤ 2-4% blasts, <$1x10^9$/L monocytes	Unilineage or multilineage dysplasia, no Auer rods, 5-9% blasts
RAEB-II	Cytopenia(s), ≤ 5-19% blasts, <$1x10^9$/L monocytes	Unilineage or multilineage dysplasia, Auer rods ±, 10-19% blasts
MDS-U	Cytopenias	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, < 5% blasts
MDS associated with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del(5q), <5% blasts

Adapted from Swerdlow and International Agency for Research on Cancer, 2008[17]

calculated from three parameters at the diagnosis: number of cytopenias, bone marrow blast percentage, and karyotype. The IPSS provides a valuable working tool to initiate discussions with patients about their management in the context of their expectations and goals; however, each IPSS category has a large confidence interval for overall survival (Table 4).[6] The cytogenetic changes found in MDS are not unique to the disease, and both structural and numerical cytogenetic changes can occur.[19, 20] The incidence of chromosomal abnormalities is about 20-50% in primary MDS. The deletions of chromosomes 5, 7, 11, 12 and 20, and trisomy 8 are the most frequent chromosomal abnormalities in MDS, while translocations are rare.[7] A novel prognostic system, the WHO classification–based Prognostic Scoring System (WPSS), has been supported by recent data, and is derived from the WHO classification, transfusion need, and karyotype.[21]

International recommendations are based on the fact that on patients with IPSS categories of low risk and intermediate-1 risk (low-risk MDS) experience longer survival and limited risk of AML, and therefore, the main purpose of the treatment is the correction of cytopenias, notably anemia, whereas in intermediate-2 risk and high-risk patients (high-risk MDS) AML transformation is frequent, and the immediate priority is to extend survival and suppression of leukemogenic potential.[22] The treatment can also be oriented from biology, this way we can divide the drugs in six different categories (Table 5).

In low and intermediate-1 IPSS risk, supportive treatment remains the primary management for most of patients, which includes transfusions of red blood cells (RBC), platelets, and the use of hematopoietic cytokines. In order to avoid iron overload (especially when transfusion burden exceeds 30 units), iron chelators like desferrioxamine or defirasirox can be used.[23] Iron chelation remains controversial; although increased ferritin is associated with inferior survival, is not clear that reduction in ferritin leads to improved survival.[24] Guidelines from the National Comprehensive Cancer Network recommend considering iron chelation in patients who have received more than 20-30 units of RBC transfusions.

Erythropoiesis-stimulating agents (ESAs), alone or combined with granulocyte colony stimulating factor (G-CSF) correct anemia in about 60% of low-risk patients, with an average response duration of two years.[25, 26] Prognostic factors for ESAs' response are low endogenous erythropoietin level (<500 U/L) and relatively low RBC transfusion requirements. Although not formally

Table 3. IPSS Classification Criteria

	Score				
Prognostic variable	0	0.5	1.0	1.5	2.0
Bone marrow blasts	< 5%	5-10%	-	11-20%	21-30%
Karyotype*	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

IPSS Scores as for risk group as follows: Low = 0; Intermediate-1 = 0.5-1.0; Intermediate-2 = 1.5-2.0; High ≥ 2.5
*Good = normal, -Y, del(5q), del(20q); poor = complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate = other abnormalities.
Adapted from Greenberg et al., 1997[18]

approved by Food and Drug Administration (FDA) or European Medicines Agency in this indication, ESAs may be considered as the first-line treatment of anemia in low-risk MDS with favorable prognostic factors for ESAs response, with the exception of low-risk MDS with del(5q), where lenalidomide yields erythroid response in 76% of cases and 73% cytogenetic responses.[27]

Recombinant myeloid growth factors, granulocyte macrophage colony-stimulating factor (GM-CSF) and G-CSF, restore granulocyte production in 75 to 90% of neutropenic patients,[28] however, due to their cost and necessity for continuous administration, they are used only in the management of neutropenic patients with intercurrent infection.

Two agents, antilymphocyte serotherapy and Ciclosporine-A, which target the ineffective erythropoiesis, offer high response rates in selected candidates with low-risk disease.[29, 30] Nevertheless the inexistence of randomized comparative trials, some series suggest that erythropoietic response is associated with longer survival and time to disease progression compared to nonresponders.[31] Ages lower than 60 years old, followed by shorter duration of red cell transfusion dependence and expression of HLA-DR15 allele, have shown the greatest predictive power to respond to immunosuppressive therapy in multivariate analysis.[32] On the other hand, unselected patients have shown a low-rate response, with significant treatment-associated morbidity.[33] Lenalidomide, a potent 4-amino glutarimide, was approved by the FDA in 2005 for the treatment of transfusion-dependent patients with low-risk MDS and chromosome 5q deletion.[27]

As for intermediate-2 and high-risk IPSS, since the management of these patients has greater urgency, the goal is to extend the survival by suppressing the leukemogenic potential of the clone.

Thanks to progress in reduced intensity conditioning (RIC) and better matching unrelated donor, allogeneic stem cell transplant (allo-SCT) can be offered to a great number of MDS patients. However, it's generally considered that it must be restricted to high-risk MDS patients, and delayed until progression in low-risk MDS.[34] Although there aren't randomizing studies about RIC, retrospective studies didn't show improved overall survival when compared to conventional allo-SCT.[35] It's believed that although it provides a lower toxicity, it may have higher relapse rate. It's unknown if or what patients should be pretreated with intensive chemotherapy before allo-SCT. A recent retrospective study found no impact of intensive chemotherapy before myeloabalative SCT.[36] Recent data suggest RIC may be as effective as conventional SCT only in patients transplanted in complete response (CR). Relapse after SCT remains frequent. Iron overload appears to increase

Table 4. MDS Risk Stratification Using the IPSS

Risk Category	Total Score	Median Survival	Median Survival for Patients ≤ 60 yr old	Median Survival for Patients ≥ 60 yr old	25% AML progression
Low	0	5.7 yr	11.8 yr	4.8 yr	9.4 yr
Int-1	0.5-1.0	3.5 yr	5.2 yr	2.7 yr	3.3 yr
Int -2	1.5-2.0	1.2 yr	1.8 yr	1.1 yr	1.1 yr
High	≥ 2.5	0.4 yr	0.3 yr	0.5 yr	0.2 yr

yr = years; Int = intermediate

Adapted from Greenberg et al., 1997[18]

the risk of early and late complications after SCT.[37]

There are just a few studies evaluating intensive chemotherapy focused solely on MDS. Rather, most publications have evaluated AML and high-risk MDS together, using definitions of high-risk not based on the IPSS, and not focused only on MDS. Different chemotherapy regimens applied in AML carry significant treatment-related mortality and generally are not curative.[38-40] Intensive chemotherapy with anthracycline-cytarabine have shown high CR rates, however they showed short CR duration, important toxicities in elderly patients and low response rates in high-risk cytogenetics patients.[41-43]

Several works have confirmed a role for hypomethylating agents in MDS. Results from a trials analysis demonstrated an azacitidine (AZA) global response rate of 40-47% (10-17% CR) and median response duration of 13 months.[44] In a large randomized phase III study with high-risk MDS patients, AZA was compared with conventional care regimens (low-dose cytarabine, induction chemotherapy for AML, or best supportive care) in high-risk MDS patients and showed a significant median overall survival advantage with AZA, found irrespective of patient and disease characteristics.[45] However there is no evidence that AZA had advantage on overall survival over intensive chemotherapy.[46]

Results from studies trying to understand the role of decitabine in the treatment of high-risk IPPS patients, showed that although it may delay time to develop AML or death when compared to best supportive care, overall survival wasn't improved.[46, 47] Treatment with histone deacetylase inhibitors is also promising.[48] An outpatient alternative with reduced treatment-related morbidity is low-dose cytarabine (Ara-C) or melphalan monotherapy, but may result in prolonged myelosupression while inducing remissions in less than 30% of patients.[49-52]

As for young individuals, allo-SCT after high-dose chemotherapy and radiotherapy conditioning remains the standard of care. The probability for sustained remission and possible cure in selected patients with low-risk features, favorable cytogenetics, and a histocompatible related or volunteer donor, ranges from 40 to 60%. [53-55] However, this is a high-risk procedure with a mortality of 25 to 40% directly related to age. Different variables such as IPSS risk category, cytogenetic pattern and percentage of blasts, affect the probability of relapse after transplantation, whereas age, duration of disease, platelet count, comorbidities, and donor major histocompatibility complex compatibility affect procedure-related mortality.

In a study that tried to understand which patients have the greatest potential to benefit from allo-SCT,[34] in intermediate-2 and high-risk IPSS patients the overall

Table 5. Different mechanisms of action of different drugs used in MDS

Mechanism of Action	Drug
Inhibition of Apoptosis	Erythropoietin and Granulocyte Colony Stimulating Factor
Immunosuppression	Anti-thymocyte globulin and Cyclosporin A
Immunomodulation	Thalidomide and Lenalidomide
Hypomethilation	Azacitidine and Decitabine
Histone deacetylase inhibitors	Valproic acid and Sodium phenylbutyrate
Oncogenes deactivation	Farnesyltransferase inhibitor

survival was maximized when transplantation was made at the time of diagnosis. As opposed, in low-risk and intermediate-1 risk patients, allo-SCT should be reserved for those individuals in whom the disease has progressed. [56]

Different less aggressive approaches have emerged, targeting epigenetic control of gene expression, however comparative studies are still enrolling.

The new biologic targets in MDS are raising hopes of new therapies, and trials enrollment should be encouraged for those in whom the traditional therapy has little to offer.

Case report

A 48-year-old Caucasian man was admitted to our Department of Hematology in March 2009 for anemia and presence of blasts in a routine complete blood count (CBC). In our interview patient revealed nothing but tiredness since six months. Physical examination was normal and no hepatosplenomegaly was detected. The CBC at admission showed leucopenia with neutropenia, hypochromic and microcytic anemia, and thrombocytopenia: leukocytes $2.73x10^9$/L (neutrophils $0.63x10^9$/L, lymphocytes $1.26x10^9$/L, monocytes $0.33x10^9$/L, eosinophils $0.11x10^9$/L and basophils $0.00x10^9$/L), hemoglobin 7.0g/dL, hematocrit 22.4%, mean corpuscular volume 77.8 fL, mean corpuscular hemoglobin concentration 31.3g/dL, platelet count was $37x10^9$/L, serum lactate dehydrogenase 1321 U/L at 37°C (reference range 135-225). The bone marrow aspiration results were 11% blasts, dysplastic features in all three lineages, and a complex karyotype (del(5q), del(9q),+2,+12,…). From these results, a MDS diagnosis was made, classified as RAEB-II with high-risk IPSS. Attending to patient's age, general status, and presence of many siblings, the patient was treated with an induction cycle of idarubicine (IDA) and Ara-C with the goal of allotransplant of bone marrow. Complete remission wasn't achieved with leukocytes $2.74x10^9$/L, neutrophils $1.18x10^9$/L, hemoglobin 7.6g/L, platelets $24x10^9$/L, and 7.3% of blasts in the bone marrow. This way, a new approach with AZA was made. After two cycles of AZA, patient had an infectious intercurrence and when reevaluated there was neither recovery of hematological parameters nor cytogenetic response. Clinical history was complicated fifteen days later, in August, with generalized algic pain, suggestive of leukemic infiltration. There was evidence of progression, with aggravated cytopenias (leukocytes $1.59x10^9$/L, neutrophils $0.52x10^9$/L, hemoglobin 8.9g/L, platelets $36x10^9$/L), 9.3% blasts in the bone marrow, and increase in the needed for transfusion support. At this point, salvage therapy was initiated with fludarabine, cytarabine, and filgrastim (FLAG), but without response. Patient died on day 31 of internment as result of progression of the disease.

Discussion and conclusion

Was reported here the case of a patient who came to our Department of Hematology with symptoms of anemia and as result of our study we found a MDS, classified as RAEB-II, high-risk IPSS. Facing this, and since patient's general status was good and that he had many siblings, our first choice was to make an induction therapy with IDA+Ara-C with the goal of allo-SCT. Patient clinical history complicated later and as there was evidence of progression, salvage therapy with FLAG was initiated, but without response. Patient died a few days later as result of progression of the disease.

This case describes a patient that although symptoms and signals weren't exuberant (disease was discovered in routine exams), his initial diagnosis after coming to our Department was a MDS, high-risk IPSS (score >2.5). As showed on Table 4, the median survival in this group for patients with 60 or lower years old is 0.3 years.

Our first treatment option, with a curative goal, was the allotransplant, since patient had many siblings, was young and had high-risk IPSS; however induction was needed. Our patient didn't respond well to induction with standard chemotherapy. There was no response to the second line therapy and while disease continued to progress, a salvage therapy was tried, with no results.

Although allotransplant is the only possible cure in MDS, not only the procedure has his own risks, but also there's still a doubt about the best way to reach a response so transplant can be made. Today, the greatest limitation in transplant is the treatment related mortality of about 20-30%.[1] There are several studies running proposing induction therapies in high-risk patients who are candidates for allotransplant.

New approaches are being studied trying to select the best patients, and the best timing to perform the allo-SCT. One option, proposed by the Groupe Francophone des Myelodysplasies, says that the immediate allo-SCT should be realized in all high-risk MDS patients with less than 10% of blast in the bone marrow. In patients with increased blasts, therapy before transplant seems the best option. This therapy should be with intensive chemiotherapy in patients with normal karyotype, and hypomethylating agents in patients with unfavorable karyotype. In some centers, like the Fred Hutchinson Cancer Research Center, there is a tendency to use intensive chemotherapy in high-risk IPSS patients with more than 10% blasts who are candidates to allo-SCT.

The MDS are a heterogeneous disorders and still a difficult disease to treat. Ten years ago, there was little to offer MDS patients other than transfusion support. This way, there is an increased need to better understand the biology of the disease and to identify new cellular and molecular therapy targets. Since there is not one universal pathogenic mechanism that operates in all cases of MDS, it's unlikely that a single agent will be applicable to all patients.

Acknowledgments: The Author gratefully acknowledges the precious assistance of Alexandra Mota.

References

1. Scott BL, Estey E. Management of myelodysplastic syndromes: 2008 update. Oncology (Williston Park). 2008 Nov 15;22(12):1344-52.
2. Disperati P, Ichim CV, Tkachuk D, Chun K, Schuh AC, Wells RA. Progression of myelodysplasia to acute lymphoblastic leukaemia: implications for disease biology. Leuk Res. 2006 Feb;30(2):233-9.
3. Germing U, Strupp C, Kundgen A, Bowen D, Aul C, Haas R, et al. No increase in age-specific incidence of myelodysplastic syndromes. Haematologica. 2004 Aug;89(8):905-10.
4. Iglesias Gallego M, Sastre Moral JL, Gayoso Diz P, Garcia Costa A, Ros Forteza S, Mayan Santos JM. Incidence and characteristics of myelodysplastic syndromes in Ourense (Spain) between 1994-1998. Haematologica. 2003 Oct;88(10):1197-9.
5. Rollison DE, Howlader N, Smith MT, Strom SS, Merritt WD, Ries LA, et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the

NAACCR and SEER programs. Blood. 2008 Jul 1;112(1):45-52.
6. Hellstrom-lindberg E. Myelodysplastic Syndromes. 1 ed: Remedica Pub Ltd, 2008.
7. Hofmann WK, Koeffler HP. Myelodysplastic syndrome. Annu Rev Med. 2005;56:1-16.
8. Pedersen-Bjergaard J, Christiansen DH, Andersen MK, Skovby F. Causality of myelodysplasia and acute myeloid leukemia and their genetic abnormalities. Leukemia. 2002 Nov;16(11):2177-84.
9. Pedersen-Bjergaard J, Pedersen M, Roulston D, Philip P. Different genetic pathways in leukemogenesis for patients presenting with therapy-related myelodysplasia and therapy-related acute myeloid leukemia. Blood. 1995 Nov 1;86(9):3542-52.
10. Krishnan A, Bhatia S, Slovak ML, Arber DA, Niland JC, Nademanee A, et al. Predictors of therapy-related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. Blood. 2000 Mar 1;95(5):1588-93.
11. Pedersen-Bjergaard J, Andersen MK, Christiansen DH. Therapy-related acute myeloid leukemia and myelodysplasia after high-dose chemotherapy and autologous stem cell transplantation. Blood. 2000 Jun 1;95(11):3273-9.
12. Wu PS, Hay AE, Thomas GE, Bowen DT. Latency of onset of de novo myelodysplastic syndromes. Haematologica. 2004 Nov;89(11):1392-4.
13. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood. 2002 Oct 1;100(7):2292-302.
14. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol. 1982 Jun;51(2):189-99.
15. Verhoef GE, Pittaluga S, De Wolf-Peeters C, Boogaerts MA. FAB classification of myelodysplastic syndromes: merits and controversies. Ann Hematol. 1995 Jul;71(1):3-11.
16. Jaffe ES. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon ; Washington, D.C.: IARC Press, 2001.
17. Swerdlow SH, International Agency for Research on Cancer. WHO Classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: International Agency for Research on Cancer, 2008.
18. Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997 Mar 15;89(6):2079-88.
19. Mecucci C, La Starza R. Cytogenetics of myelodysplastic syndromes. Forum (Genova). 1999 Jan-Mar;9(1):4-13.
20. Fenaux P, Morel P, Lai JL. Cytogenetics of myelodysplastic syndromes. Semin Hematol. 1996 Apr;33(2):127-38.
21. Malcovati L, Germing U, Kuendgen A, Della Porta MG, Pascutto C, Invernizzi R, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol. 2007 Aug 10;25(23):3503-10.
22. Wintrobe MM, Greer JP. Wintrobe's clinical hematology. 12th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health, 2009.
23. Pippard MJ, Callender ST. The management of iron chelation therapy. Br J Haematol. 1983 Aug;54(4):503-7.
24. Malcovati L, Della Porta MG, Cazzola M. Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. Haematologica. 2006 Dec;91(12):1588-90.
25. Jadersten M, Malcovati L, Dybedal I, Della Porta MG, Invernizzi R, Montgomery SM, et al. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. J Clin Oncol. 2008 Jul 20;26(21):3607-13.
26. Park S, Grabar S, Kelaidi C, Beyne-Rauzy O, Picard F, Bardet V, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood. 2008 Jan 15;111(2):574-82.
27. List A, Dewald G, Bennett J, Giagounidis A, Raza A, Feldman E, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med. 2006 Oct 5;355(14):1456-65.
28. Greenberg PL. Treatment of myelodysplastic syndromes with hemopoietic growth factors. Semin Oncol. 1992 Feb;19(1):106-14.
29. Molldrem JJ, Leifer E, Bahceci E, Saunthararajah Y, Rivera M, Dunbar C, et al. Antithymocyte globulin for treatment of the bone marrow failure associated with

myelodysplastic syndromes. Ann Intern Med. 2002 Aug 6;137(3):156-63.
30. Jonasova A, Neuwirtova R, Cermak J, Vozobulova V, Mocikova K, Siskova M, et al. Cyclosporin A therapy in hypoplastic MDS patients and certain refractory anaemias without hypoplastic bone marrow. Br J Haematol. 1998 Feb;100(2):304-9.
31. Killick SB, Mufti G, Cavenagh JD, Mijovic A, Peacock JL, Gordon-Smith EC, et al. A pilot study of antithymocyte globulin (ATG) in the treatment of patients with 'low-risk' myelodysplasia. Br J Haematol. 2003 Feb;120(4):679-84.
32. Sauntharajah Y, Nakamura R, Wesley R, Wang QJ, Barrett AJ. A simple method to predict response to immunosuppressive therapy in patients with myelodysplastic syndrome. Blood. 2003 Oct 15;102(8):3025-7.
33. Steensma DP, Dispenzieri A, Moore SB, Schroeder G, Tefferi A. Antithymocyte globulin has limited efficacy and substantial toxicity in unselected anemic patients with myelodysplastic syndrome. Blood. 2003 Mar 15;101(6):2156-8.
34. Cutler CS, Lee SJ, Greenberg P, Deeg HJ, Perez WS, Anasetti C, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood. 2004 Jul 15;104(2):579-85.
35. Martino R, Caballero MD, Perez-Simon JA, Canals C, Solano C, Urbano-Ispizua A, et al. Evidence for a graft-versus-leukemia effect after allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning in acute myelogenous leukemia and myelodysplastic syndromes. Blood. 2002 Sep 15;100(6):2243-5.
36. Alessandrino EP, Della Porta MG, Bacigalupo A, Van Lint MT, Falda M, Onida F, et al. WHO classification and WPSS predict posttransplantation outcome in patients with myelodysplastic syndrome: a study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Blood. 2008 Aug 1;112(3):895-902.
37. Majhail NS, Lazarus HM, Burns LJ. Iron overload in hematopoietic cell transplantation. Bone Marrow Transplant. 2008 Jun;41(12):997-1003.
38. Wattel E, De Botton S, Luc Lai J, Preudhomme C, Lepelley P, Bauters F, et al. Long-term follow-up of de novo myelodysplastic syndromes treated with intensive chemotherapy: incidence of long-term survivors and outcome of partial responders. Br J Haematol. 1997 Sep;98(4):983-91.
39. Estey EH, Thall PF, Cortes JE, Giles FJ, O'Brien S, Pierce SA, et al. Comparison of idarubicin + ara-C-, fludarabine + ara-C-, and topotecan + ara-C-based regimens in treatment of newly diagnosed acute myeloid leukemia, refractory anemia with excess blasts in transformation, or refractory anemia with excess blasts. Blood. 2001 Dec 15;98(13):3575-83.
40. Kantarjian H, O'Brien S, Cortes J, Giles F, Faderl S, Jabbour E, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. Cancer. 2006 Mar 1;106(5):1090-8.
41. Deschler B, de Witte T, Mertelsmann R, Lubbert M. Treatment decision-making for older patients with high-risk myelodysplastic syndrome or acute myeloid leukemia: problems and approaches. Haematologica. 2006 Nov;91(11):1513-22.
42. Kantarjian H, Beran M, Cortes J, O'Brien S, Giles F, Pierce S, et al. Long-term follow-up results of the combination of topotecan and cytarabine and other intensive chemotherapy regimens in myelodysplastic syndrome. Cancer. 2006 Mar 1;106(5):1099-109.
43. Knipp S, Hildebrand B, Kundgen A, Giagounidis A, Kobbe G, Haas R, et al. Intensive chemotherapy is not recommended for patients aged >60 years who have myelodysplastic syndromes or acute myeloid leukemia with high-risk karyotypes. Cancer. 2007 Jul 15;110(2):345-52.
44. Silverman LR, McKenzie DR, Peterson BL, Holland JF, Backstrom JT, Beach CL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol. 2006 Aug 20;24(24):3895-903.
45. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009 Mar;10(3):223-32.
46. Gurion R, Vidal L, Gafter-Gvili A, Belnik Y, Yeshurun M, Raanani P, et al. 5-azacitidine prolongs overall survival in patients with myelodysplastic syndrome--a systematic review

and meta-analysis. Haematologica. 2010 Feb;95(2):303-10.
47. Kantarjian H, Issa JP, Rosenfeld CS, Bennett JM, Albitar M, DiPersio J, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer. 2006 Apr 15;106(8):1794-803.
48. Griffiths EA, Gore SD. DNA methyltransferase and histone deacetylase inhibitors in the treatment of myelodysplastic syndromes. Semin Hematol. 2008 Jan;45(1):23-30.
49. Miller KB, Kim K, Morrison FS, Winter JN, Bennett JM, Neiman RS, et al. The evaluation of low-dose cytarabine in the treatment of myelodysplastic syndromes: a phase-III intergroup study. Ann Hematol. 1992 Oct;65(4):162-8.
50. Hellstrom-Lindberg E, Robert KH, Gahrton G, Lindberg G, Forsblom AM, Kock Y, et al. A predictive model for the clinical response to low dose ara-C: a study of 102 patients with myelodysplastic syndromes or acute leukaemia. Br J Haematol. 1992 Aug;81(4):503-11.
51. Denzlinger C, Bowen D, Benz D, Gelly K, Brugger W, Kanz L. Low-dose melphalan induces favourable responses in elderly patients with high-risk myelodysplastic syndromes or secondary acute myeloid leukaemia. Br J Haematol. 2000 Jan;108(1):93-5.
52. Omoto E, Deguchi S, Takaba S, Kojima K, Yano T, Katayama Y, et al. Low-dose melphalan for treatment of high-risk myelodysplastic syndromes. Leukemia. 1996 Apr;10(4):609-14.
53. Sierra J, Perez WS, Rozman C, Carreras E, Klein JP, Rizzo JD, et al. Bone marrow transplantation from HLA-identical siblings as treatment for myelodysplasia. Blood. 2002 Sep 15;100(6):1997-2004.
54. Deeg HJ, Storer B, Slattery JT, Anasetti C, Doney KC, Hansen JA, et al. Conditioning with targeted busulfan and cyclophosphamide for hemopoietic stem cell transplantation from related and unrelated donors in patients with myelodysplastic syndrome. Blood. 2002 Aug 15;100(4):1201-7.
55. Castro-Malaspina H, Harris RE, Gajewski J, Ramsay N, Collins R, Dharan B, et al. Unrelated donor marrow transplantation for myelodysplastic syndromes: outcome analysis in 510 transplants facilitated by the National Marrow Donor Program. Blood. 2002 Mar 15;99(6):1943-51.
56. Nakai K, Kanda Y, Fukuhara S, Sakamaki H, Okamoto S, Kodera Y, et al. Value of chemotherapy before allogeneic hematopoietic stem cell transplantation from an HLA-identical sibling donor for myelodysplastic syndrome. Leukemia. 2005 Mar;19(3):396-401.