The revolution of myelodysplastic syndromes

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***Abstract*:** Myelodysplastic syndromes (MDS) are clonal disorders of the hematopoietic system with resultant cytopenias and shortened survival. Better recognition of MDS and an aging population, some of whom have been treated with chemotherapy and radiation therapy for other cancers, is largely responsible for the growing incidence of this malignancy, which is divided into lower- and higher-risk subtypes. Erythropoiesis-stimulating agents are the first-line treatment options for patients with lower-risk MDS and symptomatic anemia or for those requiring transfusion support. Lenalidomide has been successfully used for patients with the del(5q) chromosomal abnormality who are also transfusion dependent. Hypomethylating agents, such as azacitidine and decitabine, are indicated for patients with higher-risk disease, with azacitidine demonstrating a survival advantage. Hematopoietic stem cell transplantation (HSCT) is a curative therapeutic approach available to less than 5% of patients with MDS. Combination therapies and newer single agents targeting the important cellular pathways are being explored for treatment of MDS with promising results.

***Keywords*:** myelodysplastic syndromes, MDS, treatment, therapy, ESAs, growth factors, hypomethylating agents

Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous spectrum of clonal hematopoietic diseases typified by varying progression of peripheral blood cytopenias in the setting of bone marrow hypercellularity, cytologic dysplasias, and inadequate hematopoiesis. The heterogeneity of these disorders is related to differences in morphology, types and number of involved cell lines, bone marrow blast counts, and underlying cytogenetic abnormalities.

MDS have been classified by the World Health Organization (WHO) into a number of subtypes based on their morphological and, in one case, cytogenetic characteristics [Arber *et al.* 2008]. Clinically, these subtypes are categorized into lower-risk (refractory anemia, refractory neutropenia, refractory thrombocytopenia, refractory anemia with ring sideroblasts, refractory cytopenia with multilineage dysplasia, MDS with deletion 5q chromosomal abnormality, MDS unclassified) and higher-risk (refractory anemia with excess blasts-1 and refractory anemia with excess blasts-2) groups based on their responses to certain therapeutic agents, disease outcomes, and prognosis.

MDS are thus considered to be cancers of hematopoietic cell origin with an increased risk of evolution to secondary acute myelogeneous leukemia (AML), which has poorer prognosis compared with *de novo* AML. The risk of AML transformation is especially pronounced in patients with higher-risk MDS.

In order to risk stratify patients with *de novo* MDS, the International Prognostic Scoring System (IPSS) has been commonly used in clinical settings to tailor treatment and to estimate a patient's overall survival [Greenberg *et al.* 1997]. The IPSS is calculated based on the number of peripheral blood cytopenias, bone marrow blast count, and cytogenetic abnormalities. According to the IPSS, MDS are classified into low, intermediate 1 (both considered lower risk), intermediate 2 and high-risk (both considered higher risk) groups, with median overall survival ranging from 5.7 years among patients with low-risk disease to 0.4 years among patients with high-risk MDS.

While the IPSS has been considered the standard bearer of prognostic schemas since its publication in 1997, and has even been incorporated into drug labeling, it has some well recognized limitations.

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Most patients (92%) used to derive the IPSS were untreated, and thus its applicability to the majority of patients with MDS in the USA, who are treated [Sekeres *et al.* 2008a], is unvalidated. Patients with secondary MDS, or those with overlap MDS/myeloproliferative neoplasms, were excluded from the original system, yet some patients who would now be considered to have AML (those with up to 30% myeloblasts) were included. Certain clinical and outcome diversities may also be observed among patients within the same IPSS risk groups. As an example, the IPSS does not address blood product transfusion burden or the degree of cytopenias, so patients with weekly transfusions may be classified similarly as those with no transfusion needs, as would patients with platelet counts of 99,000/μl *versus* 2000/μl.

One solution was the WHO Classification-Based Prognostic Scoring System (WPSS), which superseded the IPSS and incorporated red cell transfusion dependence as a negative prognostic marker for lower-risk subgroups [Malcovati *et al.* 2005]. In addition, the WPSS provided more refined prediction of AML progression among individual risk groups, such that the risk of leukemia evolution is less than 10% at 15 years for patients with low-risk MDS compared with more than 50% at 1 year for those with high-risk disease. In addition, the WPSS is considered dynamic, with the ability to be applied to individual patients multiple times in their disease course.

In addition, investigators from the MD Anderson Cancer Center (MDACC) analyzed a cohort of close to 2000 patients with MDS to generate a novel prognostic model of disease [Kantarjian *et al.* 2008]. An important advantage of this model includes its applicability to both treatment-naïve and previously treated patients with MDS, along with patients with secondary MDS and MDS/myeloproliferative neoplasms. The model also includes prognostic factors such as performance status, age, and degree of cytopenias, transfusion dependency and cytogenetic abnormalities. Four risk groups are identified (low, intermediate 1, intermediate 2, high) with patient's median overall survival varying between 54 and 6 months from low- to high-risk groups.

It is anticipated that a revised IPSS will be developed through a worldwide collaboration of databases that will include elements of the WPSS and MDACC system, along with consideration of prognostic factors such as lactate dehydrogenase and the presence of bone marrow fibrosis.

Epidemiology

Since the start of mandatory reporting of MDS by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry in 2001, the incidence of MDS has been rising yearly: not because of an epidemic of the disease, but as a result of cancer registries becoming more sophisticated at recognizing and documenting it, and increasing referrals to specialists of geriatric patients with what would have been previously dismissed as 'normal' age-related anemia. The estimated incidence of MDS in 2004 was 3.8 per 100,000 person-years, which would make it more common than AML, and predicted to translate to approximately 15,000 diagnoses yearly [Sekeres, 2010; Rollison *et al.* 2008]. Although prevalence is difficult to determine, extrapolating data from Germany predict that 60,000 people are living with MDS in the USA.

MDS are diseases of older adults, with a median age of 71 years at diagnosis. Men are affected slightly more than women [Sekeres *et al.* 2008a]. The incidence of MDS correlates with advancing age. It is estimated at five per 100,000 person-years for ages 60–69 years in contrast to over 50 per 100,000 person-years among patients older than 70 years old [Oscier, 1987]. One study reports the incidence of MDS among people aged 65 years and older in the Medicare Standard Analytic Files to be 162 per 100,000. However it is believed that the incidence rate of MDS in this patient population was significantly over reported due to inaccuracies in reported diagnosis [Goldberg *et al.* 2010].

MDS rarely affect the pediatric population, and in those cases it may be associated with certain inherited disorders such as Down syndrome, Shwachman–Diamond syndrome, Fanconi anemia, neurofibromatosis type 1, congenital neutropenias and mitochondrial cytopenias.

Approximately 10% of patients with newly diagnosed MDS have secondary disease, though in some regions of the USA it may be as high as 25% [De Roos *et al.* 2010; Sekeres *et al.* 2008a]. Treatment-related MDS account for about 70% of secondary MDS whereas other etiologies of secondary MDS include prior radiation therapy and chemical exposures. Complex cytogenetic abnormalities are commonly detected among patients with

secondary MDS and the prognosis is poorer compared with those with *de novo* MDS [Estey, 2007].

It is expected that rates of secondary MDS will continue to rise with the increased use of chemotherapy and radiation therapy for unrelated malignancies. Whether secondary disease is equally responsive to disease-modifying therapies has only been explored in a preliminary manner [Sekeres *et al.* 2010c].

Treatment

Recommending appropriate treatment modalities for MDS depends on both the MDS disease risk group and on the presence of specific cytogenetic abnormalities [Greenberg, 1998]. Disease-modifying therapies have only been approved by the US Food and Drug Administration since 2004; prior to that (and since), recombinant humanized erythropoietin, darbepoietin, and colony-stimulating factors have been used off label, although they are not felt to alter the disease course directly. Azacitidine and decitabine, although approved for all subtypes of MDS, are most effective for higher-risk disease; while lenalidomide is approved for lower-risk, transfusion-dependent MDS with del(5q) chromosomal abnormality [Kantarjian *et al.* 2006; List *et al.* 2006; Silverman *et al.* 2002].

Despite the recent advances in therapy for MDS, none of the available agents are curative. Only hematopoietic stem cell transplantation (HSCT) can eradicate the disease permanently, and this is a treatment modality only considered in less than 5% of patients with MDS, primarily because of the age and comorbidities of patients and potential sibling donors, and reluctance on the part of both patients and treating physicians to embark on dramatic, toxic therapy [Greenberg, 2010; Sekeres *et al.* 2008a].

Treating lower-risk MDS

Patients with lower-risk disease may be either asymptomatic or have significant symptoms caused by their cytopenias. Usually asymptomatic patients have no transfusion needs and are followed closely with periodic evaluation of their peripheral blood counts, sometimes for years. Prophylactic antibiotics are generally recommended for patients with MDS with persistent neutropenia in order to reduce infection-related mortality [Gafter-Gvili *et al.* 2005; Reuter *et al.* 2005]. The most common symptoms include persistent fatigue and exertional dyspnea as a result of ineffective erythropoiesis. In the lower-risk group 22% of patients are red cell transfusion dependent, in contrast to 68% for higher-risk MDS [Sekeres *et al.* 2008a].

The goal of therapy in these patients is to minimize the need for blood product transfusions and maximize their quality of life [Cheson *et al.* 2001]. In general, any type of active therapy is considered for symptomatic anemia, as the hemoglobin decreases below 9 g/dl; or for transfusions needs, particularly when they exceed a frequency of every 4 weeks.

Generally, erythropoiesis-stimulating agents (ESAs) such as epoetin or darbepoetin are the first-line treatment agents used to treat these patients. ESAs are indicated for patients with MDS and symptomatic anemia with hemoglobin below 10 g/dl. Peripheral blood counts should be closely monitored throughout the course of therapy, with a target hemoglobin below 12 g/dl. The risk of cerebrovascular accidents has been noted to increase among patients who continue to receive ESAs with higher hemoglobin values, although studies demonstrating this risk have not included patients with MDS. ESAs may provide an overall survival benefit and decrease the rate of disease progression compared with non-ESA therapies, based on a meta-analysis of 162 MDS trials conducted from 1985 to 2005 [Golshayan *et al.* 2007]. The overall response to therapy with ESAs was estimated at approximately 40%, as assessed by International Working Group 2000 (IWG 2000) criteria. Two other groups have demonstrated similar, retrospective survival advantages for ESAs when compared with best supportive care [Jadersten *et al.* 2008; Park *et al.* 2008].The highest response to ESA therapy (74%) has been demonstrated among patients with both low plasma erythropoietin level (<500 IU) and infrequent red blood cell (RBC) transfusion need (defined as <2 units/month). The response to ESAs can be as low as 7% among patients with higher plasma erythropoietin level and heavier RBC transfusion requirements [Hellstrom-Lindberg *et al.* 2003, 1997].

Clinical and hematological responses to ESAs are usually seen within the first 2 months of therapy, and if durable response is achieved it lasts a median of approximately 2 years [Jadersten *et al.* 2008]. A decision analysis has been published to guide ESA *versus* non-ESA treatment considerations among patients with lower-risk MDS [Sekeres *et al.* 2007].

Granulocyte colony-stimulating factors (G-CSFs) are occasionally added to ESAs in an effort to augment the hematological response. This combined therapy has been shown to improve the erythroid response rate up to 40–50%, particularly among patients with increased number of ring sideroblasts in bone marrow [Casadevall *et al.* 2004; Hellstrom-Lindberg *et al.* 2003, 1997; Negrin *et al.* 1996]. An Eastern Cooperative Oncology Group study additionally demonstrated a 36% overall response in patients treated with ESAs, with an increased survival among patients with an erythroid response [Greenberg *et al.* 2009].

Patients with lower-risk MDS who are refractory to ESA therapy have limited treatment options. Many are being treated with lenalidomide, off label in the absence of the del(5q) abnormality. Transfusion independence was achieved in 26% of patients with lower-risk MDS and no del5q abnormality treated with lenalidomide in a phase II multicenter trial. The median duration of transfusion independence was 41 weeks, and a 29% response rate to lenalidomide was seen in patients with no previous exposure to ESAs [Raza *et al.* 2008]. A US Intergroup study is exploring the use of lenalidomide with or without ESAs in the non-del(5q) population. Drugs used for treatment of patients with lower-risk MDS are summarized in Table 1.

Successful use of immunosuppressive agents such as antithymocyte globulin, cyclosporine and alemtuzumab (anti-CD52 antibody) are also described in patients with MDS, with higher responses seen in those with the HLA-DR15 histocompatibility type, hypocellular bone marrow (<30% cellularity), of younger age (<60 years old), or with coexisting paroxysmal nocturnal hemoglobinuria

Table 1. Drugs used for treatment of patients with lower-risk MDS.

MDS drug/dosing schedule	Indication	Response	Duration (months)	Studies
ESAs Epoetin 40,000–80,000 units weekly Darbepoetin 100–500 μg every 1–3 weeks	Lower- risk MDS	40% OR Survival benefit	24	Golshayan *et al.* [2007] Park *et al.* [2008] Jadersten *et al.* [2008] Gabrilove *et al.* [2008]
ESAs + G-CSF Epoetin 10,000 units 5 days a week Filgrastim 75–300 μg/day 3 times a week	Lower- risk MDS	40–50% OR	11–24	Negrin *et al.* [1996] Hellstrom-Lindberg *et al.* [1997, 2003] Casadevall *et al.* [2004] Greenberg *et al.* [2009]
Lenalidomide 10 mg/day for 21–28 days of a 28-day cycle	Lower-risk MDS with del(5q)	67% transfusion independence 45% cytogenetic CR 73% PR No survival benefit	>24	List *et al.* [2006]
Lenalidomide 10 mg/day for 21–28 days of a 28-day cycle	Lower-risk MDS non-del(5q)	26% transfusion independence 29% OR in no previous ESA use group	9.6	Raza *et al.* [2008]
Romiplostim 500 or 750 μg SC/QW 750 μg in three different dosing schedules: subcutaneous weekly or biweekly, intravenous biweekly	Lower-risk MDS with thrombocytopenia	30–46% durable platelet response	4.6 with weekly schedule	Kantarjian *et al.* [2010] Sekeres *et al.* [2010a]

ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony stimulating factor; IWG, International Working Group; MDS, myelodysplastic syndromes; OR (CR + PR), overall response (complete response + partial response); OS, overall survival; PR, partial response.

clone [Lim *et al.* 2007; Sloand *et al.* 2005; Sauntharajah *et al.* 2002].

Immunosuppressive therapy was also found to be effective in patients with isolated trisomy 8 chromosomal abnormality based upon the postulated immune phenotype of this disease [Galili *et al.* 2007; Sloand *et al.* 2005].

Patients who have cytopenias other than anemia can be treated with specific supportive therapy. G-CSF is most frequently given to patients with MDS and neutropenic fever or in the presence of serious infection. However, there is no evidence-based indication for prophylactic use of G-CSF among otherwise asymptomatic patients with MDS manifesting with neutropenia [Negrin *et al.* 1993].

In cases of MDS with severe thrombocytopenia, platelet transfusion is indicated in asymptomatic patients with platelet counts less than 10,000/ml to minimize life-threatening bleeding complications. Recent phase II data demonstrated achievement of durable platelet responses in 46% of patients treated with the thrombopoietin receptor analog romiplostim, some of which were durable [Kantarjian *et al.* 2010; Sekeres *et al.* 2010a].

Another thrombopoietin agonist, eltrombopag, has also entered MDS clinical trials.

For patients with lower-risk MDS and the del(5q) cytogenetic abnormality who are transfusion dependent, an immunomodulatory agent lenalidomide is indicated. Lenalidomide purportedly works through inhibition of phosphatase activity in the common deleted region that plays a key role in cell cycle regulation; through a defect in ribosomal protein function; via direct cytotoxic mechanisms in patients with the del(5q) cytogenetic abnormality; and through effects on the bone marrow microenvironment in patients without this lesion [Wei *et al.* 2009; Ebert *et al.* 2008]. In the phase II registration trial for this indication, transfusion independence was achieved in 67% of patients. The median duration of the response exceeded 2 years [List *et al.* 2006]. Cytogenetic complete responses occurred in 45% of patients, and 73% of study participants experienced partial responses. Further studies have demonstrated that a decline in platelet count of at least 50% within the first 8 weeks of treatment with lenalidomide predicted RBC transfusion independence and was correlated with significant cytogenetic responses in patients with the del(5q) chromosomal abnormality [Sekeres *et al.* 2008b]. Despite encouraging responses to lenalidomide in patients with MDS and the del(5q) chromosomal abnormality, no significant survival benefit has been shown, even with long-term use of this drug, although a randomized phase III study is attempting to answer this question [Fenaux *et al.* 2009].

A small subset of patients with lower-risk MDS carrying either the t(5;12) or 5q33 variant [platelet-derived growth factor receptor B (PDGFR-B) gene] or del(4q12) chromosomal abnormalities have mutation in the tyrosine kinase receptor family and may subsequently benefit from targeted therapy with imatinib mesylate [Galili *et al.* 2007].

Treating higher-risk MDS

Eligibility for allogeneic HSCT should be determined among all patients with higher-risk MDS, as in appropriately selected patients, HSCT can cure up to 40% [Scott *et al.* 2006; Cutler *et al.* 2004; Sierra *et al.* 2002]. Unfortunately, there is limited evidence supporting the use of reduced-intensity *versus* fully ablative HSCT; related *versus* unrelated donors; or the use of pre-HSCT remission induction chemotherapy [Oliansky *et al.* 2009]. For the majority of patients with higher-risk MDS, the best therapeutic responses can be seen with the DNA methyltransferase inhibitors azacitidine and decitabine. A higher number of methylated loci, the purported targets of these drugs, were shown to correlate with higher-risk MDS in one study employing methylation array technology [Jiang *et al.* 2009]. In addition, the increase in a number of aberrantly methylated loci paralleled progression of disease from lower to higher risk.

Azacitidine's approval in the USA was based on a phase III study in which it was compared with best supportive care in 191 patients with MDS of all subtypes [Silverman *et al.* 2002]. Although it demonstrated an advantage in terms of survival and delay in AML transformation, it did not significantly prolong survival as an isolated endpoint, likely because of crossover from supportive to active treatment arms. Azacitidine was subsequently compared with conventional care regimens (best supportive care, low-dose cytarabine, or induction chemotherapy) in a phase III randomized trial involving 179 patients with higher-risk MDS in each study group

[Fenaux *et al.* 2009]. A 29% overall response rate was seen with azacitidine, compared with 21% in the conventional care arm. More importantly, the median overall survival was significantly prolonged in the azacitidine arm (24.4 months) compared with the conventional care arm (15 months) [hazard ratio (HR) = 0.58, $p = 0.0001$]. Patients enrolled in the azacitidine arm received 75 mg/m^2 daily doses for 7 consecutive days of a 28-day cycle, with a median of nine treatment cycles.

Some authors recommend treatment with four to six initial cycles until the best response is achieved followed by at least four additional cycles of therapy [Silverman, 2009]. However, earlier studies emphasized the importance of maintenance therapy as long as patients had sustained a response [Kantarjian *et al.* 2007]. In the survival study, azacitidine was continued *ad infinitum*, until loss of response, and those who achieved a hematologic improvement or better were more likely to appreciate a survival advantage [List *et al.* 2008].

Administration of azacitidine for 7 consecutive days is not always feasible in a day-to-day clinical practice because of medical understaffing on weekends. According to a recent prospective database study, 52% of all patients treated with azacitidine received the drug for less than 7 days; 29% of patients had an interrupted 7-day course of therapy; and only 17.5% received a 7-day continuous course of therapy, of a 28-day cycle [Sekeres *et al.* 2009]. It remains unclear if survival benefit holds for these alternate treatment regimens. The drugs approved for treatment of patients with higher-risk MDS are summarized in Table 2.

Decitabine is another hypomethylating agent with a mechanism of action similar to azacitidine. It was originally approved in the USA at a dose of 15 mg/m^2 every 8 h over 3 days, repeated every 6 weeks, and more recently at a dose of 20 mg/m^2 over 1 h intravenously daily for 5 days of a 28-day cycle [Steensma *et al.* 2009; Kantarjian *et al.* 2006].

Decitabine was compared to best supportive care in two phase III randomized trials. The first study was a single institution trial of 179 patients with mixed MDS risk groups. The overall complete and partial response rate for all patients treated with decitabine reached 17%, compared with 0% in the best supportive care arm. A statistically significant benefit in delay in AML transformation was detected only in patients with higher-risk MDS (12 months *versus* 6.8 months, $p = 0.03$); however there was no survival benefit observed [Kantarjian *et al.* 2006].

A second trial was conducted in Europe among 119 patients with higher-risk MDS randomized to receive decitabine, and 114 to receive best supportive care, and has been reported in preliminary form [Wijermans *et al.* 2008]. This study showed an overall complete and partial response rate of 19%, similar to azacitidine, although without a significant survival advantage. Median overall survival in the decitabine arm was 10.1 months in contrast to 8.5 months in the best supportive care arm (HR = 0.88, $p = 0.38$). Median treatment duration was limited to four cycles of decitabine therapy. It is possible that the either the short duration of therapy, use of the 8 h dosing schedule as opposed to the commonly used daily dosing schedule, or patient selection differences between this study and the AZA-001 study (as evidenced by differences in survival in control arms) could be responsible for the lack of the significant survival benefit.

When three different treatment schedules of decitabine were studied, with a median treatment duration of seven cycles, complete remission was achieved in 35% of patients. The median remission duration for the entire cohort was 20 months. The median overall survival was 22 months, with estimated 2-year overall survival of 41% [Kantarjian *et al.* 2007]. The 5-day daily dosing schedule was explored in a phase II study of 99 patients in the USA. Response rates were more modest in this study (19%), but validated the alternate, daily dosing schedule as being at least equivalent to the 8 h dosing regimen [Steensma *et al.* 2009]. An ongoing randomized trial will evaluate whether the response rate of one hypomethylating agent is superior to the other. Enrolled patients with intermediate- and high-risk MDS will be randomized to receive decitabine (20 mg/m^2/day intravenous infusion for 5 days every 28 days) or azacitidine (75 mg/m^2/day subcutaneous injection for 7 days every 28 days). Unfortunately, overall survival will not be a primary endpoint.

Intensive, AML induction-type chemotherapy remains a viable option for younger patients being treated with curative intent, or in patients

Table 2. Drug approved for treatment of patients with higher-risk MDS.

MDS drug/dose	Indication	Response/median duration	Survival data	Study design/ references
Azacitidine (AZA) 75 mg/m^2/day for 7 days of a 28-day cycle	Higher-risk MDS	16% OR for AZA for all MDS subtypes 15 months median response Median number of cycles >7 for responders	21 months time to AML progression or death for AZA arm (*versus* 12 months for BSC, $p=0.007$) No survival benefit likely due to crossover allowed for BSC group	CALBG 9221 phase III Silverman *et al.* [2002]
		29% OR for AZA for higher-risk MDS (*versus* 21% for CC) 13.6 months median response Median number of cycles 9	24.4 months median OS for AZA (*versus* 15 months for CC; HR = 0.58, $p=0.0001$)	AZA- 001 phase III Fenaux *et al.* [2009]
Decitabine (DAC) 15 mg/m^2 every 8 h over 3 days of a 6-week cycle	Higher-risk MDS	17% OR for DAC for all MDS subtypes 10.3 months median response Median number of cycles 3	11 months time to AML progression or death for DAC in higher-risk group (*versus* 6 months for BSC) No OS benefit thought to be due to few number of cycles	Phase III Kantarjian *et al.* [2006]
		19% OR for DAC for higher-risk MDS 8.6 months median response Median number of cycles 4	10.1 months median OS for DAC (*versus* 8.5 months for BSC; HR = 0.88, $p=0.38$)	EORTC 06011 phase III Wijermans *et al.* [2008]

AML, acute myelogeneous leukemia; BSC, best supportive care; HR, hazard ratio; MDS, myelodysplastic syndromes; OR (CR + PR), overall response (complete response + partial response); OS, overall survival.

developing disease progression on hypomethylating agents [Beran *et al.* 2001]. It is possible that these patients, however, are less responsive to induction chemotherapy following hypomethylating agents [Mohan *et al.* 2010]. One retrospective analysis has demonstrated improved survival for decitabine therapy over intensive chemotherapy among patients with higher-risk MDS [Kantarjian *et al.* 2007].

Treating iron overload

Iron chelation therapy is indicated for patients with increased transfusion requirements (>20–50 lifetime RBC transfusions) or with serum ferritin levels above 2000 ng/ml. Oral deferasirox and parenteral deferoxamine are the two iron-chelating agents currently available in the USA. Both medications have similar efficacy in depleting iron stores in patients with MDS [Piga *et al.* 2006]. Chelation therapy should be initiated with extreme caution, however. It has never been shown prospectively to have an impact on end-organ function or on survival in patients with MDS, and was approved by the US Food and Drug Administration based on limited data in patients with MDS. Moreover, its use should be further limited to patients with lower-risk disease with a predicted prolonged survival because patients with higher-risk disease are unlikely to live long enough to appreciate any benefits from chelation. Chelation may have a role in patients with MDS with preexisting iron overload who undergo allogeneic HSCT because these patients have an increased risk of graft *versus* host disease and an increased rate of post-transplant mortality by 50% ($p=0.017$) [Alessandrino *et al.* 2010]. A multicenter randomized phase III trial (TELESTO) is ongoing for patients with low- and intermediate-1-risk MDS with transfusion-related iron overload, with the primary objective of evaluating the efficacy and safety of iron chelation with deferasirox compared with placebo.

Treating MDS: future directions

Several novel agents or drug combinations have been studied in patients with higher-risk MDS with promising results.

Clofarabine is a purine nucleoside antimetabolite studied in patients with higher-risk MDS and AML, some of whom were previously treated with hypomethylating agents. The overall response rate was 34%, with a 20% response to clofarabine monotherapy in previously treated patients [Faderl *et al.* 2008]. This drug is being explored in both intravenous and oral formulations.

For patients with lower-risk MDS, the drug ezatiostat (TLK 199), a glutathione-S transferase P1-1 inhibitor, has been tested in a phase I study of 45 patients. No dose-limiting toxicity was reached; 17 patients (38%) achieved a hematologic improvement response using IWG (2000) criteria. Extended oral dosing schedules are being evaluated in a phase II study, with preliminary response rates similar to the phase I study [Raza *et al.* 2009].

Histone deacetylase inhibitors (HDACs) appear to have a synergistic effect when combined with hypomethylating agents in *in vitro* studies via inhibition of the nuclear factor kappa-B (NF-κB) pathway in malignant myeloblasts [Fabre *et al.* 2008]. This creates further opportunities for epigenetic therapy in patients with higher-grade MDS. A phase II US Intergroup study randomized patients to receive azacitidine, or azacitidine with entinostat, an HDAC inhibitor. No differences between the two arms were seen with respect to trilineage responses, the study's primary endpoint. Other single-arm studies have shown impressive results with similar HDAC combinations [Garcia-Manero *et al.* 2008].

Combination therapy with azacitidine and lenalidomide resulted in a 44% complete remission rate and in a 67% overall response rate in a phase I trial in patients with higher-risk MDS. Of note, those patients with normal single nucleotide polymorphism (SNP) arrays and cytogenetic profile had the best response to this regimen, which is now being explored in the phase II setting [Sekeres *et al.* 2010b].

Conclusion

There has been a revolution in our understanding of and treatment for MDS. The incidence of MDS continues to increase because of better recognition of this hematological malignancy. Therapeutic agents currently approved for MDS have for the first time changed the natural history of the disease, although they are not curative, and thus there is significant room for improvement. As we better define MDS, using increasingly sophisticated technology such as SNP arrays, novel targeted agents have the potential to further improve the outcomes of MDS.

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