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REVIEW ARTICLE

Hypomethylating Agents and Other Novel Strategies in Myelodysplastic Syndromes

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ABSTRACT

Over the last decade, treatment approaches for patients with myelodysplastic syndromes (MDS) have improved significantly. Treatment of MDS is tailored to the specific risk characteristics of the patient. In general, patients are divided into lower- and higher-risk categories. Without therapy, prognosis of patients with higher-risk MDS is poor, and treatments should be directed to improve survival. Prognosis of patients with lower-risk MDS is more heterogeneous, and therapies are usually directed to minimize transfusion needs and potentially to alter the natural course of the disease. Treatment options for patients with higher-risk MDS include hypomethylating agents (azacitidine and decitabine), intensive chemotherapy (ICT), and allogeneic stem-cell transplantation (alloSCT). The use of the hypomethylating agents has transformed the approach to this patient population, in particular older individuals, for whom ICT and alloSCT are not an option. In lower-risk MDS, treatment strategies are used sequentially and usually include observation in patients with low risk and no transfusion dependency, growth factors, and lenalidomide for patients with alteration of chromosome 5 and anemia. The use of hypomethylating agents is less understood in this group of patients. AlloSCT is usually reserved for patients with lower-risk MDS closer to the time of transformation. In this short review, we discuss treatment alternatives for patients with MDS and delineate some of the ongoing challenges, including the development of better front-line strategies for patients with higher-risk disease, the concept of altering the natural course of the disease in lower-risk MDS, and the development of new treatment approaches for patients who do not benefit from hypomethylating agents.

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INTRODUCTION

Myelodysplastic syndromes (MDS) are clonal hematopoietic stem-cell disorders characterized by ineffective hematopoiesis, peripheral-blood cytopenias, and increased tendency to progress to acute myeloid leukemia (AML).[1] Median age of patients with MDS is approximately 70 years.[2] This patient population is frequently affected by other comorbid conditions, a factor that often influences treatment decisions. Treatment of MDS is based on prognostic factors that predict survival and progression to AML. The most widely used prognostic system for therapeutic decision making is still the International Prognostic Scoring System.[3] This system stratifies patients into the following four groups: low, intermediate-1, intermediate-2, and high risk. Risk is based on number of cytopenias, percentage of bone marrow blasts, and karyotype. Low risk and intermediate-1 risk are usually grouped together as lower-risk disease, whereas intermediate-2 risk and high risk are grouped together as higher-risk disease. Several other factors have recently been shown to have prognostic value. These include, among others, the need for RBC transfusions[4] and the presence of reticulin marrow fibrosis.[5] Analysis of recently identified genetic and immunophenotypic alterations has not yet been introduced in the therapeutic decision making of MDS.[1]

The survival of patients with higher-risk MDS is significantly different than that of patients with lower-risk disease. Without intervention, median survival of higher-risk patients is close to 12 months.[3] Survival of patients with lower-risk disease is more diverse and ranges from a few months (poor-prognosis, lower-risk disease) to more than a decade (Fig 1 and Tables 1 and 2).[3,6] Risk of transformation to AML in lower-risk MDS is less than 30%.[6] A recent analysis has indicated that most patients with lower-risk MDS die from causes directly related to complications of MDS.[7] Therefore, the objectives of therapy are different in lower- versus higher-risk disease. In higher-risk MDS, treatment options should impact survival as a primary end point. In lower-risk MDS, therapies should be adapted to specific patient situation, including severity and type of cytopenias and expected survival.[6] Therefore, in lower-risk MDS, therapies should have

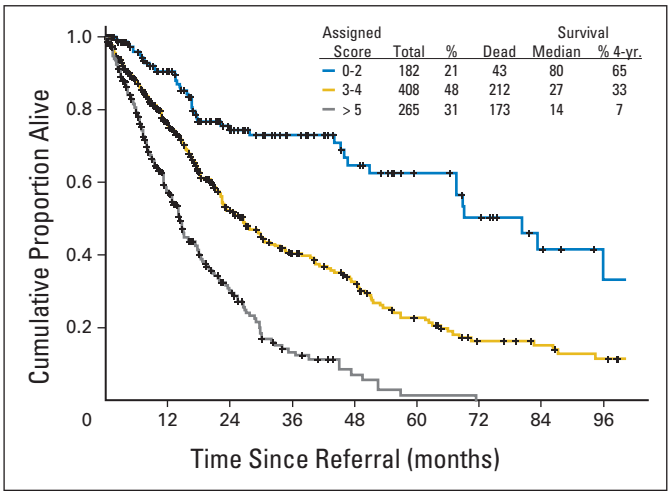

Fig 1. Prognosis of patients with lower-risk myelodysplastic syndrome (MDS). A prognostic model has been developed that allows the calculation of survival in patients with low and intermediate-1 MDS.[6] Characteristics include age, hemoglobin level, platelet count, percentage of blasts, and cytogenetics (Table 1). Score can vary from 0 to 7 points (Table 2). Survival is indicated in months.

the capacity to improve transfusion needs and potentially survival. Current potential treatment strategies are summarized in Figure 2.

STANDARD OF CARE FOR PATIENTS WITH HIGHER-RISK MDS

Three different therapeutic alternatives are currently available for patients with higher-risk MDS. These include hypomethylating agents, intensive chemotherapy (ICT), and allogeneic stem-cell transplantation (alloSCT). Only one of three options, the use of the hypomethylating agent azacitidine, has been formally shown in a randomized clinical trial to improve survival of patients with higher-risk MDS.[8] Durable responses compatible with long-term survival have been documented with the use of ICT and alloSCT.[9]

Hypomethylating Agents: Azacitidine and Decitabine

Two agents with the capacity to induce DNA hypomethylation in vivo are currently available; these are azacitidine and decitabine.[8,10] The mechanism of action of these agents is not understood, but it is well documented that these drugs can induce gene and global hypomethylation in vivo.[11] Because of the possibility that these agents work via other mechanisms other than induction of DNA hypomethylation, it is also adequate to refer to them as DNA methyltransferase inhibitors or azanucleosides based on the enzyme they inhibit or their structure, respectively. It should be noted that aberrant DNA methylation is a poor prognostic feature in MDS.[12]

Azacitidine has been studied in higher-risk MDS in two major randomized multicenter trials, Cancer and Leukemia Group B (CALGB) 9221[13] and AZA-001.[8] In the CALGB 9221 study,[13] 191 patients with MDS were randomly assigned to either azacitidine (75 mg/m^2/d for 7 consecutive days every 28 days) or best supportive care (BSC). Median age was 68 years. Sixty percent of patients in the azacitidine arm, compared with 5% of patients in the control arm, responded to treatment ($P < .001$). The median time to leukemic transformation or death was 21 months in patients treated with azacitidine compared with 12 months in the BSC arm ($P = .007$). No significant difference in survival was observed. A landmark analysis suggested a survival advantage for patients initially on azacitidine or who had crossed over to azacitidine within 6 months of inclusion on study ($P = .03$). A significant improvement in quality of life was documented in patients treated with azacitidine compared with BSC.[14] AZA-001 was a randomized study designed to test the hypothesis that treatment with azacitidine resulted in improved survival compared with a menu of standard-of-care options.[8] These options included BSC, low-dose cytarabine (ara-C), and ICT. In AZA-001, 358 patients with higher-risk MDS were randomly assigned to either azacitidine (as per CALGB 9221 schedule) or to standard of care. Median age of patients was 69 years. Median survival time was significantly better in patients treated with azacitidine versus standard-of-care options (24.5 *v* 15 months, respectively; $P = .001$). With azacitidine, progression to AML was significantly delayed, and RBC transfusion requirements and rate of infections were significantly improved. The survival advantage with azacitidine was irrespective of age (including patients older than age 75 years), percentage of marrow blasts (including patients with 20% to 30% blasts, now classified as AML using WHO criteria), or karyotype. This effect was significant when compared with BSC and low-dose ara-C. The number of patients treated with ICT was too small to allow comparison with azacitidine.

Decitabine is another nucleoside analog with the capacity to induce DNA hypomethylation. This agent has had a parallel development to that of azacitidine in the United States. A randomized study

Table 1. Prognostic Model of Lower-Risk Myelodysplastic Syndrome: Multivariate Analysis Poor-Prognosis Parameters and Assigned Score

Adverse Factor	*P*	Assigned Score
Unfavorable cytogenetics	< .001	1
Age ≥ 60 years	< .001	2
Hgb < 10 g/dL	< .001	1
Plt, $\times 10^9$/L		
< 50	< .001	2
50-200	< .001	1
BM blasts ≥ 4%	< .001	1

NOTE. Data adapted.[6]
Abbreviations: Hgb, hemoglobin, Plt, platelets; BM, bone marrow.

Table 2. Prognostic Model of Lower-Risk Myelodysplastic Syndrome: Estimated Survival Outcome Within Each Score Range

Score	No. of Patients	Median Survival (months)	4-Year Survival Rate (%)
0	11	NR	78
1	58	83	82
2	113	51	51
3	185	36	40
4	223	22	27
5	166	14	9
6	86	16	7
7	13	9	NA

NOTE. Data adapted.[6]
Abbreviations: NR, not reached; NA, not available.

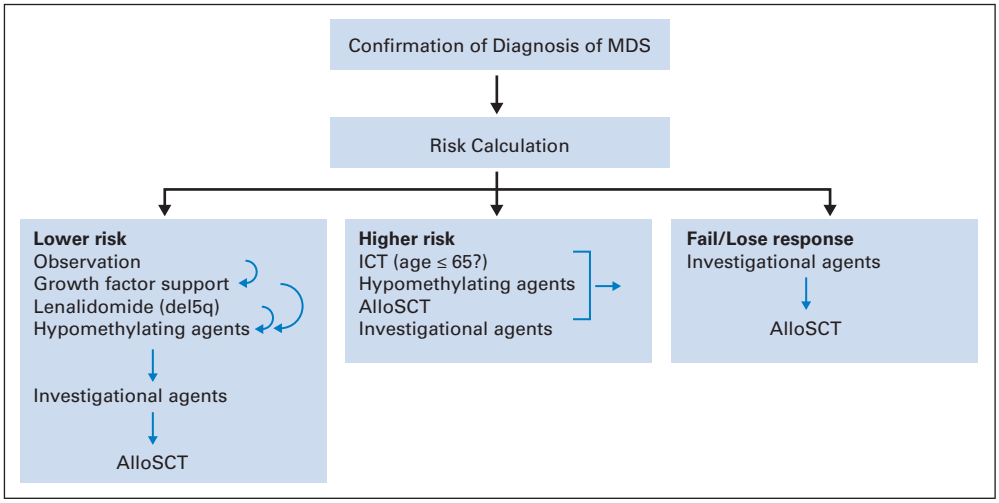

Fig 2. Treatment algorithm for patients with myelodysplastic syndrome (MDS). The first step when evaluating a patient with MDS is confirmation of diagnosis. Risk can be calculated using a number of classifications. Traditionally, patients with lower-risk disease are those with low or intermediate-1 by the International Prognostic Scoring System.[3] Patients with higher-risk disease are those with intermediate-2 and high risk. A number of options exist for patients with lower-risk disease. One option is observation (for patients who are transfusion independent and have an expected long survival and minimal risk of transformation[3,6]). Growth factor support with erythroid-stimulating agents is usually recommended for patients with anemia early in the course of disease. Lenalidomide is the standard of care for patients with anemia and a deletion of chromosome 5 (del5q). Results with lenalidomide are better in patients early in the course of their disease, patients who are minimally transfused, and patients with no severe thrombocytopenia. As indicated by the arrows, these approaches are sequential. A patient can be initially observed and started on growth factors and then eventually receive a hypomethylating agent. Investigational agents are considered in patients who have not benefitted from standard approaches. Allogeneic stem-cell transplantation (alloSCT) is usually reserved for patients who have received all of these approaches or who are considered to be at high risk of progression or death.[6] Options for patients with higher-risk disease are more limited. Observation is rarely an option for this group of patients. Main options include intensive chemotherapy (ICT) or a hypomethylating agent. ICT is usually reserved for younger patients who are expected to transition to alloSCT in a short period of time after induction. Results with ICT are better in patients with diploid karyotypes. Most patients are candidates for a hypomethylating agent. Younger patients with abnormal karyotypes, particularly those with alterations of chromosome 7, should be considered for a hypomethylating agent instead of ICT. Finally, all potential candidate patients (younger, available donor, no excess comorbidities) should be considered for alloSCT. Most patients receive some form of therapy before proceeding to alloSCT. The timing of alloSCT for patients who respond to ICT or hypomethylating agent is controversial. Some investigators recommend proceeding with alloSCT as soon as possible, whereas others recommend using hypomethylating agents for as long as possible before relapse or transformation.

was performed in the United States that compared decitabine with BSC.[15] In this study, the dose of decitabine was 15 mg/m^2 intravenous (IV) infused over 3 hours every 8 hours for 3 days (at a dose of 135 mg/m^2 per course) and repeated every 6 weeks (the so-called 3-day schedule). Although there was no clear benefit in terms of survival in this study, the use of decitabine was associated with a complete response (CR) rate of 9% and overall response rate of 17%. These results led to the approval of decitabine in the United States. In parallel with these results, investigators at the MD Anderson Cancer Center developed pharmacodynamically targeted schedules of decitabine in patients with MDS.[16] In an initial phase I trial, a daily dose schedule of decitabine administered for 5 to 20 days was shown to be safe.[16] Of interest, responses in this study were more frequently observed in patients receiving a schedule of 15 mg/m^2 IV daily for 10 days.[16] It should be noted that this study was performed mainly in patients with AML. On the basis of these results, a Bayesian randomized phase II trial of three different doses and schedules of decitabine was conducted.[17] In this study, a 5-day schedule of decitabine administered daily at a dose of 20 mg/m^2 was shown to be superior to a 10-day or subcutaneous schedule. A multicenter phase II trial of decitabine (Alternative Dosing for Outpatient Treatment [ADOPT]) using the 5-day schedule confirmed the safety of this schedule, although response rates were significantly lower than those reported by the MD Anderson group.[18] In the ADOPT study, the median number of courses administered was five courses, the CR rate was 17%, and the median survival time was 19.4 months. No randomized survival study of a 5-day schedule of decitabine has been conducted in MDS. In parallel with this work, European investigators developed a randomized study of decitabine using the initial 3-day schedule. The major objective of the study was survival. Although this study has not yet been published, results presented at an American Society of Hematology meeting in 2008 indicated that decitabine, when used according to the 3-day schedule, did not impact survival of patients with higher-risk MDS. Despite these data, the final dose and schedule of decitabine are not fully understood. Recently, Blum et al[19] have indicated that a 10-day schedule of decitabine has significant activity in AML.

Dynamics of Response With Hypomethylating Agents: When to Stop Therapy?

CR rates with both azacitidine and decitabine are relatively low compared with AML induction-like programs. This lower response rate is balanced by a low induction mortality rate. In most series, mortality is usually less than 5% in the first 6 to 8 weeks. This may result in the survival benefits observed with these agents in MDS. In both the CALGB 9221 and AZA-001 trials of azacitidine,[8,13] several courses of therapy (four to six cycles) were required to achieve response. Thus, at least six cycles of azacitidine seem to be required to document lack of response. It should be noted that in a small percentage of patients, responses can be observed after up to 12 cycles of therapy. In the AZA-001 trial,[8] the median number of cycles of azacitidine administered was nine cycles (14 cycles in responders). This further suggests that prolonged treatment with azacitidine may be a key factor for the survival advantage observed with azacitidine. To further complicate matters, in addition to patients who achieved CR

or partial response (PR), patients who achieved hematologic improvement (characterized by achievement of RBC transfusion independence and/or improvement in platelet count) also seemed to have a survival benefit in AZA-001. These data indicate that continuation of therapy for as long as possible, even in patients who do not achieve a CR, is recommended at the present time. These same principles probably apply to decitabine.

Continuation of therapy is particularly important in patients who achieve a CR. In two studies of combination of decitabine or azacitidine with valproic acid[11,20] in patients with AML, patients who achieved a CR and discontinued therapy at 24 months (as mandated per protocol) universally experienced relapse once therapy was stopped. Median time to relapse was short (2 to 4 months), and prognosis of such patients was poor, with a median survival time of less than 4 months (unpublished data). Although it is possible that relapses could have occurred even if therapy was continued, it is our experience that once treatment with a hypomethylating agent is stopped, most patients lose response.

Chemotherapy in Higher-Risk MDS

ICT protocols in higher-risk MDS have generally used classical anthracycline/ara-C combinations similar to those used in de novo AML.[21,22] No drug in combination with ara-C, including fludarabine or topotecan, has so far proved superior to anthracycline/ara-C combinations.[23] When used in MDS or AML after MDS, ICT results in lower CR rates (40% to 60%) and shorter CR duration (median duration, 10 to 12 months) and tends to be associated with more prolonged periods of aplasia. In addition, the feasibility of ICT is also reduced by the advanced median age of patients with MDS. The most important prognostic factor of response to ICT is karyotype; patients with unfavorable karyotype (−7/del 7q or complex karyotype) have a low CR rate and short duration of response. This is of importance because, at least in the AZA-001 study,[8] patients with alterations of chromosome 7 had a significant benefit with azacitidine versus other therapies. Recently, microRNA 29b has been suggested to be involved in the preferential response rate observed with decitabine in patients with chromosome 7 alterations.[19] Currently, ICT is recommended for relatively younger patients with favorable karyotype, particularly candidates for alloSCT when a rapid blast percent reduction before transplantation is needed.

A commonly used treatment approach for higher-risk MDS in Europe is the use of low-dose ara-C. At doses of 20 mg/m^2/d for 14 to 21 days every month, this approach results in CR and PR rates of 15% and 20%, respectively.[24] As with ICT, responses are mainly observed in patients with favorable karyotype.[25] Myelosuppression is often severe. In the AZA-001 study, low-dose ara-C was shown to be inferior to azacitidine.[8] Therefore, we do not routinely recommend the use of low-dose ara-C in MDS.

AlloSCT in Higher-Risk MDS: When Is the Optimal Time?

AlloSCT is reported to be the only curative treatment of higher-risk MDS. Results from selected studies report prolonged disease-free survival in approximately 30% to 50% of patients.[9] However, the use of alloSCT is mainly restricted to younger patients with an appropriate donor. Different transplantation modalities of different intensities and donor sources are now in use. Most of them remain investigational, and therefore, in our opinion, all patients should receive transplantation in the setting of a clinical trial. Current advances in transplantation technology are allowing the consideration of older patients and alternative donors. This should result in a greater number of older patients benefitting from this potentially curative treatment modality.

Probably the most important question for the practicing physician is the timing of transplantation. A study from the International Bone Marrow Transplant Registry indicated that early transplantation in higher-risk MDS was associated with longer life expectancy.[26] This study was performed before the mature use of hypomethylating agents, and it was a retrospective Markov analysis. Current questions are whether patients in CR using a hypomethylating agent should receive transplantation at the time of best response if a donor exists or should delay transplantation until the time of progression. No recommendation can be given at this time. Other questions include whether or not alloSCT should be preceded by a cytoreductive regimen (with chemotherapy or perhaps hypomethylating agents). In the absence of prospective studies, many authors consider that when marrow blasts are greater than 10% at the time of transplantation, because of the high relapse risk after transplantation, pretransplantation therapy is required. ICT is recommended in the presence of favorable karyotype, and a hypomethylating agent is recommended if karyotype is abnormal. A recent preliminary report from the European Group for Blood and Marrow Transplantation has indicated that long-term survival of patients with monosomy 7 is poor with alloSCT.[27] Although these data need to be validated in more recent series, these results have significant implications for the use of alloSCT in MDS, because this suggests that the current practice of reserving transplantation for patients with poor prognostic features may not be indicated.

STANDARD OF CARE FOR PATIENTS WITH LOWER-RISK MDS

Until recently, treatment approaches in patients with lower-risk MDS have focused on improving transfusion needs. It should be noted that we consider transfusions as part of supportive care in MDS. In general, patients with lower-risk MDS do not receive therapy until they become transfusion dependent. This notion could be challenged by the recent report that the prognosis of patients with lower-risk MDS is heterogeneous, ranging from 9 months to more than a decade.[6] This model may allow the identification of patients with lower-risk disease and poor prognosis (Fig 1). The question is whether the more aggressive treatment of these patients, including alloSCT, can favorably change the natural history of this group of patients with poor prognosis and lower-risk disease. This concept needs to be tested in prospective clinical trials. Current strategies for patients with lower-risk disease include growth factor support, iron chelation, lenalidomide, hypomethylating agents, immunosuppressive therapy, and alloSCT. ICT is rarely used in lower-risk MDS.

Growth Factors

Erythroid responses to high-dose recombinant epoetin (EPO) alfa or beta or darbepoetin alfa are observed in approximately 20% of patients with MDS. This figure increases to approximately 50% to 60% if treatment is restricted to patients with lower-risk MDS, minimal RBC transfusion requirements (< 2 concentrates/month), and serum EPO level less than 500 U/L and if granulocyte colony-stimulating factor is added to EPO.[28] Erythroid-stimulating agents

(ESAs) are generally the first-line treatment for anemia in lower-risk MDS except in cases of both serum EPO greater than 500 U/L and high transfusion requirement. In this situation, the response rate is only 15% to 20%. Responses to ESA are usually observed within 12 weeks of treatment. Median duration of responses is approximately 2 years.[28] ESAs are able to not only decrease or avoid the need for RBC transfusions, but also improve quality of life. Importantly, whereas ESAs have been suspected of shortening survival in patients with solid tumors, two studies have shown that ESAs do not increase the risk of progression to higher-risk MDS and AML and strongly suggest that they may even improve survival, compared with treatment of anemia with RBC transfusions alone.[28] This effect could be a result of the fact that ESAs can, at least in responders, maintain higher median hemoglobin levels than RBC transfusions. Chronic anemia reduces survival by increasing the risk of cardiovascular events and potentially decreasing the complications of cardiac failure and iron overload. It should be noted that no prospective randomized study has demonstrated any benefit of growth factor support in MDS.

Lenalidomide in Lower-Risk MDS With 5q Deletion

Lenalidomide is approved in the United States for patients with lower-risk MDS with del5q and transfusion-dependent anemia. This was based on results of a phase II trial of 148 patients with these characteristics.[29] In this study, transfusion independence was achieved in 67% of patients, and the mean duration of transfusion independence was 2.2 years. Cytogenetic response was documented in 73% of patients. Grade 3 or 4 myelosuppression, mainly during the 3 first months, is the most common adverse event with lenalidomide. Lenalidomide is considered the first-line treatment for patients with lower-risk MDS with del5q and anemia. Lenalidomide is not approved in Europe because of concerns regarding potential increased risk of progression to AML. Several large series of patients with lower-risk MDS with del5q treated with or without lenalidomide are being analyzed to study this issue. Preliminary results from randomized studies do not support the notion that lenalidomide increases the risk of AML.[30]

Hypomethylating Agents in Lower-Risk MDS

There is less experience with the hypomethylating agents in lower-risk MDS. Several studies have shown that azacytidine and decitabine can yield an erythroid response in 30% to 40% of patients with lower-risk MDS resistant to an ESA.[31] Platelet responses are also observed in thrombocytopenic patients. On the basis of these results, azacitidine and decitabine are also approved in the United States for the treatment of lower-risk MDS with symptomatic cytopenias. The question is whether the currently approved doses and schedules of decitabine and azacitidine are appropriate for patients with lower-risk disease. For instance, a 5-day schedule of azacitidine has shown activity and safety in a community-based trial for patients with MDS.[31] The question is whether lower-dose schedules of hypomethylating agents in lower-risk MDS are more appropriate. This is discussed later.

Immunosuppressive Drugs in Lower-Risk MDS

On the basis of evidence that involves immune deregulation with MDS,[32] antithymocyte globulin (ATG; with or without cyclosporine) has been used in MDS, with reversal of anemia and other cytopenias in 30% to 40% of lower-risk patients (generally resistant to ESAs).[33,34] Response is seen mainly in relatively young patients and patients with relatively recent RBC transfusion need, no or limited excess of blasts, normal karyotype, and HLA-DR15 positivity.[33] However, the proportion of patients with MDS with such features is relatively low in the general MDS population. Experience with ATG at other centers has not fully confirmed these results. In these other series, responses to ATG have more frequently been observed in patients with hypoplastic MDS.[35]

EMERGING STRATEGIES IN THE TREATMENT OF MDS

The approach to MDS has changed from considering the disease a preleukemic condition for which there was almost no therapeutic alternative to considering it a complex group of hematopoietic disorders with diverse natural histories and treatment alternatives. The three main objectives in clinical research in MDS are to improve current results with azacitidine in front-line therapy in higher-risk MDS, to develop novel strategies for patients with lower-risk MDS, and to developed new therapies for patients who lose response to hypomethylating agents.

Improving Current Approaches in Higher-Risk MDS

The optimal use of hypomethylating agents is still to be determined, particularly because their mode of action remains uncertain. Although hypomethylation certainly plays a role, epigenetic changes in genes associated with response have not yet been identified, and no clear correlation has been found between response and induction of hypomethylation in vivo.[36] The optimal duration of treatment with hypomethylating agents is also unknown, but our recommendation, as discussed earlier, is to prolong therapy as much as possible, probably until disease progression. Regarding schedule, a 5-day regimen of azacitidine has shown similar erythroid response rates as 7-day schedules in lower-risk MDS,[31] but it cannot be ascertained whether the 5-day regimen will result in the same survival benefit as the classical 7-day regimen in higher-risk MDS.

Despite the encouraging results with azacitidine, it is obvious that it will be important to have access to second-generation agents with the capacity to increase faster early response rates with acceptable toxicity profiles. We do not have such a drug at the present time. Recently, preliminary results of an oral formulation of azacitidine have been presented.[37] In a follow-up phase I study, the compound was used orally daily for 7 days. Of interest, pharmacokinetic and pharmacodynamic studies comparing the subcutaneous and oral routes within patients indicated that the oral route was associated with significant less exposure than the subcutaneous route. That said, a CR rate of close to 30% was observed in previously untreated patients with MDS. These responses have been durable, with a median duration of response of more than 12 months at the time of initial report of this trial.[38] Another approach is to develop combination strategies using either azacitidine or decitabine. Several such approaches are currently in place. These include the addition of histone deacetylase (HDAC) inhibitors[39] and tumor necrosis factor α inhibitors, among others. In vitro, the combination of an HDAC inhibitor with either azacitidine or decitabine results in synergistic antileukemia activity.[40] In early clinical studies with the HDAC inhibitor valproic acid, faster and increased response rates have been documented.[11,20] The data of these early phase I/II trials are encouraging enough that this combination is being tested in several randomized clinical trials. Data with other combinations, including the use of lenalidomide,[41] are promising but not yet fully understood.

Other alternatives with the hypomethylating agents include their use before or after other treatments. Hypomethylating agents are being investigated before alloSCT to reduce the tumor burden and particularly the marrow blast percentage as a means to reduce the risk of relapse after transplantation. Hypomethylating agents could be especially attractive in patients with unfavorable karyotype, where ICT yields low response rates. Azacitidine and decitabine are also being evaluated after alloSCT to reduce relapse after transplantation.[42] Azacitidine has also been used in higher-risk MDS or in AML after MDS, after having achieved CR or PR with ICT, with disease-free survival rates being at least similar to those obtained with consolidation chemotherapy, but with less myelosuppression.[43]

Another recent approach is the use of lenalidomide in higher-risk MDS with alteration of chromosome 5 based on the fact that lenalidomide seems to be capable of targeting the del5q clone in MDS (as shown, in particular, by the cytogenetic CRs obtained and in vitro data on cell lines with del5q). Lenalidomide is also currently being tested in higher-risk MDS (and even AML) with del5q. A preliminary report indicated that lenalidomide could have activity in this setting. It seems that responses are limited to patients with isolated del5q.[44] In those patients, higher lenalidomide doses and/or combinations with other drugs, including azacitidine or anthracycline/ara-C chemotherapy, are being tested.[41]

New Drugs in Higher-Risk MDS: Alternatives for Patients Who Stop Benefitting From Hypomethylating Agents

One of the main current problems in the treatment of MDS is the treatment of patients who do not respond or lose response to hypomethylating agents. The prognosis of these patients is poor. In a series reported from MD Anderson, survival after decitabine failure was less than 5 months.[45] Furthermore, these patients seem to acquire cross resistance to other hypomethylating agents and ara-C–based therapies. A number of new agents are being studied in higher-risk MDS for this group of patients. Most of these agents are classic cytotoxic compounds. This is in part because of the fact that no mechanism of resistance is currently known. Examples of agents being investigated include clofarabine,[46] sapacitabine,[47] topoisomerase I inhibitors, and a compound known as ON1910. On average, response rates are approximately 30%, with responses documented in patients who have experienced treatment failure with prior hypomethylating-based therapy. Ongoing phase II trials are evaluating the activity of these compounds in higher-risk MDS.

New Approaches in Lower-Risk MDS

One logical approach is the use of lenalidomide in lower-risk MDS without del5q. Lenalidomide has been studied in this context; RBC transfusion independence was documented in 25% to 30% of patients with lower-risk MDS without del5q resistant to ESAs. Responses were of shorter duration than those observed in patients with del5q.[48]

Other alternatives in MDS include the use of new growth factors targeted for patients with severe thrombocytopenia and iron chelation for patients with chronic transfusion needs and evidence of iron overload. Thrombocytopenia is difficult to treat in lower-risk MDS. Androgens like danazol can result in transient response in one third of patients, whereas some patients may respond to hypomethylating agents or ATG. Two thrombomimetic agents are approved in the United States for patients with idiopathic thrombocytopenic purpura. One of these, romiplostim, is being extensively studied in patients with MDS.[49] These studies include an ongoing phase II randomized clinical trial. Because of data indicating that these agents could be involved in induction of marrow fibrosis and leukemia transformation, they cannot be recommended at the present time outside the setting of a clinical trial. Romiplostim, when used as a single agent, can significantly improve platelet counts in approximately 50% of patients with lower-risk MDS with thrombocytopenia. However, a transient increase in marrow blast percentage, sometimes to greater than 20%, can be observed in 15% of patients, concordant with the presence of thrombopoietin receptors on blast cells in MDS. Romiplostim can also significantly reduce thrombocytopenia and/or platelet transfusions in patients with MDS receiving azacitidine, decitabine, or lenalidomide and could become an important adjunct to those treatments.[50] Eltrombopag is also being developed in MDS.

Iron overload caused by repeated RBC transfusions is clearly associated with liver and cardiac failure in thalassemia major, and iron-chelating agents have demonstrated a beneficial impact on survival in those patients. In MDS, the deleterious effect of iron overload and the beneficial role of chelating agents in multitransfused patients are more controversial. This is because patients with MDS have usually received fewer transfusions than patients with thalassemias and have shorter survival but also often comorbidities, making it more difficult to attribute organ failure to a given cause, including iron overload, in MDS. In the absence of prospective studies, a few retrospective studies have suggested a survival benefit of iron chelation therapy in heavily transfused patients. Several consensus expert statements have been published. They generally recommend starting iron chelation in patients with relatively favorable prognosis who have received at least 20 to 40 RBC concentrates and/or have a serum ferritin level greater than 1,000 to 2,500 ng/mL.[51] Such guidelines have not been prospectively validated, and some authors even consider that treatment of iron overload has no demonstrated indication in MDS. Two iron-chelating agents are approved in the European Union for MDS—deferoxamine, used IV or subcutaneously, and more recently deferasirox, used orally. Recent preliminary studies have shown that prolonged use of deferasirox for 1 year in heavily transfused patients with MDS reduced the median serum ferritin level by one third and that the drug, despite its potential renal toxicity, can be used safely in most elderly patients with MDS.[51]

A number of new agents are in development for lower-risk MDS. These include single-agent HDAC inhibitors, new p38MAPK inhibitors, glutathione *S*-transferase π inhibitors, alemtuzumab for patients who meet criteria for immunosuppressive-based therapy, and lower doses/schedules of hypomethylating agents in lower-risk MDS. Thus far, the experience with single-agent HDAC inhibitors in lower-risk MDS has been limited. Phase II studies with vorinostat and panabinostat are ongoing. In terms of response, the experience with alemtuzumab and a low-dose schedule of decitabine reported at the American Society of Hematology meeting in 2009 is of interest. In the study of alemtuzumab, Sloand et al[52] used a low-dose schedule of the drug (10 mg daily for 10 days) in patients selected to achieve response to immunosuppressive therapy. Response was observed in a significant fraction of patients treated. The study of low-dose decitabine randomly assigned patients between low-dose schedules of the drug (20 mg/m^2 subcutaneously daily for 3 days or weekly for 3 weeks, both every 4 weeks). Although the CR rate was low ($< 10\%$), disease

stabilization was achieved in close to 70% of patients. The daily for 3 days schedule seems to be superior to the weekly schedule. Complications from myelosuppression were minimal with these schedules. These data, together with the results with oral azacitidine, indicate that low-dose schedules of hypomethylating agents may be beneficial in patients with lower-risk MDS.[53]

A Final Concept: Early Treatment of Poor-Prognosis Patients With Lower-Risk MDS

As discussed earlier, in-depth analysis of patients with lower-risk MDS[6] has demonstrated that the prognosis of these patients is significantly more heterogeneous than previously reported[3] and that a significant fraction of patients with lower-risk disease and a short survival can be identified using these tools. This finding and the realization that most patients with MDS die from MDS[7] indicate that early treatment of this group of patients, regardless of their transfusion needs, could alter their natural history. Therefore, interventions directed to this situation are of significant importance.

SUMMARY

Treatment options for patients with MDS have improved significantly over the last decade for both patients with higher- and lower-risk disease. The use of hypomethylating agents has resulted in improved survival of patients with MDS. Despite these advances, prognosis of patients with MDS is still poor, and investigators and clinicians in this area face a number of challenges. These include the development of better front-line therapies for patients with higher-risk disease, new treatment strategies for patients who lose response to hypomethylating agents, and new therapeutic alternatives that improve survival of patients with lower-risk disease.

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