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Use of azacitidine for myelodysplastic syndromes: controversial issues and practical recommendations

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Abstract

Azacitidine is recommended for patients with higher-risk myelodysplastic syndromes (MDS) who are not eligible for intensive therapy or for patients with lower-risk MDS who have thrombocytopenia or neutropenia or have anemia that is unresponsive to other therapies. However, standard treatment with azacitidine has not been optimized and many issues about the use of azacitidine remain unresolved. The use of azacitidine is expanding rapidly, but limited comparative clinical trial data are available to (i) define the optimal use of azacitidine in patients with higher-risk MDS or around the time of allogeneic hematopoietic stem cell transplantation, (ii) identify those patients with lower-risk MDS who may benefit from treatment, and (iii) guide physicians on alternative therapies after treatment failure. Increasing evidence suggests that the clinical features, prognostic factors, and cytogenetic profiles of patients with MDS in Asia differ significantly from those of patients in Western countries, so the aim of this review is to summarize the evidence and provide practical recommendations on the use of azacitidine in patients with MDS in the Republic of Korea. Evidence considered in this review is based on published clinical data and on the clinical experience of an expert panel from the acute myeloid leukemia/MDS Working Party of the Korean Society of Hematology.

Key Words Azacitidine, Hypomethylating agents, Myelodysplastic syndromes, Practice guidelines as topic

INTRODUCTION

Myelodysplastic syndromes (MDS) consist of a diverse group of clonal hematopoietic stem cell disorders characterized by impaired blood cell production, abnormal blood cell morphology, and peripheral cytopenias.As most patients are not eligible for allogeneic hematopoietic stem cell transplantation (HSCT), treatment options for patients with a poor prognosis for survival are limited and focus on controlling symptoms, slowing disease progression, and avoiding any severe side effects of treatment [1]. Several prognostic scoring systems are available to help clinicians decide when to treat patients with MDS and with which therapeutic option [1]. The most commonly used scoring system is the International Prognostic Scoring System (IPSS), which categorizes patients into 4 risk groups (low, intermediate-1, intermediate-2, or high) according to the number of cytopenias, percentage of blasts in the bone marrow, and type of cytogenic abnormalities [2]. In general, management of patients with lower-risk MDS is more supportive and aims to improve cytopenias to reduce the need for red blood cell or platelet transfusion, whereas management of patients with higher-risk MDS is more intensive and aims to slow disease progression, prevent progression to acute myeloid leukemia (AML), and prolong survival [1].

The hypomethylating agents azacitidine and decitabine are recommended for patients with higher-risk MDS who are not eligible for intensive therapy (e.g., HSCT or intensive chemotherapy) or for patients with lower-risk MDS who have thrombocytopenia or neutropenia or who have anemia that is not responsive to other therapies [1, 3, 4]. The use of azacitidine, compared with supportive or conventional care, results in significant improvements in response rates,

overall survival, and quality of life as well as prolonged time to AML transformation [5, 6]. Several practical guidelines describing the general use of azacitidine in patients with MDS are available [7, 8], but there is relatively little information on the use of azacitidine in patients with lower-risk MDS. In addition, many issues about the use of azacitidine remain unresolved, such as how azacitidine can be used around the time of HSCT or the optimal dosing schedules for various risk groups.

Increasing evidence suggests that the clinical features, prognostic factors, and cytogenetic profiles of patients with MDS in Asia differ significantly from those of patients in Western countries [9-16]. For example, patients with MDS in Asia are younger than patients with MDS in Western countries [11, 13, 14, 16] and have a lower incidence of the chromosome 5q deletion [9, 11, 12, 14, 15]. Differences in the availability and provision of treatments for MDS between Asian and Western countries (e.g., different blood cell thresholds for red blood cell transfusion [9, 11], reimbursement policies) can also contribute to disparities in clinical decision making about treatment for MDS. DNA methylation profiles are currently being investigated as potential biomarkers for predicting and monitoring the clinical response to hypomethylating drugs [17]. Although there is preliminary evidence to suggest that specific gene mutations and mutation combinations may be associated with the clinical response to hypomethylating drugs [18] (and Traina *et al.* American Society of Hematology [ASH] Annual Meeting. Abstract 461. Blood 2011;118), a consistent correlation has not yet been demonstrated for the clinical response to azacitidine and a patient's DNA methylation profile before treatment. Hence, current clinical decision making in the Republic of Korea is based on scoring systems that were developed for use in Western populations or based on recommendations created from clinical experience in Western populations that may not be as applicable in Asian populations [15].

The aim of this review is to summarize the evidence and provide practical recommendations on the use of azacitidine in patients with MDS in the Republic of Korea. This review will focus on (i) general considerations for the use of azacitidine and (ii) special considerations for the use of azacitidine in patients with lower- and higher-risk MDS. Evidence for recommendations provided in this review is based on published clinical data and the clinical experience of an expert panel from the AML/MDS Working Party from the Republic of Korea.

GENERAL CONSIDERATIONS

1. Background

The use of azacitidine in clinical practice is based primarily on the findings of 2 phase 3 randomized clinical trials of azacitidine (75 mg/m^2 per day for 7 days every 28 days) conducted in patients with MDS in the United States [6] and Europe [5]. Patients in both trials had a median age of 68 or 69 years, and most had higher-risk MDS as defined using the IPSS or French-American-British (FAB) classification system. In the Cancer and Leukemia Group B (CALGB) 9221 trial, 191 patients were randomized to treatment with either azacitidine or best supportive care; patients who received supportive care could switch to azacitidine if their disease worsened [6]. Of the evaluable patients, 60% (60/99) treated with azacitidine responded (CALGB criteria) to treatment compared with 5% (5/92) who received supportive care. Progression to AML or death was delayed significantly in patients who were treated with azacitidine versus best supportive care (21 months vs. 12 months, P=0.007), and the median survival in patients randomized to treatment with azacitidine was significantly longer than that in patients who received supportive care and never switched to azacitidine or who switched after 6 months (18 months vs. 11 months, P=0.03) [6]. In addition, findings from a pooled analysis of 3 CALGB clinical trials showed that between 10% and 17% of patients treated with azacitidine (N=268) achieved complete remission [19].

In the AZA-001 trial, 358 patients were randomized to treatment with either azacitidine or conventional care with 3 options for active therapy (best supportive care, intensive chemotherapy, or low-dose cytarabine) and the median time of follow-up was 21 months [5]. Treatment with azacitidine, compared with conventional care, resulted in significantly improved overall survival (24.5 months versus 15.0 months, log-rank P=0.0001) and significant delays in progression to AML (17.8 months vs. 11.5 months, $P<0.0001$). The improvement in overall survival was consistent across all IPSS cytogenic subgroups, including those with unfavorable cytogenetic abnormalities. Of the 111 patients who were transfusion dependent at baseline, 45% became transfusion independent during treatment with azacitidine.

One prospective, noncomparative clinical trial examined the pharmacokinetics, efficacy, and safety of azacitidine in 53 patients with MDS from Japan [20]. Patients in this trial had intermediate- or high-risk MDS (defined using the IPSS), were a median age of 65 years, and were treated with azacitidine 75 mg/m^2 per day for 7 days every 28 days by either subcutaneous or intravenous administration. There were no apparent differences in the pharmacokinetics of azacitidine between patients from Japan and Western countries. One-third (10/30) of patients with higher-risk MDS had a hematologic response (28.3% [15/53] of all patients), and of the 27 patients who were transfusion dependent at baseline, 55.6% became transfusion independent during treatment. There were no differences in efficacy or safety outcomes for the different routes of administration.

Two retrospective studies were conducted in the Republic of Korea to assess the factors affecting survival in patients with MDS who were treated with azacitidine [21, 22]. Patients in these studies had a median age of 59 [21] and 64 [22] years, and approximately one-third were classified as having higher-risk MDS (defined using the IPSS). In general, the findings from these studies were comparable with those from the CALGB and AZA-001 trials. Approximately

17% of patients achieved a complete response [21, 22], and the median overall survival was 20 months [22].

2. Issue for consideration 1: dosing schedule

The standard dosing schedule for azacitidine is subcutaneous or intravenous administration of 75 mg/m^2 per day for 7 consecutive days every 28 days. In practice, 7 consecutive days of treatment may be problematic for outpatients who cannot attend weekend clinic visits or for outpatient clinics that do not offer weekend treatment. Alternative dosing schedules that eliminate the need for weekend treatment have been assessed in an open-label randomized trial [23]. In this study, patients were assigned to (i) a 5-2-2 schedule (5 days of azacitidine at 75 mg/m^2 per day followed by a 2-day break and an additional 2 days of azacitidine, total cumulative dose=525 mg/m^2), (ii) a 5-2-5 schedule (5 days of azacitidine at 50 mg/m^2 per day followed by a 2-day break and an additional 5 days of azacitidine, total cumulative dose=500 mg/m^2), or (iii) a 5-day schedule (5 days of azacitidine at 75 mg/m^2 per day, total cumulative dose=375 mg/m^2). Findings from this study showed similar hematologic improvement across all groups (44% to 56%) and similar rates of transfusion independence (50% to 64%). As expected, the lowest total cumulative dose (5-day schedule) was better tolerated, with more patients completing 6 cycles of treatment than patients who received the higher total cumulative doses (5-2-2 or 5-2-5 schedules). However, the findings of this study should be interpreted with caution, particularly for patients with higher-risk MDS, because the standard dosing schedule was not included in this study as a control arm and almost two-thirds of patients had lower-risk MDS (defined using the FAB system). In addition, because overall survival or progression to AML was not assessed in this study, it is not possible to determine the effect of a modified dosing schedule on the survival benefit of azacitidine.

Recommendation

The expert panel recommends that, in the absence of alternative evidence, the standard dosing schedule of azacitidine 75 mg/m^2 per day for 7 consecutive days every 28 days should be adopted wherever possible, particularly for patients with higher-risk MDS. If the standard 7-day dosing schedule for azacitidine is not feasible, a minimum of 5 consecutive days of treatment at 75 mg/m^2 can be considered for patients with lower-risk MDS and a 5-2-2 schedule comprising 5 days of azacitidine at 75 mg/m^2 per day followed by a 2-day break and an additional 2 days of azacitidine should be considered for patients with higher-risk MDS. A reduction in the total cumulative dose or fewer than 5 consecutive days of treatment is not recommended for patients with higher-risk or lower-risk MDS.

3. Issue for consideration 2: treatment duration

Although the minimum duration of treatment needed with azacitidine to discriminate between responsive and unresponsive patients is unknown, between 4 and 6 cycles are in general sufficient to demonstrate a response to treatment for most patients [19, 24]. Findings from the CALGB and AZA-001 trials showed that the median time to a first response was 2 to 3 cycles, with approximately 90% of responses occurring within the first 6 cycles of treatment [19, 24]; the overall survival benefit in the AZA-001 trial was shown in a median of 9 cycles [5]. Indeed, findings from a retrospective study of clinical practice in the Republic of Korea showed that 95% of responses to azacitidine in patients with MDS (33% with higher-risk MDS and 57% with intermediate-1 MDS defined using the IPSS) occurred within 4 cycles of treatment, with only 3 additional patients showing a response after 5 cycles [22].

More recently, a subgroup analysis of the AZA-001 trial data showed that although most patients (91%) responded within the first 6 cycles, the best response was achieved by 92% of responders after treatment with azacitidine was continued for an additional 6 cycles [24]. This finding is supported by a recent study in the Republic of Korea comparing outcomes of patients with MDS (65% with lower-risk MDS) who received between 4 and 8 cycles (N=106) with those who received more than 8 cycles (median=11 cycles, N=34) (Moon *et al.* 17th Congress of the European Hematology Association. June 14–17, 2012. Amsterdam, the Netherlands). Patients who were treated with more than 8 cycles of azacitidine had higher response rates (67.6% vs. 29.2%) and prolonged overall survival (890 days vs. 612 days).

Recommendation

The expert panel recommends that, in the absence of disease progression or unacceptable toxicity, patients should be treated initially for a minimum of 4 to 6 cycles. At least 1 bone marrow evaluation should be conducted after 2 to 4 cycles of azacitidine in patients with higher-risk MDS and in patients with lower-risk MDS who have greater than 5% blasts in the bone marrow, persistent cytopenias, or cytogenic abnormalities. A bone marrow evaluation may not be necessary for patients with lower-risk MDS who have less than 5% blasts in the bone marrow and no aggravation of cytopenias.

Treatment should be continued for as long as a clinical benefit is evident or until disease progression or unacceptable toxicity for patients with evidence of a treatment response (complete response, partial response, hematologic improvement). A reduced dose of azacitidine may be considered for patients with complete remission on bone marrow biopsy without any hematologic improvement. The decision to continue treatment with azacitidine in patients who have achieved stable disease after 4 to 6 cycles should be made by the attending physician after an assessment of the clinical benefits of continuing treatment and patients' individual needs.

4. Issue for consideration 3: management of adverse events: supportive care and dose modification

The adverse events that are commonly encountered during treatment with azacitidine include hematologic adverse

events (neutropenia, thrombocytopenia, and anemia), gastrointestinal adverse events (primarily nausea, vomiting, diarrhea, and constipation), injection-site reactions, fatigue, and pyrexia [5, 6, 20, 25]. However, most adverse events are transient, occur primarily within the first 2 cycles of treatment, and decrease in frequency with ongoing treatment [25].

Infection and bleeding episodes can worsen with azacitidine treatment.In the patients who were randomized to azacitidine in the CALGB trial (N=150), the number of grade 3 or 4 infections and bleeding episodes was estimated to be 0.21 and 0.14 events per patient-year of exposure, respectively [25]. In the subgroup of patients in the AZA-001 trial who were preselected to receive best supportive care and who were randomized to azacitidine (N=114), the number of grade 3 or 4 infections and bleeding episodes was estimated to be 0.51 and 0.34 events per patient-year of exposure, respectively [25]. The number of infections requiring treatment with intravenous antimicrobial drugs in all patients randomized to azacitidine (N=175) in the AZA-001 trial was 0.6 per patient-year [5]. Although most deaths during the first 3 months of treatment in the AZA-001 trial (11% of patients on azacitidine) occurred because of underlying disease, there were 2 cases of sepsis and 2 cases of bleeding that were thought to be related to treatment and resulted in death [5].

Most adverse events can be managed effectively without the need for treatment discontinuation, dose delays, or dose reductions [25]. Findings from the AZA-001 trial showed that 86% of patients treated with azacitidine were able to remain on the standard dose without the need for a dose adjustment and, of the 32 patients who received 6 or more cycles, 62.5% did not require a dose adjustment [5, 25]. These findings are supported by a retrospective analysis of patients in clinical practice in the Republic of Korea showing that 76% of patients were able to receive 80% of their dose per cycle [21].

Insufficient data are available to support the prophylactic use of antiviral or antifungal agents or granulocyte colony-stimulating factor (G-CSF) in patients with MDS. However, some evidence is available to support the use of prophylactic antibiotics in the reduction of the incidence of fever. Findings from a retrospective study in the Republic of Korea showed that oral administration of prophylactic antibiotics reduced the incidence of febrile episodes in patients with MDS [26].

Recommendation

Effective management of adverse events resulting from treatment with azacitidine may help to prolong treatment duration and exposure of patients to therapeutically effective doses. The expert panel recommends careful and regular monitoring for adverse events, particularly within the first 2 to 3 cycles in patients treated with azacitidine. Full blood counts should be conducted every week during the first 2 cycles and thereafter every 2 weeks or at the discretion of the treating physician. Patients should be reminded to report symptoms of fever or any signs or symptoms of bleeding as soon as possible. Management of patients with cytopenias should follow local guidelines for red blood cell or platelet transfusion.

Dose delays or dose reductions as recommended by Fenaux *et al.* [7] can be considered for management of hematologic adverse events and in accordance with the approved prescribing information (Fig. 1). Dose reductions or delays may decrease exposure of patients to therapeutically effective levels of drug. As such, dose modifications are not recommended in the early treatment phase (first 3 cycles) in patients with

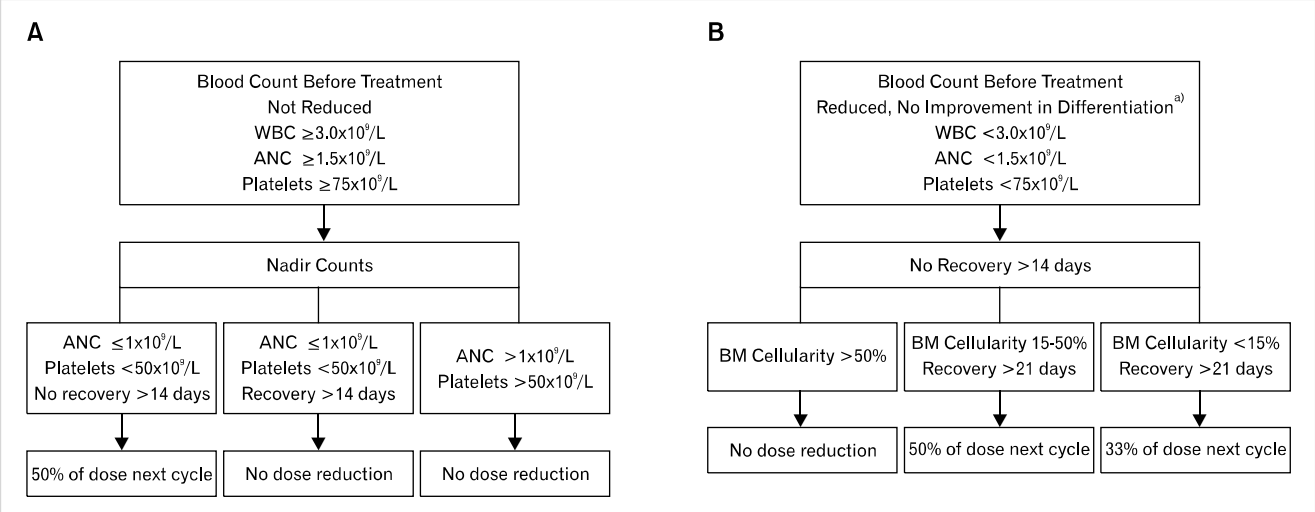

Fig. 1. Recommended dose adaptations for patients with MDS who experience hematologic toxicity after treatment with azacitidine and who have **(A)** no reduction or **(B)** a reduction in blood counts before treatment [7]. Nadir is the lowest count reached in a given cycle. Recovery is defined as a blood count greater than the nadir count+(0.5×baseline count-nadir count). [a)]Improvement in differentiation includes any cell line, not only the cell line with decreased counts before treatment (e.g., percent counts are higher without transfusion than baseline counts). Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; WBC, white blood cell.

more advanced disease (i.e., a high blast percentage or a complex karyotype).

Concomitant medications, such as antiemetics, laxatives, or antidiarrheals, can be administered as required. Prophylactic use of antiemetics may be considered before the administration of each dose of azacitidine. Most injection-site reactions do not require intervention but can be managed with corticosteroids or antihistamines if needed. Although rare, severe skin rash (e.g., Sweet syndrome, neutrophilic panniculitis) has been reported in patients with MDS who are treated with azacitidine. However, these events can be actively treated with corticosteroids [27-29].

Intravenous antibiotics are recommended for the treatment of fever. Findings from a retrospective study in the Republic of Korea showed that oral administration of prophylactic antibiotics reduced the incidence of febrile episodes in patients with MDS [26]. Hence, prophylactic use of oral antimicrobial agents can be considered in patients who may be at increased risk of infection, including secondary prophylaxis for patients who have already experienced severe infection, elderly patients, patients with comorbidities, or those who are anticipated to have severe and prolonged neutropenia (>7 days). In the absence of supporting evidence, the panel does not recommend the use of prophylactic antiviral or antifungal agents. Although G-CSF is not recommended for routine prophylaxis, current guidelines suggest that G-CSF may be used for patients with neutropenia and recurrent or resistant bacterial infections [1] or in patients with febrile neutropenia [30] after azacitidine treatment.

SPECIAL CONSIDERATIONS

1. Issue for consideration 4: treatment of patients with lower-risk MDS

Traditionally, the goals of treatment for patients with lower-risk MDS have been to improve hematologic outcomes, improve quality of life, and reduce the risk of progression to higher-risk MDS or AML. The choice of treatment is currently based on the individual patient's transfusion needs and the presence of clinically significant cytopenias [1]. In general, treatment with a hypomethylating agent is recommended for patients with thrombocytopenia or neutropenia or in patients with anemia who are unresponsive to other therapies [1]. However, the prognosis of patients with lower-risk MDS is highly variable, with survival rates that vary from several months to many years [31] and with most patients dying because of secondary infections and systemic hemorrhage before progression to AML [32, 33]. As such, patients with lower-risk MDS and a poor prognosis may benefit from early and more aggressive therapeutic interventions, irrespective of their transfusion needs [34].

A better understanding of the natural course of disease and prognostic variables that influence survival is fundamental to improving outcomes for patients with MDS. However, a major challenge in improving the survival of patients with lower-risk MDS is identifying which patients have a poor prognosis for survival. Although simple to use, the IPSS does not accurately predict the prognosis of patients with lower-risk MDS and does not take into account the more recently identified prognostic variables, including the considerable influence of specific cytogenic abnormalities on prognosis [31, 35-37]. The World Health Organization classification-based Prognostic Scoring System incorporates variables known to affect prognosis that are not included in the IPSS (e.g., transfusion dependency) [38, 39] and can identify some subgroups of patients at risk for a poor prognosis in the lower-risk IPSS groups [40]. In addition, the recently published revised-IPSS [37] stratifies patients into 5 rather than 4 prognostic risk groups and has incorporated revised low marrow blast categories and cutoff points for cytopenias, 5 (vs. 3) cytogenetic subgroups and 16 (vs. 6) specific cytogenic abnormalities, and additional prognostic variables for survival (age, performance status, serum ferritin level, lactate dehydrogenase level, beta2-microglobulin level, complex [>3] cytogenic abnormalities). However, external validation of the revised-IPSS is now required to confirm whether this system allows better prediction of clinical outcomes in patients with MDS, particularly lower-risk MDS, in clinical practice.

Currently, there is limited clinical information to support the use of azacitidine for the treatment of patients with lower-risk MDS. Most studies assessing the use of azacitidine in patients with lower-risk MDS are small, noncomparative studies that focus primarily on treatment response (Table 1). Findings from these studies show that azacitidine is a feasible option for patients with lower-risk MDS who are elderly, transfusion dependent, have severe thrombocytopenia or neutropenia, and are refractory to previous treatment. In addition, findings from these studies have shown that the adverse event profile of azacitidine in patients with lower-risk MDS is acceptable [41] (and Bally *et al.* ASH Annual Meeting. Abstract 2786. Blood 2011;118; Filì *et al.* ASH Annual Meeting. Abstract 4029. Blood 2010;116; Garcia *et al.* ASH Annual Meeting. Abstract 3801. Blood 2009;114; Grinblatt *et al.* ASH Annual Meeting. Abstract 1646. Blood 2008;112; Tobiasson *et al.* ASH Annual Meeting. Abstract 3798. Blood 2011;118). Consistent with findings from the AZA-001 and CALGB clinical trials, the most frequently reported adverse events in these studies were myelosuppression and gastrointestinal conditions.

Two prospective studies have assessed the use of shorter dosing schedules of azacitidine for patients with lower-risk MDS [23] (and Filì *et al.* ASH Annual Meeting. Abstract 4029. Blood 2010;116). Similar hematologic improvement was demonstrated in response to azacitidine with a 5-day (50%) and a 7-day interrupted (49%) dosing schedule in patients with lower-risk MDS (defined using the FAB system) [23]. In comparison, a 5-day dosing schedule in elderly patients with lower-risk MDS (defined using the IPSS) who were transfusion dependent elicited a lower hematologic response (39%) (Filì *et al.* ASH Annual Meeting. Abstract 4029. Blood 2010;116). The use of a shorter dosing schedule has yet to be validated. At least one study is under way

Table 1. Studies assessing patients with lower-risk myelodysplastic syndromes treated with azacitidine.

Reference, country	Study design (Dosing schedule)	Patient characteristics at baseline	Treatment duration	Response to treatment and survival outcomes
Grinblatt *et al.* (ASH Annual Meeting Abstract 1646. Blood 2008;112), USA	Patient registry study (NR)	N=130, median age 75 yr 100% lower risk (IPSS)	97% median 3 cycles	TI=46% (24/52) Survival NR
Garcia *et al.* (ASH Annual Meeting Abstract 3801. Blood 2009;114), Spain	Patient registry study (86% of patients were treated with 75 mg/m^2: 7-day [31% of patients], 5-2-2[a] [37% of patients], 5-day [37% of patients])	N=100, median age 70 yr 100% transfusion dependent	Mean 7 cycles	CR=21%, PR=3%, mCR=11%, HR=27% Survival NR
Lyons *et al.* [23], USA	Prospective, randomized comparison of various dosing schedules (75 mg/m^2: 5-2-2[a] and 5-day; 50 mg/m^2: 5-2-5[b])	N=151, median age 73 to 76 yr 63% lower risk (FAB) 47% transfusion dependent	52% completed 6 cycles	Minor or major HI in FAB lower-risk px: - 75 mg/m^2 5-2-2[a]=49% - 50 mg/m^2 5-2-5[b]=41% - 75 mg/m^2 5 days=50% Survival NR
Fili *et al.* (ASH Annual Meeting Abstract 4029. Blood 2010;116), Italy	Prospective, nonrandomized assessment (75 mg/m^2: 5-day)	N=30, median age 71 yr 100% lower risk (IPSS) 100% transfusion dependent	77% completed 8 cycles	CR=22%, HI=39%, SD=39% Survival NR
Musto *et al.* [41], Italy	Retrospective case review (75 mg/m^2: 7-day [58% of patients], 5-day [39% of patients], 10-day [3% of patients])	N=74, median age 70 yr 100% lower risk (IPSS) 84% transfusion dependent 73% failed to respond to previous treatment	Median 7 cycles	CR=10.8%, PR=9.5%, mCR=5.4%, HI=20.3% 1-year OS=74.9%
Bally *et al.* (ASH Annual Meeting Abstract 2786. Blood 2011;118), France	Retrospective case review (75 mg/m^2: 7-day [12 patients], 5-day [1 patient])	N=13, median age 71 yr 100% lower risk (IPSS) at start of treatment with lenalidomide 100% failed to respond to treatment with lenalidomide	Median 6 cycles	Response (CR, PR, HI) and TI=5 px Median survival from start of treatment with AZA: - All px=8.8 mo - Responders=3+ to 25+ mo - Nonresponders=8.7 mo
Tobiasson *et al.* (ASH Annual Meeting Abstract 3798. Blood 2011;118), Europe	Prospective, nonrandomized (75 mg/m^2: 5-day)	N=28, median age 69 yr 100% lower risk (IPSS), chromosome 5q deletion 61% failed to respond to previous treatment	NR	TI=13% (2/13) Survival NR
Moon *et al.* (17th Congress of the European Hematology Association June 14–17, 2012. Amsterdam, the Netherlands), Republic of Korea	NR (NR)	N=140, median age NR 65% lower risk (IPSS)	4 to 8 or >8 cycles	Response NR 4 to 8 versus >8 cycles in lower-risk px - Median OS=668 versus 890 days

[a]5-2-2, 5 days on treatment, 2 days off treatment, then 2 days on treatment; [b]5-2-5, 5 days on treatment, 2 days off treatment, then 5 days on treatment.
Abbreviations: AZA, azacitidine; CR, complete response; FAB, French-American-British classification; HI, hematologic improvement; HR, hematologic response; IPSS, International Prognostic Scoring System; mCR, marrow complete response; NR, not reported; OS, overall survival; PR, partial response; px, patients; SD, stable disease; TI, transfusion independent.

Table 2. Studies assessing the feasibility of treatment with a hypomethylating agent before allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndromes.

Reference, country	Study design	Patient characteristics at baseline	Indication (number of patients)	Pretreatment duration	Response to pretreatment	Outcomes
De Padua Silva *et al.* [59], USA	Prospective noncomparative subgroup	N=17, median age 55 yrs 100% higher risk (IPSS)	DEC before HSCT	Median 5 cycles in 14 patients	CR=47% PR=18% HI=12%	Median follow-up 12 mo: - Alive=65% - Dead=35%
Lubbert *et al.* [60], Europe	Prospective noncomparative subgroup	N=10, age ≥60 yrs 100% higher risk (IPSS)	DEC before HSCT	Median 5 cycles	CR=40% HI=20%	Survival from treatment: - Alive=40% (2 to 23 mo) - Dead=60% (0.5 to 29 mo)
Cogle *et al.* [48], USA	Retrospective case review	N=8, median age 61 yrs	AZA (4), DEC (4) before HSCT	Median 8 cycles	NR	5-year OS=42%
Field *et al.* [47], USA	Retrospective case review	AZA group N=30, median age 56 yrs 43% higher risk (IPSS) No AZA group N=24, median age 54 yr 42% higher risk (IPSS)	Pretreatment with AZA versus no AZA before HSCT	Median 4 cycles	CR=13% PR=33% SD=33%	1-year survival (AZA versus no AZA): - OS=47% versus 60% - RFS=41% versus 51% - CIR=20% versus 32%
Gerds *et al.* [46], USA	Retrospective case review	AZA group N=35, median age 60 yrs 51% higher risk (IPSS) BM cellularity >60% IC group N=33, median age 47 yrs 70% higher risk (IPSS) BM cellularity >60%	AZA versus IC before HSCT	Median AZA 3 cycles Median IC 2 mo	NR	1-year OS: - AZA=57% - IC=36%
Kim *et al.* [45], Korea	Retrospective case review	N=19, median age 47 yrs 42% higher risk (IPSS) Median BM cellularity 70%	AZA (10), DEC (9) before HSCT	Median 3 cycles	CR=11% PR=5% mCR=32% HI=16%	2-year OS: - All=60% - With CR/mCR=88% - Without CR/mCR=48%
Yahng *et al.* [49], Korea	Retrospective case review	N=56, median age 49 yrs 57% higher risk (IPSS)	AZA (49), DEC (4), switched AZA/DEC or DEC/AZA (3) before HSCT	At least one cycle	CR=5% mCR=41% HI=5%	2-year disease-free survival: - Transformed to AML=25% - Continuous response=73% - No change in response=68% - Loss of response=50% - Disease progression=21%

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; BM, bone marrow; CIR, cumulative incidence of relapse; CR, complete response; DEC, decitabine; HI, hematologic improvement; HSCT, allogeneic hematopoietic stem cell transplantation; IC, induction chemotherapy; IPSS, International Prognostic Scoring System; mCR, marrow complete response; NR, not reported; OS, overall survival; PR, partial response; RFS, relapse-free survival; SD, stable disease.

in the Republic of Korea (NCT01652781, clinicaltrials.gov) to directly compare the administration of azacitidine using a 5-day dosing schedule with the standard approved dosing schedule in patients with lower-risk MDS.

Recommendation

The expert panel acknowledges the potential usefulness of azacitidine in patients with lower-risk MDS and a poor prognosis for survival. Selection of patients with lower-risk MDS for treatment with azacitidine should take into account the individual patient's severity of symptoms and the potential benefits and risk of treatment. Patients who warrant careful consideration include the elderly; patients with severe cytopenias, poor quality of life, and comorbidities; and patients who were unresponsive to previous treatment. Specifically, the expert panel recommends treatment for patients with low absolute neutrophil counts and repeated infections, anemia and a repeated need for transfusions, or thrombocytopenia and bleeding events. Until the use of shorter dosing schedules in patients with lower-risk MDS has been validated, the panel recommends that the standard 7-day schedule for azacitidine be initiated wherever possible and that other prognostic scoring systems (e.g., revised-IPSS [37], modified World Health Organization classification-based Prognostic Scoring System [39], or the MD Anderson prognostic scoring system [42]) be used for further risk assessment. The 7-day schedule can then be modified in response to any toxicities experienced. Future analysis of the efficacy and safety of azacitidine should be conducted in the context of the revised prognostic scoring systems that effectively identify patients with lower-risk MDS who may benefit from treatment.

2. Issue for consideration 5: treatment of patients with higher-risk MDS with azacitidine before and after HSCT

Allogeneic HSCT is the only treatment available with the potential to cure patients with higher-risk MDS [34]. Findings from a retrospective analysis of 178 patients aged between 60 and 70 years with MDS suggests that there may be a survival benefit for allogeneic HSCT compared with azacitidine [43]. However, the therapeutic options for patients who experience a relapse after HSCT are limited [44] and many issues remain unresolved with regard to the timing of transplantation and the need to reduce the risk of relapse.

Pretransplantation therapy with a hypomethylating agent is currently recommended for patients who are eligible for HSCT but who are awaiting availability of a donor or who require treatment to reduce the risk of relapse after transplantation [1]. However, because of poor accrual rates, no prospective controlled trials have been conducted to evaluate the effect of pretreatment on outcomes after transplantation. Findings from retrospective studies (Table 2) that have been conducted to investigate the feasibility of pretransplantation therapy with azacitidine before HSCT [45-49] suggest that pretransplantation therapy with azacitidine is feasible and there does not appear to be an increased incidence of post-transplantation toxicities compared with no treatment or compared with standard induction chemotherapy [45-48]. In addition, a good response to azacitidine appears to be a predictor of better post-transplantation outcomes [45, 49]. Although favorable effects on survival and the risk of relapse after transplantation have been reported in patients receiving pretransplantation therapy with azacitidine, the retrospective nature of the studies precludes any firm conclusions.

The treatment options for patients who experience a relapse after HSCT include a second HSCT, salvage chemotherapy, and/or donor lymphocyte infusion [44]. Despite these options, the long-term survival for many patients with relapsed AML is poor [50, 51] and alternative treatment options are needed. As azacitidine is relatively well tolerated and can confer a survival benefit in patients with higher-risk MDS [6], several small clinical studies have investigated the use of azacitidine as pre-emptive therapy in patients with minimal residual disease [51] and as maintenance [52] or salvage therapy [52, 53] for recurrent MDS or AML after HSCT. Findings from these preliminary studies are encouraging; however, prospective randomized controlled trials in larger patient populations are needed to confirm the role of azacitidine after HSCT.

Recommendation

In the absence of definitive evidence of a survival benefit for hypomethylating agents of HSCT and in accordance with the National Comprehensive Cancer Network guidelines [1], the expert panel does not recommend routine use of pretransplantation therapy with azacitidine if an appropriate donor is available. However, pretransplantation therapy with azacitidine can be considered in patients with higher-risk MDS in clinical trial settings or in patients with MDS who (i) have rapid progression or a high burden of disease, (ii) require an improvement in performance status before transplantation, or (iii) are awaiting the availability of an appropriate donor.

3. Issue for consideration 6: treatment of patients with higher-risk MDS who are not eligible for HSCT or who fail to respond to treatment with a hypomethylating agent

The therapeutic options for patients with higher-risk MDS who are not eligible for HSCT include high-intensive induction chemotherapy, hypomethylating agents, or supportive care [1]. Before the availability of hypomethylating agents, high-intensive chemotherapy was used to treat relatively younger patients with MDS. However, the response rate for these patients is lower than for patients with de novo AML and results in short duration of remission, particularly in patients with unfavorable cytogenetics [54]. Recent findings from a phase 2 clinical trial have demonstrated the efficacy of the thrombopoietic compound romiplostim for increasing platelet levels and decreasing thrombocytopenic adverse events [55] in patients with lower-risk MDS. However, the potential benefit of romiplostim and other stimulating agents, such as erythropoietin or G-CSF, or iron chelation for patients with higher-risk MDS is unclear.

In the AZA-001 trial, patients who received azacitidine

had significantly longer overall survival than patients who received conventional care [5]. In this trial, conventional care comprised best supportive care, low-dose cytarabine, or intensive chemotherapy as recommended by the treating physician. Subgroup analyses showed that treatment with azacitidine resulted in significantly longer overall survival than best supportive care (21.1 months vs. 15.5 months, P=0.0045) or low-dose cytarabine (24.5 months vs. 15.3 months, P=0.0006). Although overall survival was numerically longer with azacitidine than intensive chemotherapy (25.1 months vs. 15.7 months, P=0.51), the trial was not designed or powered to demonstrate a statistically significant difference in overall survival between treatment with azacitidine and intensive chemotherapy.

Despite the favorable outcomes that can be achieved in patients with MDS who are treated with hypomethylating agents, up to 50% do not respond and most responders will experience disease progression within 2 years of a response [5]. Because of the limited treatment options available after treatment failure, patients with higher-risk MDS who fail to respond to treatment with hypomethylating agents have a very poor prognosis for survival [56, 57]. Retrospective analysis of patients with higher-risk MDS who failed treatment with azacitidine suggests that the factors associated with worse outcomes are older age, male sex, unfavorable cytogenetics, higher bone marrow blasts, and no previous hematologic response [57].

Of the limited options available for patients who fail treatment with azacitidine, allogeneic HSCT or treatment with an investigational agent is associated with better outcomes than best supportive care, low-dose chemotherapy, or intensive chemotherapy [57] (Lee J. 10th Korean Society of Hematology AML/MDS Working Party Spring Symposium. April 14, 2012. Seoul, Republic of Korea). A retrospective analysis of 435 patients who failed treatment with azacitidine showed that the median overall survival was 19.5 months for those receiving HSCT, 13.2 months for those receiving investigational therapy, 7 to 9 months for those receiving chemotherapy, and 4 months for those receiving best supportive care [57]. In addition, retrospective analysis of patients from the Republic of Korea showed that of the patients who fail hypomethylating treatment and undergo HSCT (N=23), better outcomes can be achieved if transplantation occurs before progression to AML (Lee J. 10th Korean Society of Hematology AML/MDS Working Party Spring Symposium. April 14, 2012. Seoul, Korea). The probability of 2-year overall survival in this study was 78.6% for patients who underwent HSCT during MDS versus 33.3% for patients who underwent HSCT after progression to AML. Limited information is available on the treatment options for patients who fail hypomethylating treatment and progress to AML. Findings from a recent retrospective analysis of these patients (N=46) in Korea suggests that active treatment with HSCT following intensive chemotherapy can confer a survival benefit over HSCT or intensive chemotherapy alone [58]. In this study, the median overall survival was 15 months for HSCT following intensive chemotherapy, 3.8 months for HSCT alone, 6.3 months for intensive chemotherapy alone, and 1.4 months for supportive care.

Recommendations

The expert panel recommends use of hypomethylating agents wherever possible in patients with higher-risk MDS who are not eligible for HSCT. However, limited options are available for these patients if treatment with a hypomethylating agent fails. The options available include enrollment in clinical trials of investigational therapies, intensive chemotherapy, or best supportive care. The decision on the most suitable treatment option should be based on whether patients are medically fit to receive investigational therapy or intensive chemotherapy and on the individual patient's preferences for treatment.

CONCLUSION

Evidence from pivotal clinical trials conducted in the United States and Europe has demonstrated clear improvements in delaying progression to AML and in survival for patients with higher-risk MDS treated with azacitidine [5, 6]. However, standard treatment with azacitidine has not been optimized and many questions remain with regard to the most effective dose, treatment duration, and management of adverse effects in these patients and with regard to the identification of patients who may benefit from treatment. In addition, it is not yet known whether the differences between patients with MDS from Asian and Western countries [9-16] translate to differences in clinical decision making. Although azacitidine is approved for the treatment of patients with higher-risk MDS who are not eligible for HSCT, the potential use of azacitidine in clinical practice is rapidly expanding. Findings from studies of azacitidine in patients with lower-risk MDS and in patients requiring pretransplantation therapy is encouraging, but much of the evidence has been collected in retrospective or noncomparative settings and is focused on treatment responsiveness rather than survival outcomes. Prospective, comparative clinical trials are needed to better define the optimal use of azacitidine in patients with higher-risk MDS who are not eligible for HSCT and to confirm the efficacy and safety of azacitidine in patients with a poor prognosis for survival who may benefit from treatment.

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