Survey of experts on therapeutic policies and proposals for the optimal timing for allogeneic peripheral blood stem cell transplantation in transfusion-dependent patients with myelodysplastic syndrome-refractory anemia

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Background
Most hypomethylating agent (HMA) responders with myelodysplastic syndrome (MDS) eventually need allogeneic stem cell transplantation (SCT) because they often acquire resistance to HMAs within two years of treatment. Considering the nature of MDS and the poor outcomes of SCT when performed after confirming the progression of MDS to acute myeloid leukemia (AML), allogeneic SCT should be performed with caution in patients with low-risk MDS.

Methods
To address low-risk MDS, the Korean AML/MDS working party group designed a survey for 34 MDS experts in Korea on therapeutic HMA and allogeneic SCT policies for low-risk MDS. The level of consensus was defined as the percentage of agreement among the experts.

Results
With regard to the optimal time for allogeneic SCT for HMA responders with MDS-RA, 76% experts agreed that allogeneic SCT should be performed when a patient has a low platelet count. With regard to the relapse pattern that was most commonly found during HMA treatment in responding patients with MDS-RA, 54% experts agreed that the most common pattern that indicated HMA failure was the gradual worsening of cytopenia.

Conclusion
The optimal time to perform allogeneic SCT in RA patients who achieved hematologic complete remission during HMA treatment is when the platelet count decreases. However, these suggestions need to be evaluated in larger future studies. Therefore, careful decisions should be taken at each step of allogeneic SCT to maximize the outcomes for patients with MDS-RA and iron overload.

Key Words   Myelodysplastic, Transfusion, Hypomethylating, Allogeneic

INTRODUCTION

Iron toxicity is inevitable for low/intermediate-1 risk in patients with myelodysplastic syndrome (MDS) or refractory anemia (RA) who require transfusion on a regular basis to maintain the quality of life (QOL). Moreover, iron overload is known to have a negative impact on survival during medical therapy or allogeneic stem cell transplantation (SCT) [1, 2]. For this reason, therapeutic strategies aimed at reversing transfusion dependency are needed in transfusion-dependent patients with MDS-RA. The availability of hypomethylating agents (HMAs), including azacitidine and decitabine, has changed the clinical course of MDS by improving the hematologic responses and survival rates [3].

Although HMA treatment is limited in terms of curing MDS, approximately 50% of the patients with MDS-RA subjected to HMA therapy can benefit from continued HMA treatment because these patients avoid transfusions and this treatment increases the survival duration in responders [4,

5]. In particular, for young responding patients (aged ≤50 yr) with MDS-RA subjected to HMA therapy, the optimal timing for allogeneic SCT is not easy to determine in clinical practice when the poor outcome of transplantations undertaken after confirmation of MDS progression to acute myeloid leukemia (AML) or the acquisition of resistance to HMA is considered [6]. Therefore, the Korean AML/MDS working party group designed a survey for 34 MDS experts in Korea on the therapeutic policies and the optimal timing for allogeneic SCT in patients with MDS-RA.

MATERIALS AND METHODS

To address controversial issues in the treatment of low-risk MDS or MDS with fewer than 5% blasts in the bone marrow (BM), the Korean AML/MDS working party group designed a survey for MDS experts in Korea on the therapeutic HMA and allogeneic SCT policies for low-risk MDS. One or two clinical experts on MDS were selected from each university hospital in Korea and they were asked to respond to 12 questions on HMA treatment, iron overload, and strategies for allogeneic SCT in patients with low-risk MDS. The survey was ultimately undertaken by 34 MDS experts. The level of consensus was defined as the percentage agreement among the experts.

RESULTS

The questionnaire and survey results were as follows.

1. What is your preferred frontline treatment for low-risk MDS or RA?
a) Erythropoietin (24%)
b) Immunosuppressive therapy (0%)
c) HMA (32%)
d) Supportive care with transfusion or anabolic steroids (41%)
e) Other (3%)

2. What is the main reason for choosing HMA treatment as a frontline therapy for patients with low-risk MDS or RA?
a) Because other treatment modalities, including erythropoietin or immunosuppressive therapy, do not provide a satisfactory outcome (32%)
b) Because the use of HMA is allowed by the government insurance system (5%)
c) Because HMA therapy can provide a better outcome in terms of hematological response than other treatment modalities (32%)
d) Because HMA can delay or prevent MDS progression to AML in high- or low-risk MDS or RA (14%)
e) Other (18%)

3. Which of the following patterns of relapse have you

most commonly experienced when HMA treatment is maintained in responding patients with low-risk MDS or RA? (the total percentage should be 100%)
a) Gradual development of cytopenia during MDS (54%)
b) Sudden development of cytopenia during MDS (30%)
c) Progression to AML (16%)
d) Other (0%)

4. What is the upper age limit for which you would recommend allogeneic SCT for patients with low-risk MDS?
a) <50 yr (28%)
b) <55 yr (25%)
c) <60 yr (6%)
d) <65 yr (34%)
e) <70 yr (3%)
f) No age limit (3%)

5. What is the most important consideration when choosing whether to perform allogeneic SCT in patients with low-risk MDS or RA?
a) Degree of cytopenia (25%)
b) Red blood cell (RBC) or platelet transfusion dependency (35%)
c) Cytogenetics (10%)
d) Percentage of BM blast (13%)
e) Refractoriness to frontline therapy (23%)
f) Other (0%)

6. What is the optimal timing for performing allogeneic SCT in patients with low-risk MDS or RA who have an excellent hematologic response to HMA treatment?
a) Perform allogeneic SCT as soon as possible, regardless of the response to HMA treatment (9%)
b) Perform allogeneic SCT, regardless of the response to HMA treatment, but after at least 4 or 6 cycles of HMA treatment (3%)
c) Continue the HMA treatment if the patient shows a continuing hematologic response, then perform allogeneic SCT when the patient shows hematologic remission (3%)
d) Continue the HMA treatment if the patient shows a continuing hematologic response, then perform allogeneic SCT when the patient shows a decrease in platelet count, and continue the HMA cycles (74%)
e) Continue the HMA treatment if the patient shows a continuing hematologic response, then perform allogeneic SCT after the worsening of MDS or its progression to AML is confirmed (11%)

7. What is your opinion on the following recommendation: continue the HMA treatment if the patient shows a continuing hematologic response, then perform allogeneic SCT when the patient shows a decrease in platelet count, and continue the HMA cycles in patients with low-risk MDS or RA.
a) I agree (76%)
b) I do not agree (12%)

c) Other (12%)

8. What is your preferred conditioning intensity for allogeneic SCT in patients with low-risk MDS or RA?
a) Myeloablative conditioning (MAC), regardless of patient age (6%)
b) Nonmyeloablative conditioning (NMC), regardless of patient age (39%)
c) Differs according to patient age (55%)
d) Other (0%)

9. What is your preferred conditioning regimen for myeloablative SCT in patients with low-risk MDS or RA?
a) High-dose busulfan combined with a cyclophosphamide regimen (44%)
b) BuFlu regimen (Busulfex at 3.2 mg/kg for 4 days combined with fludarabine at 30 mg/m^2 for 6 days) (44%)
c) Total body irradiation (TBI)-based regimen (12%)
d) Other (0%)

10. What is your preferred stem cell source for allogeneic SCT in patients with low-risk MDS or RA?
a) Peripheral blood (85%)
b) BM (9%)
c) Cord blood (0%)
d) It does not matter (6%)

11. What is your preferred therapeutic strategy for complicated iron overload (ferritin level >1,000 ng/mL) before allogeneic SCT in patients with low-risk MDS or RA?
a) Perform SCT when a ferritin level <1,000 ng/mL is achieved with iron chelation therapy (15%)
b) Start iron chelation therapy and perform SCT regardless of the ferritin level (79%)
c) Start iron chelation therapy in cases of high ferritin levels (>3,000 ng/mL) and then perform SCT when a ferritin level <1,000 ng/mL is achieved (3%)
d) Start iron chelation therapy in cases of high ferritin levels (>3,000 ng/mL) and then perform SCT regardless of the ferritin level (3%)
e) Iron chelation therapy is not needed before allogeneic SCT (0%)

12. What is your therapeutic strategy for complicated iron overload (ferritin level of >1,000 ng/mL) after allogeneic SCT in patients with low-risk MDS or RA?
a) Start iron chelation therapy if the ferritin level is >1,000 ng/mL (76%)
b) Start iron chelation therapy if the ferritin level is >3,000 ng/mL (6%)
c) Iron chelation therapy or the monitoring of the ferritin level is not needed after allogeneic SCT (9%)
d) Other (9%)

DISCUSSION

A serum ferritin level between 500 and 1,500 ng/mL has been associated with a poorer survival rate in patients with MDS who receive medical therapy or allogeneic SCT [7, 8]. Moreover, RBC transfusion is known to be associated with an increased risk of disease progression and leukemic transformation [7].

Iron-chelating therapy (ICT) is known to prolong survival for transfusion-dependent MDS patients who receive both medical therapy and allogeneic SCT [9, 10]. Delforge et al. [10] suggested that adequate ICT for at least 6 months could lead to markedly prolonged overall survival (OS) in transfusion-dependent patients with lower-risk MDS (median OS was 10.2 years for chelated patients and 3.1 years for non-chelated patients: $P < 0.001$).

In allogeneic SCT candidates, pre- or post-SCT ICT is expected to lower the non-relapse mortality (NRM) or transplant-related mortality (TRM) after allogeneic SCT. According to current guidelines, ICT is recommended for MDS-RA patients with a serum ferritin level of >1,000 ng/mL who are candidates for allogeneic SCT with a dependence on transfusions of 2 units/month for more than 1 year [11, 12].

In recipients who have successfully undergone SCT but have a persisting iron overload, a short period of ICT may improve QOL after the SCT period. In the current survey, 76% of experts agreed on the performance of ICT post-SCT in recipients with a ferritin level >1,000 ng/mL after SCT. Meanwhile, only 15% of the experts preferred to perform SCT after achieving a ferritin level <1,000 ng/mL via ICT before SCT whereas 79% preferred to perform SCT regardless of the ferritin level before SCT.

There is no consensus about how to treat low-risk patients with HMAs on the basis of the International Prognostic Scoring System (IPSS) score, especially those with RA. HMAs have been approved for use in several countries, including the United States, with reports of independence on RBC transfusion in responding patients, and HMAs have also been approved for other cytopenias in low-risk MDS [13]. Because patients with low-risk MDS who develop early resistance to currently available therapies and cytogenetic abnormality or life-threatening thrombocytopenia during supportive care have a relatively poor survival, HMA treatment is being increasingly used in RA patients with transfusion dependency.

Even in excellent responders, cycling of HMA treatment should be continued to maintain the inhibition of DNA methylation because HMA-induced hypomethylation occurs progressively within the MDS clone; therefore, minimal demethylation may require continued exposure to the drug [14].

The impact of long-term use of HMA on SCT needs to be clarified if the institution's HMA treatment policy is adopted for symptomatic low-risk MDS. However, no prospective studies are currently available on this issue. Previous studies that compared the effect of HMA treatment and the absence of HMA treatment with intensive chemotherapy in high-risk MDS [15, 16] found no negative effects of the

use of HMA on the outcomes of allogeneic SCT. This observation provides another reason to begin and maintain HMA treatment for symptomatic patients with MDS-RA, even for those who are candidates for allogeneic SCT [6].

It is important to have a reliable clinical predictor of response or benefit in patients with MDS who are starting HMA treatment. A prospective study found a significant association between platelet count doubling after the first HMA cycle and the probability of achieving an objective response, with a statistically significant reduction in the risk of death in patients who achieved platelet count doubling compared with those who did not (P=0.04) [17].

The appropriate time to perform allogeneic SCT has been a controversial issue in low-risk patients with a hematological response to continued cycles of HMA treatment. When considering the limitations of HMA treatment—including the rarity of long-term responders to HMA with median hemoglobin response duration of 14 months—curative management is eventually needed at some point during HMA treatment before MDS worsens or progresses to AML.

According to a recent study based on the modeling of the natural course of MDS [18], delayed allogeneic SCT is advisable for patients with a low IPSS score and a very low or low World Health Organization Classification–based Prognostic Scoring System (WPSS) risk. However, the authors highlighted that allogeneic SCT should be offered to eligible patients who belong to intermediate-risk categories, in particular to those with an intermediate-1 IPSS score or intermediate WPSS risk [18]. This suggestion indicates that allogeneic SCT needs to be performed before a patient develops progressive iron overload, considering that the WPSS considers transfusion dependency as an independent negative prognostic factor for SCT outcome. However, a previous study analyzing 95 MDS patients treated with HMA followed by allogeneic SCT did not find a significant difference in the SCT outcomes between the recipient groups, which comprised low/intermediate-1 risk patients who achieved complete remission (CR) and whose disease progressed during HMA treatment [19]. These authors suggested that the failure to respond to HMA did not adversely affect the SCT outcomes and that allogeneic SCT should be delayed as long as possible or until confirmation of HMA failure [19].

In a study of 63 patients with AML arising from MDS after HMA failure, the therapeutic outcome was extremely poor, with a 2-year OS rate of 8% and a CR rate of 10% even after active salvage therapy [20]. According to Prébet et al. [21], MDS patients whose disease worsened during HMA therapy also showed a very poor prognosis, with a median survival of 5.6 months and 2-year OS of 15%. These authors suggested that patients with MDS-RA who underwent HMA therapy and were candidates for SCT should undergo transplantation before MDS-RA worsens or progresses to AML [21], However, it is not clear how long allogeneic SCT should be postponed in responders with MDS-RA. The early recognition of worsening cytopenia, increased number of blasts, and karyotypic evolution can

guide clinicians on the optimal timing for allogeneic SCT in responders with RA [13]. The optimal time to perform allogeneic SCT in RA patients who achieved complete hematologic CR during HMA treatment is immediately after the platelet count decreases [6].

Della Porta et al. [22] demonstrated that the platelet count at the time of SCT was an independent predictive factor for allogeneic SCT outcomes, with a significantly higher 5-year OS rate in the group with a platelet count > 100,000/μL (47%) compared with the groups with a count of 50,000–100,000 or <50,000/μL (38% or 33%). The patient group with a platelet count of <50,000/μL and who underwent SCT had higher relapse and NRM incidences compared with the group with a platelet count of >50,000/μL at SCT. However, an absolute neutrophil count did not provide any predictive value for the SCT outcome and no significant difference in OS was observed between the groups with an absolute neutrophil count of <800/μL or >800/μL [22].

With regard to the optimal timing for allogeneic SCT in HMA responders with MDS-RA, 76% of the Korean MDS experts agreed that allogeneic SCT should be performed when a patient shows a decrease in the platelet count and maintains HMA treatment. In a survey on the relapse pattern most commonly observed during HMA treatment in responding patients with MDS-RA, 54% of the experts agreed that the most common pattern that indicates HMA failure is the gradual worsening of cytopenia.

The close monitoring of a patient's cytogenetic status is also important when deciding the timing of allogeneic SCT. The median OS and transformation-free survival for MDS patients with and without a complete cytogenetic response (CCyR) were 20 and 11 months (P=0.007) and 14 and 9 months (P=0.039), respectively [23]. Patients who achieved CCyR and morphologic CR tended to have better outcomes compared with those who achieved morphologic CR only, with a median OS of 18 months and 15 months (P=0.42) and a median transformation-free survival of 14 months and 9 months, respectively (P=0.32) [23].

When molecular data are available, allogeneic SCT needs to be applied early in case of life-threatening thrombocytopenia, an unfavorable genetic abnormality (including 3q26 rearrangements), and in cases of mutations in TP53, EZH2, or ASXL1, even during the response to HMA [24].

The impact of the conditioning intensity on the SCT outcome remains controversial in low-risk patients with MDS, and young patients with MDS generally have been considered candidates for MAC because of a negligible rate of TRM. However, considering the slow pace of the disease and the low percentage of BM blasts in patients with MDS-RA, the NMC regimen may be an attractive approach, even for younger patients with MDS-RA [25, 26]. A Korean retrospective study has found a higher survival rate in the NMC group compared with the MAC group (relative risk=0.08; P=0.022) primarily because of a significantly lower TRM (HR=0.08; P=0.035) in low-risk patients with MDS [25]. NMC seems to be more beneficial in terms of lower NRM compared with MAC, especially for older patients with MDS (73%

in NMC vs. 28% in MAC; $P < 0.001$ for patients aged > 50 yr) [26]. However, it is generally agreed that patients without any contraindications for MAC should not undergo NMC, except in prospective randomized trials, because of the higher risk of relapse and graft failure, particularly in the NMC setting [26, 27].

There are concerns about the high risk of graft failure, rejection, and graft-versus-host disease (GVHD) in patients with low-risk MDS who are heavily transfused before SCT. In the case of severe aplastic anemia, BM is preferred to peripheral blood as a stem cell source because of lower GVHD-related death in BM transplantation (BMT) recipients [28]. However, it is unclear whether MDS-RA with transfusion dependency, which is a type of clonal disorder, can have a clinical course as severe as aplastic anemia after allogeneic peripheral blood stem cell transplantation (PBSCT) or BMT.

Although donor age has not been defined in MDS, it should not be overlooked in MDS patients who receive allogeneic SCT to maximize the SCT outcome when considering the prevalence of MDS in older patients. For older MDS patients, it is preferable in terms of time and cost to perform allogeneic SCT with cells from a related older donor than with cells from an unrelated younger donor. However, a recent study reported that allogeneic SCT from a younger unrelated donor (< 40 yr) had a better outcome than SCT from an older related donor (> 60 yr) in patients with hematological malignancies [29]. In a retrospective comparison of the impact of young unrelated donors versus older related donors for allogeneic SCT in older AML patients (> 50 yr), the 5-year OS rate was superior for those recipients transplanted from a younger (< 39 yr) unrelated donor than from an older (> 39 yr) related donor (62% vs. 26%, $P = 0.022$) [30].

In our survey involving patients with high-risk MDS, only 24% of the Korean experts preferred a younger unrelated donor (< 40 yr) to an older related donor (> 50 yr) for these patients whereas 52% preferred an older sibling donor. Although it is difficult to find a suitable younger unrelated donor than a related donor for SCT in patients with high-risk MDS because of concerns about the worsening of MDS or its progression to AML, ICT patients with iron-overloaded MDS-RA should wait for a suitable young donor.

In conclusion, considering the limitations of the HMA treatment, allogeneic SCT will most likely be needed during the responding period before MDS worsens or progresses to AML in symptomatic patients with MDS-RA who received HMA therapy. The optimal time to perform allogeneic SCT in RA patients who achieved hematological CR during HMA treatment is immediately after the platelet count decreases. However, these suggestions need to be evaluated in future larger studies. Therefore, careful decisions at each step of allogeneic PBSCT are needed to maximize the SCT outcome for patients with MDS-RA and iron overload.

ACKNOWLEDGMENTS

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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