KJIM

No benefit of hypomethylating agents compared to supportive care for higher risk myelodysplastic syndrome

Sang Kyun Sohn[1], Joon Ho Moon[1], In Hee Lee[1], Jae Sook Ahn[2], Hyeoung Joon Kim[2], Joo Seop Chung[3], Ho Jin Shin[3], Sung Woo Park[3], Won Sik Lee[4], Sang Min Lee[4], Hawk Kim[5], Ho Sup Lee[6], Yang Soo Kim[6], Yoon Young Cho[7], Sung Hwa Bae[7], Ji Hyun Lee[8], Sung Hyun Kim[8], Ik Chan Song[9], Ji Hyun Kwon[10], and Yoo Jin Lee[1]

Department of Hematology/Oncology, [1]Kyungpook National University Hospital, Daegu; [2]Chonnam National University Hwasun Hospital, Hwasun; [3]Pusan National University Hospital, Busan; [4]Inje University Busan Baik Hospital, Busan; [5]Ulsan University Hospital, Ulsan; [6]Kosin University Gospel Hospital, Busan; [7]Daegu Catholic University Medical Center, Daegu; [8]Dong-A University Hospital, Busan; [9]Chungnam National University Hospital, Daejeon; [10]Chungbuk National University Hospital, Cheongju, Korea

Correspondence to
Yoo Jin Lee, M.D.
Department of Hematology/Oncology, Kyungpook National University Hospital, 130 Dongdeok-ro, Jung-gu, Daegu 41944, Korea
Tel: +82-53-420-5587
Fax: +82-53-426-2046
E-mail: yoojinlee0605@gmail.com

Background/Aims: This study evaluated the role of hypomethylating agents (HMA) compared to best supportive care (BSC) for patients with high or very-high (H/VH) risk myelodysplastic syndrome (MDS) according to the Revised International Prognostic Scoring System.

Methods: A total of 279 H/VH risk MDS patients registered in the Korean MDS Working Party database were retrospectively analyzed.

Results: HMA therapy was administered to 205 patients (73.5%), including 31 patients (11.1%) who then received allogeneic hematopoietic cell transplantation (allo-HCT), while 74 patients (26.5%) received BSC or allo-HCT without HMA. The 3-year overall survival (OS) rates were 53.1% ± 10.7% for allo-HCT with HMA, 75% ± 21.7% for allo-HCT without HMA, 17.3% ± 3.6% for HMA, and 20.8% ± 6.9% for BSC groups ($p < 0.001$). In the multivariate analysis, only allo-HCT was related with favorable OS (hazard ratio [HR], 0.356; $p = 0.002$), while very poor cytogenetic risk (HR, 5.696; $p = 0.042$), age ≥ 65 years (HR, 1.578; $p = 0.022$), Eastern Cooperative Oncology Group performance status (ECOG PS) 2 to 4 (HR, 2.837; $p < 0.001$), and transformation to acute myeloid leukemia (AML) (HR, 1.901; $p = 0.001$) all had an adverse effect on OS.

Conclusions: For the H/VH risk group, very poor cytogenetic risk, age ≥ 65 years, ECOG PS 2 to 4, and AML transformation were poor prognostic factors. HMA showed no benefit in terms of OS when compared to BSC. Allo-HCT was the only factor predicting a favorable long-term outcome. The use of HMA therapy did not seem to have an adverse effect on the transplantation outcomes. However, the conclusion of this study should be carefully interpreted and proven by large scale research in the future.

Keywords: Myelodysplasia; Higher risk; Revised International Prognostic Scoring System; Hypomethylating agent

Sohn SK, et al. Hypomethylating agents for high-risk MDS

KJIM

INTRODUCTION

Based on current guidelines, there is no specific recommended bridge or frontline therapy including hypomethylating agent (HMA), cytotoxic therapy or supportive care for the subgroup of patients with high or very high (H/VH) risk myelodysplastic syndrome (MDS) eligible for allogeneic hematopoietic cell transplantation (allo-HCT) [1]. However, when considering the practical aspects of allo-HCT, there may be no appropriate donor or it may take more than 5 months from identifying an appropriate stem cell source to performing allo-HCT [2].

The use of HMA such as azacitidine and decitabine has been quite successful for MDS in terms of improving the hematologic response or survival duration [3,4]. Thus, for higher risk MDS, the use of HMA therapy while waiting for allo-HCT can be an attractive option, offering the potential for successful cytoreduction before allo-HCT and improved HCT outcome [5,6].

Accordingly, the current study retrospectively compared HMA therapy and supportive care in terms of the allo-HCT outcomes for high and very high risk MDS based on the Revised International Prognostic Scoring System (IPSS-R).

METHODS

A total of 572 patients diagnosed with MDS and registered in the Korean MDS Working Party database from October 1992 to July 2013 were classified into five subgroups according to IPSS-R: very low, low, intermediate, high (H), and very high (VH) risk [7]. The clinical characteristics and treatment outcomes were retrospectively reviewed for the 279 patients with H or VH risk MDS. A standard regimen of azacitidine (75 mg/m²/day for 7 days every 4 weeks) or decitabine (20 mg/m²/day for 5 days every 4 weeks) was used. The response to HMA was estimated after three to six cycles of HMA treatment [8]. The responses were coded according to the 2006 International Working Group guidelines [9]. This study was approved by the Institutional Review Board of the Kyungpook National University Hospital (IRB No. 2017-09-018-001), with no written consent because patients records/information was anonymized and de-identified prior to analysis.

Definition

The IPSS-R prognostic risk categories were determined by combining the scores of main five features: cytogenetics, bone marrow (BM) blast, hemoglobin (Hb), platelets, and absolute neutrophil count (ANC). High risk category was defined score from 4.5 to 6 and very high risk category was defined score 6 or more. The responses were categorized as complete remission (CR), partial remission (PR), marrow CR (mCR) with or without hematologic improvement (HI), and HI. Stable disease was defined as the failure to achieve at least PR yet without evidence of progression for 8 weeks. Progressive disease was defined as the progression to a higher risk MDS category, transformation to acute myeloid leukemia (AML), or loss of response. The best response was defined as the best response achieved by a patient at any time point. Engraftment was defined as the first of three consecutive days when the ANC exceeded 0.5×10^9/L. Graft failure was defined as the lack of myeloid engraftment in patients surviving in remission for at least 28 days after transplantation. The criteria used for the diagnosis and grading of acute and chronic graft-versus-host disease (GVHD) were as previously described [10].

Statistical analysis

The categorical data were analyzed using chi-square tests. The overall survival (OS) rate was analyzed using the Kaplan-Meier method, and the treatment groups were compared using log-rank tests. The OS was calculated from the date of diagnosis to the date of death from any cause or last follow-up. Leukemia-free survival (LFS) was defined as from the date of diagnosis to time of leukemic transformation or last contact/death for LFS. Multivariate stepwise analysis was used to determine independent prognostic importance of several clinical factors, especially, IPSS-R, treatment group. The significances of the covariates affecting OS and LFS were determined using a Cox proportional hazard model. The statistical analyses were performed using IBM SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The patient characteristics are summarized in Table 1.

Table 1. Patient characteristics (n = 279)

Characteristic	Value
Age, yr	65 (15–86)
< 65	136 (48.7)
≥ 65	143 (51.3)
Sex	
Male	174 (62.4)
Female	105 (37.6)
ECOG PS	
0–1	215 (77.1)
2–4	64 (22.9)
Diagnosis	
RCUD	17 (6.1)
RARS	1 (0.4)
RCMD	38 (13.7)
RAEB-1	94 (33.9)
RAEB-2	123 (44.8)
MDS-U	3 (1.1)
5q– syndrome	0
CMML	3 (1.1)
IPSS-R risk category	
High	160 (57.3)
Very high	119 (42.7)
IPSS-R cytogenetics	
Very good	5 (1.8)
Good	116 (41.5)
Intermediate	58 (20.8)
Poor	42 (15.1)
Very poor	58 (20.8)
IPSS-R blasts, %	
≤ 2	20 (7.2)
> 2 and < 5	36 (12.9)
5–10	102 (36.6)
> 10	121 (43.4)
IPSS-R hemoglobin, g/dL	
≥ 10	32 (11.5)
≥ 8 and <10	97 (34.8)
< 8	150 (53.8)
IPSS-R platelet, × 10^9/L	
≥ 100	63 (22.6)
≥ 50 and <100	94 (33.7)
< 50	122 (43.7)
IPSS-R ANC, × 10^9/L	

Table 1. continued.

Characteristic	Value
≥ 0.8	118 (42.3)
< 0.8	158 (58.6)

Values are presented as median (range) or number (%).
ECOG PS, Eastern Cooperative Oncology Group performance status; RCUD, refractory cytopenia with unilineage dysplasia; RARS, refractory anemia with ringed sideroblast; RCMD, refractory cytopenia with multilineage dysplasia; RAEB-1, refractory anemia with excess blasts-1; RAEB-2, refractory anemia with excess blasts-2; MDS-U, myelodysplastic syndrome, unclassified; CMML, chronic myelomonocytic leukemia; IPSS-R, Revised International Prognostic Scoring System; ANC, absolute neutrophil count.

The median age was 65 years (range, 15 to 86) and 136 patients (48.7%) were under 65 years. The Eastern Cooperative Oncology Group performance status (ECOG PS) was 0 to 1 in 215 patients (77.1%) and 2 to 4 in 64 patients (22.9%). The IPSS-R H and VH risk groups included 160 patients (57.3%) and 119 patients (42.7%), respectively. The cytogenetic risk groups based on IPSS-R were as follows: very good (five patients, 1.8%), good (116 patients, 41.6%), intermediate (58 patients, 20.8%), poor (42 patients, 15.1%), and very poor (58 patients, 20.8%). The percentage of BM blasts was below 2 in 20 patients (7.2%), 2 to 5 in 36 patients (12.9%), 5 to 10 in 102 patients (36.6%), and more than 10 in 121 patients (43.4%). The ANC was < 0.8 × 10^9/L in 158 patients (58.6%), the Hb level was < 8 g/dL in 150 patients (53.8%), and the platelet count was < 50 × 10^9/L in 120 patients (43.4%). A total of 205 patients (73.5%) were treated with a median of four cycles of HMA (range, 1 to 63 cycles), including 31 patients (11.1%) who received allo-HCT following HMA therapy. Seventy-four patients (best supportive care [BSC], 69; allo-HCT, 5) were not previously treated with HMA therapy. The patients characteristics was similar except ECOG PS 0 to 1 (No HMA: n = 40, 54.1% vs. HMA: n = 175, 85.4%; p < 0.001).

A response to HMA was observed in 97 of the 205 patients (47.3%) who received HMA therapy, where 27 patients (13.2%) achieved CR, 19 (9.3%) PR, 17 (8.3%) mCR, and 34 (16.6%) HI. Eleven (one patient in CR, four in PR, four in mCR, and one in HI) of the 31 transplanted patients who received HMA therapy showed a response to HMA at the time of allo-HCT (Table 2). The median time to the transplantation of the patients transplanted with-

Table 2. Treatment outcomes when using HMA

	Total (n = 205)	HMA only (n = 174)	HMA + HCT (n = 31)	p value
Type of treatment				
Azacitidine	149 (72.7)	125 (71.8)	24 (77.4)	0.521
Decitabine	56 (27.3)	49 (28.2)	7 (22.6)	
Best response				
Cycles of HMA	4 (1–12)	4 (3–10)	4 (1–12)	
Overall response	97 (47.3)	86 (49.4)	11 (35.5)	0.071
CR	27 (13.2)	26 (14.9)	1 (3.2)	
PR	19 (9.3)	15 (8.6)	4 (12.9)	
mCR	17 (8.3)	13 (7.5)	4 (12.9)	
HI	34 (16.6)	32 (18.4)	2 (6.5)	
Stable disease	69 (33.7)	53 (30.5)	16 (51.6)	
Progressive disease	39 (19.0)	35 (20.1)	4 (12.9)	
Final response				
Cycles of HMA	4 (1–63)	4 (3–63)	4 (1–20)	
Overall response	37 (18.0)	31 (17.8)	6 (19.4)	0.269
CR	16 (7.8)	16 (9.2)	-	
PR	9 (4.4)	7 (4.0)	2 (6.5)	
mCR	12 (5.9)	8 (4.6)	4 (12.9)	
HI	10 (4.9)	-	-	
Relapse after response	22 (10.7)	19 (10.9)	3 (9.7)	
Stable disease	85 (41.5)	68 (39.1)	17 (54.8)	
Progressive disease	61 (29.8)	56 (32.2)	5 (16.1)	

Values are presented as number (%) or median (range).
HMA, hypomethylating agents; HCT, hematopoietic cell transplantation; CR, complete remission; PR, partial remission; mCR, marrow CR; HI, hematologic improvement.

Table 3. Survival data

	No HMA (n = 74)	HMA (n = 205)	p value
Survival, day	454 (259–648)	596 (532–659)	0.531
Median leukemia-free survival	NR	NR	0.240
Transformation to AML	8 (10.9)	52 (25.4)	0.009
Death	39 (52.7)	134 (65.4)	0.123
Disease progression	20 (27.0)	63 (30.7)	
Infection	16 (21.6)	50 (24.3)	
TRM	0	5 (2.4)	
Others[a]	1 (1.4)	3 (1.5)	
Follow-up loss	2 (2.7)	13 (6.3)	

Values are presented as median (range) or number (%).
HMA, hypomethylating agent; NR, not reached; AML, acute myelogenous leukemia; TRM, treatment-related mortality.
[a]Others, 1 patient died of pancreatic cancer, 1 patient died of lung cancer, 1 patient died of congestive heart failure, and 1 patient died of acute myocardiac infarction.

out HMA was 140 days (range, 90 to 253). There was no significant difference in the time to HCT according to HMA therapy by independent *t* test (*p* = 0.123). Matched sibling donor (n = 8, 32%) and matched unrelated donor (n = 14, 56%) were included in a group of patients treated with HMA followed by HCT.

AML transformation was observed in 46 of the 174 patients (26.5%) who received HMA therapy and no allo-HCT, and in six of the 31 patients (19.4%) who received HMA therapy followed by allo-HCT. In the BSC only group, eight patients (11.5%) transformed to AML (Table 3). There was no case of AML transformation in the group who received allo-HCT without HMA therapy. The median survival duration was 1,113 days (range, 755 to 1,471) for allo-HCT with HMA, 537 days (range, 455 to 619) for HMA only, and 361 days (range, 169 to 553) for the BSC only group. The median survival duration was not reached by the allo-HCT without HMA group. Even if there was no statistical significance according to HMA therapy, median survival was longer in the HMA group than no HMA group (454 days vs. 596 days, *p* =0.531). So,

the incidence of AML transformation may have been observed higher because of the prolonged survival duration.

The 3-year OS rate for the HCT group overall was
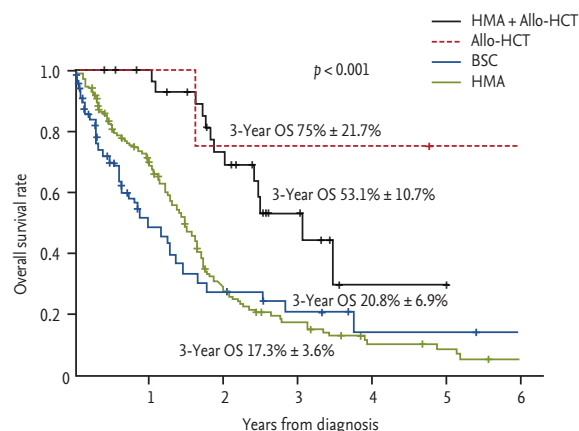
Figure 1. Overall survival curves according to treatment plan. Allo-HCT, allogeneic hematopoietic cell transplantation; OS, overall survival; HMA, hypomethylating agents; BSC, best supportive care.

Table 4. Transplantation outcomes

	HCT only (n = 5)	HMA + HCT (n = 31)	*p* value
Engraftment			
ANC > 0.5 × 10⁹/L	5 (100)	29 (93.5)	0.559
Engraftment failure	0	2 (6.5)	-
Time to neutrophil engraftment, day	12.5 (11–19)	12 (9–18)	0.346
Acute GVHD			
Grade 2–4	2 (40)	2 (6.5)	0.053
Grade 3–4	0	1 (3.2)	-
Chronic GVHD, Seattle			
Limited	0	5 (16.1)	0.207
Extensive	3 (60)	7 (22.6)	-
Chronic GVHD, NIH			
Mild	1 (20)	4 (12.9)	0.948
Moderate	0	1 (3.2)	
Severe	0	1 (3.2)	
Event[a]	3 (60)	17 (54.8)	0.829
Relapse	2 (40)	7 (22.6)	0.404
Death	1 (20)	14 (45.2)	0.290

Values are presented as number (%) or median (range).
HCT, hematopoietic cell transplantation; HMA, hypomethylating agent; ANC, absolute neutrophil counts; GVHD, graft-versus-host disease; NIH, National Institutes of Health.
[a]Event was defined as infection, hepatic veno-occlusive disease, graft failure, relapse, or death after HCT.

Sohn SK, et al. Hypomethylating agents for high-risk MDS

KJIM

61.6% ± 9.7%, which was significantly higher than that for the BSC and HMA groups (17.8% ± 3.1%, *p* < 0.001). The 3-year OS rate was 53.1% ± 10.7% for allo-HCT with HMA, 75% ± 21.7% for allo-HCT without HMA, 17.3% ± 3.6% for the HMA group, and 20.8% ± 6.9% for BSC group (*p* < 0.001) (Fig. 1). There was no significant differences by pairwise comparison in the 3-year OS rate between allo-HCT group according to HMA therapy (*p* = 0.256). There was no statistical difference in OS between the BSC and HMA groups (*p* = 0.531). The transplant outcomes are shown in Table 4 and Fig. 2. The incidence of acute or GVHD was not statistically different between the HMA-HCT and no HMA-HCT groups (*p* = 0.093).

In the multivariate analysis, for the H/VH risk pa-

Table 5. Factors affecting overall survival in high and very-high risk MDS patients

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age						
Continuous, yr	1.032	1.019–1.046	< 0.001			
< 65	1			1		
≥ 65	2.002	1.467–2.732	< 0.001	1.578	1.067–2.334	0.022
ECOG PS						
0–1	1			1		
2–4	2.818	1.986–4.001	< 0.001	2.837	1.852–4.346	< 0.001
Secondary MDS						
De novo	1					
Secondary	1.983	1.068–3.682	0.030			
IPSS-R						
High	1					
Very high	1.222	0.903–1.654	0.194			
IPSS-R cytogenetics						
Good	1			1		
Intermediate	0.818	0.522–1.281	0.380	0.730	0.222–2.404	0.605
Poor	0.728	0.409–1.296	0.281	3.976	0.883–17.907	0.072
Very poor	1.740	1.162–2.607	0.007	5.696	1.068–30.374	0.042
IPSS-R, BM blasts, %						
≤ 2	1					
> 2 and < 5	0.588	0.298–1.158	0.125			
≥ 5 and ≤ 10	0.683	0.382–1.221	0.198			
> 10	0.822	0.465–1.454	0.501			
Transformation to AML	1.653	1.202–2.274	0.001	1.901	1.310–2.757	0.001
HMA use						
No	1					
Yes	0.853	0.565–1.196	0.306			
Allogeneic-HCT						
No	1			1		
Yes	0.284	0.164–0.493	< 0.001	0.356	0.186–0.681	0.002

MDS, myelodysplastic syndrome; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; IPSS-R, Revised International Prognostic Scoring System; BM, bone marrow; AML, acute myelogenous leukemia; HMA, hypomethylating agents; HCT, hematopoietic cell transplantation.
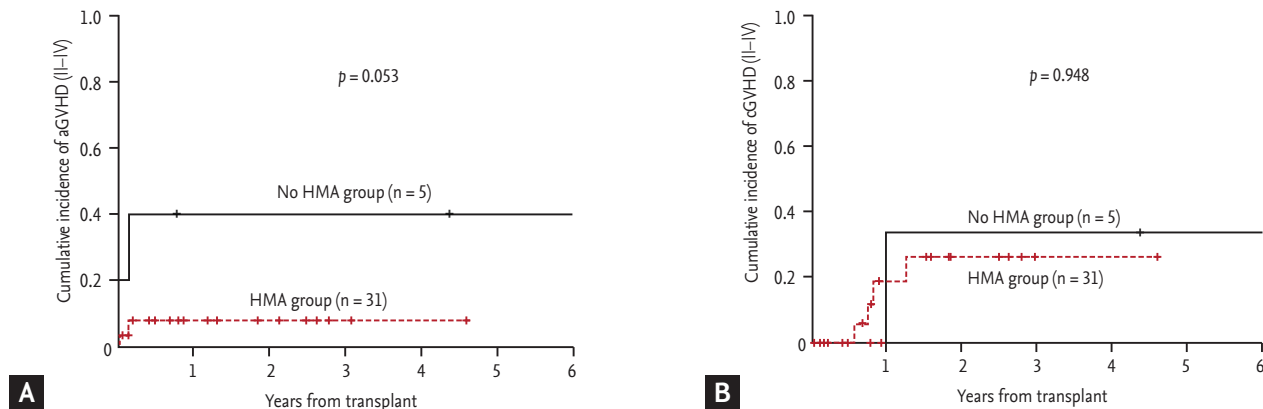
Figure 2. Incidence of acute (A) and chronic (B) graft-versus-host disease (GVHD). HMA, hypomethylating agents; aGVHD, acute GVHD; cGVHD, chronic GVHD.

tients, only allo-HCT was related to a favorable OS (hazard ratio [HR], 0.356; 95% confidence interval [CI], 0.186 to 0.681, p = 0.002), while very poor cytogenetic risk according to IPSS-R (HR, 5.696; 95% CI, 1.068 to 30.374; p = 0.042), age ≥ 65 years (HR, 1.578; 95% CI, 1.067 to 2.334), ECOG PS 2 to 4 (HR, 2.837; 95% CI, 1.852 to 4.346; p < 0.001), and transformation to AML (HR, 1.901; 95% CI, 1.310 to 2.757; p = 0.001) all had an adverse effect on OS (Table 5).

DISCUSSION

There is currently no consensus on a specific therapy for newly diagnosed higher risk MDS patients awaiting allo-HCT or those not eligible for allo-HCT. While early allo-HCT is a standard approach for HCT-eligible patients with higher risk MDS [1], in practice, some patients may require cytoreductive therapy before allo-HCT due to concerns of AML progression or a delayed search for an optimal donor. HMA can be an attractive option as a bridge therapy for higher risk MDS patients with a low toxicity profile, as it has a response rate of around 50% [11-13]. It is also not yet known whether posttransplant outcomes can be modified with pretransplant therapy with intensive chemotherapy or HMA. Randomized data are lacking. Some study showed the benefit of HMA, especially in elderly patients or patients with higher disease burden [14]. However, this study included 116 patients (49.2%) under the age of 65 years, and applied IPSS-R. IPSS-R put more weight on cytogenetics

than BM blast cut-off.

In the current study, a very poor cytogenetic risk at presentation was identified as a significant indicator predicting poor survival, while a higher percentage of BM blasts was not. However, allo-HCT with or without HMA was the only therapeutic approach for overcoming a worse prognosis. When choosing a frontline therapy for high-risk MDS, HMA should be preferentially recommended for the purpose of cytoreduction in specific cases of unfavorable cytogenetics or the presence of blasts at a certain level in the presenting BM. According to Sekeres and Cutler [15], a frontline therapy with HMA may be required to minimize the relapse risk after allo-HCT in MDS patients with blast counts > 5% to 10% and/or an unfavorable cytogenetic profile at presentation. Lubbert et al. [16] recently demonstrated in a randomized phase III trial that HMA therapy with decitabine improved progression-free survival in high-risk MDS patients with complex karyotypes harboring two or more autosomal monosomies when compared to BSC. In addition, Brierley and Steensma [17] suggested that MDS with more than 10% blasts should be considered for cytoreductive therapy using either chemotherapy or HMA, especially before reduced-intensity HCT, while patients with less than 10% blasts should proceed directly to allo-HCT. Notwithstanding, up-front allo-HCT is particularly recommended for patients with life-threatening cytopenias, as any attempt to reduce the disease burden before allo-HCT exposes a patient to the risk of complications, such as severe infection, which may then prevent them from undergoing allo-HCT [18].

Sohn SK, et al. Hypomethylating agents for high-risk MDS

KJIM

In the current study, HMA therapy did not show a favorable impact on OS when compared to BSC in the H/VH risk group. Yet, based on Kaplan-Meier survival curves, HMA therapy did show a survival advantage during the first 2 years of treatment when compared to BSC. Thus, while HMA therapy as a bridge to allo-HCT has a questionable benefit for high-risk MDS, it seems to be practically acceptable as an immediate therapy immediately after diagnosis; thus, and allo-HCT then needs to be performed as soon as possible for certain H/VH risk patients. HMA could bring a significant benefit as a bridge to allo-HCT in patients with the TET2 mutation or a less aggressive disease, whereas aggressive chemotherapy is preferred for medically fit patients with an aggressive disease [19,20]. Wermke et al. [21] suggested that up-front allo-HCT could be considered for patients with slowly progressing MDS if a donor is readily available.

In a previous survey of Korean clinicians, 88% chose HMA as a pre-HCT frontline therapy for high-risk MDS, while only 6% chose supportive care or no specific treatment before HCT [22]. In terms of the benefit of HMA as a bridging therapy for high-risk MDS patients eligible for allo-HCT, 58% of the Korean clinicians believed that HMA therapy can stabilize the disease status more safely, in terms of the side-effect profile, than intensive chemotherapy, while 27% considered that HMA therapy could ultimately improve the HCT outcome. Yet, there is still a practical dilemma when selecting a pre-HCT strategy for high-risk MDS.

Notwithstanding, it still remains whether the pretransplant use of HMA can negatively impact the outcome of a subsequent HCT as a result of damaging the patient's performance or delaying HCT. According to a previous study comparing BSC, chemotherapy, and HMA as pretransplant therapies, HMA showed no negative impact on HCT outcome compared to BSC or chemotherapy [23].

In the present study, the incidence of acute or GVHD was not statistically different between the HMA-HCT and no HMA-HCT group (Fig. 2). However, it is still unclear whether pretransplant HMA can affect immunological function in the recipient. A previous study suggested that pretransplant HMA could augment the graft-versus-leukemia effect without harm in terms of GVHD by increasing the number of T regulatory cells and inducing a cytotoxic CD8+ T-cell response [24]. Al-

though no definitive conclusions can be drawn from the present study due to the small number of patients included in the retrospective analysis, the pretransplant use of HMA did not seem to have a negative impact on the HCT outcomes in the H/VH risk MDS group when compared with historical HCT outcomes.

In conclusion, HMA showed no benefit in terms of OS in the H/VH risk group when compared with BSC. Allo-HCT was the only factor predicting a favorable long-term outcome for the patients with H/VH risk MDS. The use of HMA for higher risk MDS did not seem to have an adverse effect on the HCT outcomes when compared with historical HCT data for H/VH risk MDS. However, the conclusion of this study should be carefully interpreted and proven by large scale research in the future.

KEY MESSAGE

1. In patients with high/very high risk myelodysplastic syndrome (MDS) by Revised International Prognostic Scoring System (IPSS-R), hypomethylating agents showed no survival benefit compared to best supportive care.
2. Allogeneic hematopoietic cell transplantation was the only favorable factor for high/very high risk MDS by IPSS-R.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Greenberg PL, Stone RM, Bejar R, et al. Myelodysplastic syndromes, version 2.2015. J Natl Compr Canc Netw 2015;13:261-272.
2. Oran B, Popat U, Andersson B, Champlin R. Allogeneic hematopoietic stem cell transplantation for myelodysplastic syndromes. Clin Lymphoma Myeloma Leuk

2013;13 Suppl 2:S282-S288.

3. Sekeres MA. The euphoria of hypomethylating agents in MDS and AML: is it justified? Best Pract Res Clin Haematol 2013;26:275-278.

4. Steensma DP. Can hypomethylating agents provide a platform for curative therapy in myelodysplastic syndromes? Best Pract Res Clin Haematol 2012;25:443-451.

5. Kim Y, Kim IH, Kim HJ, et al. Multicenter study evaluating the impact of hypomethylating agents as bridging therapy to hematopoietic stem cell transplantation in myelodysplastic syndromes. Int J Hematol 2014;99:635-643.

6. Oshikawa G, Yoshioka K, Takahashi Y, et al. Impact of prior azacitidine on the outcome of allogeneic hematopoietic transplantation for myelodysplastic syndrome. Pathol Oncol Res 2015;21:1037-1043.

7. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120:2454-2465.

8. Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol 2006;24:3895-3903.

9. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-425.

10. Vigorito AC, Campregher PV, Storer BE, et al. Evaluation of NIH consensus criteria for classification of late acute and chronic GVHD. Blood 2009;114:702-708.

11. Silverman LR, Fenaux P, Mufti GJ, et al. Continued azacitidine therapy beyond time of first response improves quality of response in patients with higher-risk myelodysplastic syndromes. Cancer 2011;117:2697-2702.

12. Becker H, Suciu S, Ruter BH, et al. Decitabine versus best supportive care in older patients with refractory anemia with excess blasts in transformation (RAEBt): results of a subgroup analysis of the randomized phase III study 06011 of the EORTC Leukemia Cooperative Group and German MDS Study Group (GMDSSG). Ann Hematol 2015;94:2003-2013.

13. Musto P, Maurillo L, Spagnoli A, et al. Azacitidine for the treatment of lower risk myelodysplastic syndromes: a retrospective study of 74 patients enrolled in an Italian named patient program. Cancer 2010;116:1485-1494.

14. Lubbert M, Suciu S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. J Clin Oncol 2011;29:1987-1996.

15. Sekeres MA, Cutler C. How we treat higher-risk myelodysplastic syndromes. Blood 2014;123:829-836.

16. Lubbert M, Suciu S, Hagemeijer A, et al. Decitabine improves progression-free survival in older high-risk MDS patients with multiple autosomal monosomies: results of a subgroup analysis of the randomized phase III study 06011 of the EORTC Leukemia Cooperative Group and German MDS Study Group. Ann Hematol 2016;95:191-199.

17. Brierley CK, Steensma DP. Thrombopoiesis-stimulating agents and myelodysplastic syndromes. Br J Haematol 2015;169:309-323.

18. Gauthier J, Damaj G, Yakoub-Agha I. The role of pre-transplant debulking treatment in patients undergoing allogeneic stem cell transplantation for high-risk myelodysplastic syndrome. Bull Cancer 2015;102:340-348.

19. Bejar R, Lord A, Stevenson K, et al. TET2 mutations predict response to hypomethylating agents in myelodysplastic syndrome patients. Blood 2014;124:2705-2712.

20. Itzykson R, Kosmider O, Cluzeau T, et al. Impact of TET2 mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias. Leukemia 2011;25:1147-1152.

21. Wermke M, Gloaguen S, Platzbecker U. Preparing patients with myelodysplastic syndrome for transplant when is pre-transplant cytoreductive therapy appropriate? Curr Hematol Malig Rep 2015;10:329-333.

22. Sohn SK, Moon JH. Survey of expert opinions and related recommendations regarding bridging therapy using hypomethylating agents followed by allogeneic transplantation for high-risk MDS. Crit Rev Oncol Hematol 2015;95:243-250.

23. Oran B, Kongtim P, Popat U, et al. Cytogenetics, donor type, and use of hypomethylating agents in myelodysplastic syndrome with allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2014;20:1618-1625.

24. Martino M, Fedele R, Moscato T, Ronco F. Optimizing outcomes following allogeneic hematopoietic progenitor cell transplantation in AML: the role of hypomethylating agents. Curr Cancer Drug Targets 2013;13:661-669.