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Brief Articles

Allogeneic Hematopoietic Stem Cell Transplantation Following the Use of Hypomethylating Agents among Patients with Relapsed or Refractory AML: Findings from an International Retrospective Study

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A B S T R A C T

Patients with primary refractory or relapsed acute myeloid leukemia (RR-AML) have very poor prognosis. Due to limited treatment options, some patients are treated with hypomethylating agents (HMAs) due to their tolerability. Little is known about the role of allogeneic hematopoietic stem cell transplantation (HSCT) following HMA therapy in this setting. We retrospectively analyzed an international cohort of 655 RR-AML patients who received HMA therapy to study patterns and outcomes with HSCT. Only 37 patients (5.6%) patients underwent HSCT after HMA therapy. The conditioning regimen was myeloablative in 57% and nonmyeloablative in 43%. Patients received matched unrelated donor, matched sibling, haploidentical and mismatched unrelated HSCT in 56%, 24%, 16% and 4% of cases, respectively. Acute GvHD and chronic GvHD were observed in 40% and 17% of patients. While the median OS for the entire cohort of patients was 15.3 months (95% CI 9.5

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– 21.7 months), OS reached 29.7 months (95% CI 7.01 – not-reached) for patients who achieved a complete remission (CR) to HMA and no intervening therapies between HMA therapy and HSCT. Our study suggests that HMA therapy can effectively bridge some patients with RR-AML to HSCT.

INTRODUCTION

Patients with primary refractory and relapsed (RR) acute myeloid leukemia (AML), particularly older adults, have dismal outcomes and limited therapeutic options are available [1]. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only potentially curative treatment in this setting [2,3]. However, achieving disease control is generally necessary for successful HSCT outcomes. Intensive chemotherapy is the commonly used modality to achieve CR for patients with RR AML; however, complete remission (CR) rates generally do not exceed 20% to 40% and intensive therapy is associated with increased risks of mortality and morbidity as well as prolonged hospitalization. Given their tolerability, hypomethylating agents (HMAs) have been used in patients with AML, usually in frontline setting, who are unfit for intensive chemotherapy [1]. In a prior multicenter study, we have shown that HMAs result in CR/CR with incomplete count recovery (CRi) in 16% of patients with RR AML while offering the opportunity of outpatient therapy and lower risk of therapy-related complications [4]. Most of the data regarding transplant outcomes among patients with RR AML comes from trials and analyses of patients who received intensive salvage chemotherapy [5]. Several intensive chemotherapy regimens have been studied; however, there is no clear evidence of superiority of any particular regimen [5]. In contrast, little is known about the transplant outcomes for those patients with RR AML who are treated with HMA as salvage therapy before transplantation.

METHODS

Using a large multicenter international database, we analyzed characteristics and clinical outcomes of the subgroup of RR AML patients who underwent HSCT after HMA salvage therapy. Data of patients treated with HMAs for RR AML were collected for a period spanning 2006 to 2016, from 7 centers in the United States and 4 centers in Europe. For the subgroup of patients who underwent HSCT after HMA therapy, we assessed type of graft and conditioning regimen, lines of therapy post-HMA and before HSCT, a well as any post-HSCT therapies. Furthermore, we analyzed the rate and severity of acute and chronic graft-versus-host disease (GVHD) as well as 30-day and long-term mortality post-transplantation and their respective predictors. Kaplan-Meier methods were used to estimate overall survival (OS) from the start of HMA therapy to death or end of follow-up.

RESULTS

Of 655 patients in the database, 16% achieved a CR/CRi with HMA therapy, and only 37 patients (5.6% of the entire cohort) underwent HSCT at one point after receiving HMA salvage therapy (Table 1). Of these patients, 16 (43.2%) had relapsed and 21 (56.8%) had primary refractory AML. At the time of HMA therapy, only 1 patient had favorable risk karyotype, whereas 69% and 23% had intermediate-risk and poor-risk karyotypes, respectively. Azacitidine and decitabine were used in 34% and 66% of patients, respectively. Patients had received a median of 1 line of therapy (range, 1 to 7) before HMA therapy. Of all patients who underwent HSCT, 23 (62%) had achieved a response (CR, CRi, or hematologic improvement [HI]) to HMA therapy whereas the other 14 (38%) did not. Twenty-four (65%) patients went directly to HSCT after completing HMA therapy while 13 (35%) patients received additional therapy between HMA therapy and HSCT (Table 2).

Table 1
Patient Characteristics of the 37 Transplanted Patients

Patient characteristics	
Male/female sex	17/20 (46/54)
Age, yr	56 (22–71)
Disease status	
Relapsed	16 (43.2)
Primary treatment refractory	21 (56.8)
Karyotype risk	
Favorable	1 (8)
Intermediate	9 (69)
Poor	3 (23)
Azacitidine/decitabine	11/21 (34/66)
Response to HMA	23 (62)
CR	11 (30)
CRi	10 (27)
HI	2 (5)
No response to HMA	14 (38)
Therapy between stop of HMA therapy and HSCT	
Yes/no	13/24 (35/65)
Type of therapy administered (18 therapies prescribed to 13 patients):	
CPX	5 (27.8)
Cytarabine	5 (27.8)
Clofarabine	3 (16.8)
CLAG	2 (11.1)
MEC	1 (5.6)
FLAG Ida	1 (7.7)
Cytoxan/etoposide	1 (5.6)
Therapy after HSCT	
Yes/no	7/30 (19/81)
Type of therapy administered (13 therapies prescribed to 7 patients):	
Azacitidine, decitabine	6 (46.2)
Cytarabine	2 (15.4)
Hydroxyurea	2 (15.4)
SGI-110	1 (7.7)
ASP-2215	1 (7.7)
Sorafenib	1 (7.7)

Data are presented as n/n (%), mean (range), or n (%).
CPX-351 indicates liposomal formulation containing a fixed combination of cytarabine and daunorubicin in a 5:1 molar ratio; CLAG, cladribine, cytarabine, and filgrastim; MEC: mitoxantrone, etoposide and cytarabine; FLAG, fludarabine, cytarabine, granulocyte colony-stimulating factor; SGI-110, guadecitabine; ASP-2215, gilteritinib.

Of patients receiving no additional therapies between HMA and HSCT, a total of 16 patients had responded to HMA therapy (CR = 7, CRi = 8, HI = 1). Of patients who received some type of post-HMA therapy before HSCT, 7 patients had achieved a prior response to HMA (CR = 4, CRi = 2, HI = 1).

The median duration between last day of HMA therapy and HSCT was 50 days (range, 6 to 210 days). Approximately 57% of patients received myeloablative conditioning therapy while the other 43% received nonmyeloablative conditioning regimens. Most patients received a matched unrelated donor transplant (56%) or a matched sibling transplant (24%), whereas 16% and 4% of patients received a haploidentical or a mismatched unrelated HSCT, respectively (Table 2).

Acute GVHD was observed in 40% of patients, with 75% developing grade of 1 or 2 GVHD and 25% developing grade 3 or 4 GVHD. Acute GVHD affected skin (30%), mouth (10%), gastrointestinal tract (45%), and liver (15%). Furthermore, 17% of patients developed chronic GVHD, which was limited in

Table 2
Transplant Characteristics for Patients who underwent HSCT after HMA for RR AML

	All Patients (N = 37)	Patients with no Subsequent Therapies between HMA and HSCT (n = 24)	Patients with Subsequent Therapies between HMA and HSCT (n = 13)
Type of graft (n = 25)			
Matched sibling	6 (24)	4 (25)	2 (22.2)
Matched unrelated donor	14 (56)	9 (56.2)	5 (55.6)
Mismatched unrelated	1 (4)	0 (0)	1 (11.1)
Haplotransplant	4 (16)	3 (18.8)	1 (11.1)
Type of conditioning regimen (n = 14)			
Ablative	8 (57.1)	7 (63.6)	1 (33.3)
Nonablative	6 (42.9)	4 (36.4)	2 (66.7)
Acute GVHD:			
Presence of acute GVHD (n = 25)	10 (40)	6 (40)	4 (40)
Grade of acute GVHD (n = 8)			
1	3 (37.5)	2 (50)	1 (25)
2	3 (37.5)	1 (25)	2 (50)
3	1 (12.5)	0 (0)	1 (25)
4	1 (12.5)	1 (25)	0 (0)
Organ affected in acute GVHD (n = 20)			
Skin	6 (30)	4 (33.3)	2 (25)
Eyes	2 (10)	2 (16.7)	0 (0)
Gut	9 (45)	5 (41.7)	4 (50)
Liver	3 (15)	1 (8.3)	2 (25)
Chronic GVHD			
Presence of chronic GVHD (n = 24)	4 (16.7)	3 (21.4)	1 (10)
Severity of chronic GVHD (n = 4)			
Limited	3 (75)	3 (100)	0 (0)
Extensive	1 (25)	0 (0)	1 (100)
Organ affected in chronic GVHD (n = 5)			
Skin	2 (40)	2 (66.7)	0 (0)
Mouth	1 (20)	1 (33.3)	0 (0)
Gut	1 (20)	0 (0)	1 (50)
Liver	1 (20)	0 (0)	1 (50)

Data are presented as n (%).

75% and extensive in 25% of patients (Table 2). Chronic GVHD most commonly affected skin (40%), but also affected eyes and mouth (20%), gastrointestinal tract (20%), and liver (20%). After HSCT, 7 (19%) patients received further lines of therapy, with epigenetic therapy (HMA or histone deacetylase inhibitor therapy) (58%) being most commonly used whereas chemotherapy was rarely used (8%).

The median OS for the entire cohort of 37 patients who underwent HSCT after HMA therapy was 15.3 months (95% confidence interval [CI], 9.5 to 21.7 months) from the start of HMA therapy. This was statistically significantly longer than the median OS for all other 618 patients, who did not receive a HSCT after HMA therapy (OS, 6.4 months; 95% CI, 5.7 to 6.9 months; $P < .0001$). The median OS was 14.6 months (95% CI, 9.5 months to not reached) for patients with no therapies administered between HMA and HSCT and 15.3 months (95% CI, 9.4 months to not reached) for patients with at least 1 therapy in between HMA and HSCT, respectively ($P = .3$) (Figure 1A).

For patients, who underwent subsequent HSCT without intervening therapies between HMA and HSCT, median OS was 16.8 months (95% CI, 9.5 months to not reached) for the 16 patients who achieved a response to HMA therapy (CR/CRi/HI), whereas it was 14.5 months (95% CI, 6.7 months to not reached; $P = .4$) for the 8 patients with either stable disease or progressive disease (Figure 1B).

For patients without intervening therapies between HMA and HSCT, median OS was 29.7 months (95% CI, 7 months to not reached) for patients who achieved a CR to HMA and 14.6 months (95% CI, 9.47 months to not reached) for those not achieving CR ($P = .6$).

DISCUSSION

In summary, in one of the largest reported cohorts of patients with RR AML treated with HMAs, we determined that a minority of patients underwent HSCT after completion of HMA therapy.

While the median OS of the patients who underwent HSCT after HMA therapy was significantly longer compared with patients who did not undergo HSCT, only about 25% of the 24 patients who went to HSCT directly after HMA therapy were long term survivors (reached a plateau on the Kaplan-Meier survival curve), which translates into just 6 patients of the original 655-person cohort (<1%). Importantly, the OS for patients who achieved a CR with HMAs and went directly to HSCT was not statistically significantly different from patients who achieved a CR with HMAs but did not undergo HSCT (29.7 months versus 25.3 months; $P = .8$). Furthermore, it did not seem to make a difference whether patients achieved a response to HMA therapy or not and whether patients went directly to HSCT after HMA therapy or had any other therapy after receiving HMA and before HSCT (Figure 1). These findings could argue against a benefit specific to HMA therapy when used as a bridge therapy to HSCT. While patients who achieved a CR with HMAs and thereafter underwent HSCT without intervening therapy had a median OS reaching 30 months, this subgroup was too small to make any conclusions whether they had a statistically significantly prolonged OS compared with patients who did not achieve a CR with HMA therapy.

Our study indicates that while HMAs can allow outpatient administration with lower toxicity compared with salvage intensive chemotherapy and can be used as a bridge

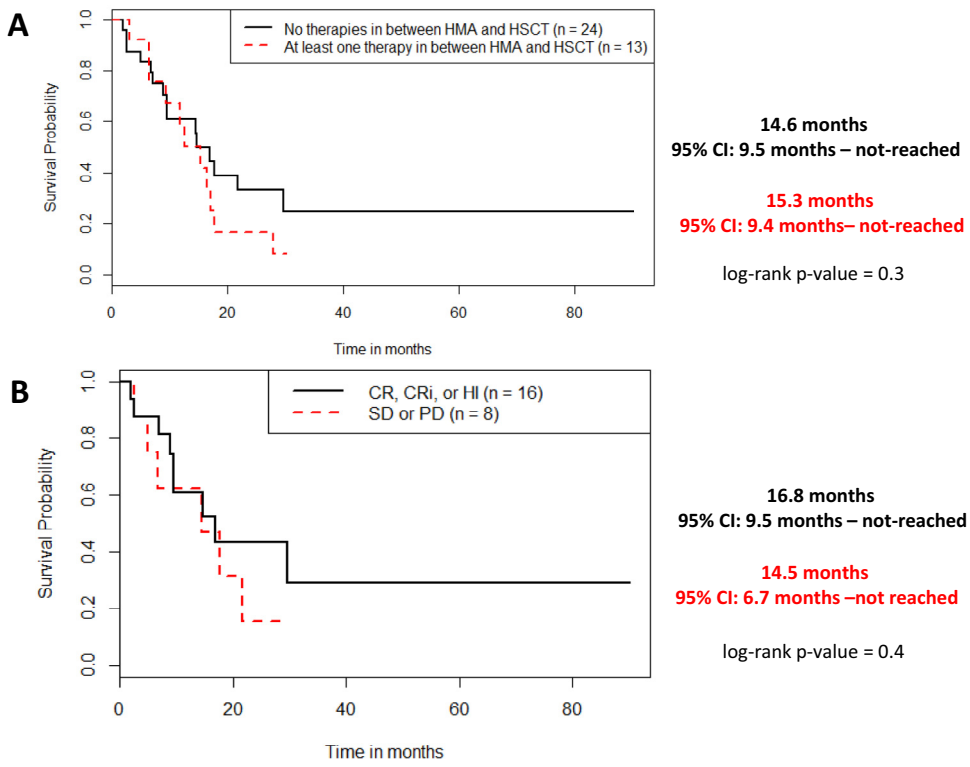

Figure 1. Probability of overall survival from start of HMA therapy. A: For patients who directly went to HSCT vs. patients, who received at least one more line of therapy between HMA and HSCT. B: For patients, who directly went to HSCT stratified by having a response (CR,CRi,HI) vs. no response (SD, PD) to HMA therapy.

to HSCT, only a minority of patients with RR AML were able to undergo transplantation and the long survival rate was quite limited. As most patients do very poorly regardless of HMA response and regardless of receiving HSCT, improved treatments are urgently needed for patients with RR AML. Combining HMAs with investigational therapies could lead to better outcomes in this difficult to treat patient population.

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