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Allogeneic hematopoietic stem cell transplantation versus hypomethylating agents in patients with myelodysplastic syndrome: A retrospective case–control study

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Abstract

Allogeneic stem cell transplantation (allo-SCT) is the only potentially curative treatment for myelodysplastic syndrome (MDS). Recently, hypomethylating agents (HMAs) have been shown to improve survival in patients with high-risk MDS. We conducted a retrospective case–control study to compare survival with these treatment modalities in patients with untreated MDS. Controls were identified using a departmental database and transplant patients were matched in at least three of the following five criteria: year of diagnosis, age, blast percentage, International Prognostic Scoring System cytogenetic risk, and time from diagnosis to treatment. Median overall survival (OS) was 26 and 25 months for, respectively, allo-SCT [(*n* = 53); range, 2–210 months] and HMA [(*n* = 40); range, 2–98 months] (*P* = 0.89). Four-year survival rates were 24 and 23% for allo-SCT patients and the nontransplant cohort, respectively. Patients undergoing allo-SCT after 2000 had longer median OS compared with those transplanted before 2000 (41 versus 7 months, *P* = 0.001). These results would suggest that prospective studies are needed to delineate the timing and efficacy of allo-SCT in the HMA era.

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Author Contributions

Designed research: EJ, GGM, and MDL; Performed research: EJ, GGM, SP, and MDL; Collected and analyzed data: EJ, MSM, GGM, JC, SP, and MDL; Provision of study material and patient care: EJ, MSM, IK, GGM, UP, ND, GR, SG, BO, SP, HK, RC, and MDL; Statistical analysis: SP; Wrote manuscript: EJ, MSM, and MDL; Edited/approved final manuscript: EJ, MSM, GGM, UP, GR, SG, JC, SP, EK, ND, BO, SP, HK, RC, and MDL.

Introduction

Myelodysplastic syndromes (MDSs) are a heterogeneous group of myeloid malignancies. Heterogeneity is illustrated by differences in outcomes such as transformation to acute myeloid leukemia (AML) and overall survival (OS) when patients are stratified by various disease factors [1, 2]. Median OS is approximately 12 months or less for the group with higher risk disease [1]. Allogeneic stem cell transplantation (allo-SCT) is regarded as the only curative intervention available for patients with MDS. A study from the International Bone Marrow Transplant Registry indicated that early transplantation in higher risk MDS was associated with the longest life expectancy [3]. This analysis, however, took place before the use of contemporary therapeutic options.

Recently, azacitidine and decitabine, drugs referred to as hypomethylating agents (HMAs), have been approved for the management of MDS [4–6]. In a randomized phase III trial of azacitidine versus conventional care, azacitidine was shown to improve the OS in patients with higher risk MDS [7].

The strategies of allo-SCT and HMA have largely been used complementarily and or sequentially, and not directly compared. Therefore, we analyzed a group of untreated MDS patients who underwent allo-SCT and compared them to a similar group who received HMA without transplant. The untreated MDS at transplant subgroup was chosen to minimize biases that would be imposed by pre-allo-SCT treatments when choosing the comparison group.

Methods

This was a retrospective case–control study of MDS patients receiving treatment at the UT/MDACC. The study was approved by the Institutional Review Board (IRB). A departmental database was searched to identify patients with MDS who were treated between January 1988 and April 2008. We first identified patients who underwent allo-SCT as a frontline approach for MDS (i.e., no specific treatment before transplant).

The control group consisted of patients who received HMA only as their initial therapy. Because the treatment period encompassed several years before HMAs were commercially available, dosing strategies and duration of therapy were quite variable. All patients were treated on clinical trials approved by the IRB of UT/MDACC. Patients were selected if they matched at least three of the following five criteria: year of diagnosis (before or after 1998), age (plus or minus 3 years was acceptable), International Prognostic Scoring System (IPSS) cytogenetic risk category, percentage of bone marrow blasts at diagnosis (matched according to IPSS category), and time from diagnosis to treatment.

Variables collected on all patients at diagnosis in both groups included the following: age, gender, white blood cell count, platelet count, hemoglobin, bone marrow blast percentage, karyotype, and history of a prior malignancy. The IPSS risk score was calculated to determine a patient's risk of leukemic transformation and survival.

Patients in the HMA group received either azacitidine or decitabine at the discretion of the treating physician.

OS was estimated using Kaplan–Meier curves, and the log-rank test was used to compare survival between the two groups. Categorical data were compared using the chi-squared or Fisher's exact test, and continuous variables were compared using Student's *t*-test.

Results

There were 152 patients that received allo-SCT for MDS between January 1988 and April 2008. Fifty-three of these patients (35%) were untreated at the time of allo-SCT, and 40 matched controls were identified for the analysis. Demographic and disease characteristics were largely similar between groups, although the allo-SCT group was slightly younger. The IPSS risk scores were similar between groups (Table I).

Eighty-two percent of the patients in the HMA group received decitabine, and 18% received azacitidine. Objective response rates were observed in 19 (47%) patients; among them 16 (40%) attained a complete response (CR), two (5%) a partial response (PR), and one (2%) hematologic improvement. Six (32%) of the responders who progressed after a median of 15 months (range, 3–43) received salvage therapy. Allo-SCT was offered as a salvage therapy to three patients who received HMA: one after previous response and two being primary resistant. These three patients were not censored at the date of allo-SCT.

Patients who received allo-SCT received stem cells from a matched related (77%) or unrelated (23%) donor. The most commonly used conditioning regimen included a combination of busulfan and fludarabine in 36% of the patients [8]. Eighty-one percent achieved CR post allo-SCT. Of the 43 responders, eight (15%) progressed after a median of 9 months (range, 3–21).

Median time from diagnosis to HMA therapy and allo-SCT was 1 (range, 0–15) and 5 (range, 1–60) months, respectively. Median follow-up of alive patients who received HMA therapy and allo-SCT was 62 (range, 40–98) and 76 (range, 5–210) months, respectively. Median OS was 26 months in the allo-SCT group compared with 25 months in the group receiving HMA (similar results whether or not patients were censored for subsequent allo-SCT in three patients) ($P = 0.89$; Fig. 1). Similarly, actuarial 4-year OS rates were similar.

Causes of treatment failure after transplant were recurrence/persistence disease in 10 patients (19%) and treatment-related mortality in 27 (51%), because of acute ($n = 7$) or chronic ($n = 2$) graft versus host disease. Of the 40 patients treated with HMA, 30 died of their disease, 10 were alive, 8 on HMA, and 2 postsalvage therapy (clofarabine in 1 and allo-SCT in 1) (Table II).

Because of substantial potential differences in transplant strategy during the treatment period, we stratified the allo-SCT group by whether they were transplanted before or after the year 2000 ($n = 32$ after 2000 and $n = 21$ before 2000). Median OS was significantly improved in the group transplanted after 2000 (41 versus 7 months, $P = 0.001$) (Table III). We also compared the median OS of patients who received busulfan- and fludarabine-based

conditioning regimens ($n = 19$, busulfan/fludarabine and $n = 34$, other) and found a statistically significant difference (38 versus 11 months, $P = 0.04$).

Because patients aged 70 years or older would not be routinely eligible for allo-SCT, we repeated the analysis removing the seven patients who received HMA and compared them to the group younger than 70 years ($n = 33$). We found a numerical difference in median OS favoring the younger patients (25 versus 15 months, $P = 0.21$) (Table III). The lack of statistical significance may have been influenced by small numbers of patients in each group.

Finally, we stratified patients by their IPSS score and found that it was not predictive of CR or for OS, although patients in both treatment groups with a high IPSS score had a much shorter median survival (Table III).

Discussion

This matched control study is one of the few direct comparisons of the two most widely used interventions in the management of MDS. Our results would suggest a lack of a major benefit for upfront allo-SCT when compared with treatment with HMA. This observation raises several points of discussion.

Most patients who undergo allo-SCT today will have had some level of exposure to HMA, as opposed to being transplanted without any therapy. One might argue that this strategy represents the current standard of care for higher risk patients, but there is no prospective evaluation of this recommendation. Pretransplant treatment with HMA appears to be safe [9], with a trend for lower relapse rate in favor of patients who received HMA pretransplant [10]. That being said, so far there has been no evidence that such a strategy substantially influences the overall outcome [10].

In addition, there is no consensus if patients should be transplanted at best response or at HMA failure. Some would argue against the latter approach when considering the dismal outcome reported for patients who fail decitabine therapy [11]. However, it is unclear if allo-SCT would improve survival in the high-risk subgroup of patients, as they may be biologically predisposed to a poor outcome. Indeed, others have reported that patients with a monosomal karyotype had a 5-year OS of 0% after allo-SCT [12]. Furthermore, it has been demonstrated that patients who undergo salvage allo-SCT after failing azacitidine have a median OS of ~19 months [13].

Our retrospective analysis is limited by the relatively small sample size, and heterogeneity in transplant approaches and the high transplant-related mortality, which has clearly improved over time [14]. This was also demonstrated in this study when we stratified the groups by year of transplant. Another potential source of bias is the matching process. Although the patients seemed very well matched, there may have been individual differences that influenced the decision of upfront transplant versus HMA. However, patients in the allo-SCT group were younger, a group of patients that is expected to benefit most from an approach with curative intent.

The predominant reason for allo-SCT failure in higher risk MDS is relapse or progression of disease [15, 16]. Despite the use of reduced intensity regimens, older MDS patients are frequently deemed not eligible for allo-SCT because of comorbidities and lack of matched related donor. Potential strategies under investigation to decrease transplant-related mortality and improve relapse rates after allo-SCT include low-dose azacitidine maintenance and incorporation of new agents in the preparative regimen [17, 18].

We were unable to show a significant survival advantage for allo-SCT over standard treatment for untreated MDS, although patients did substantially better when transplanted after 2000 or when receiving busulfan/fludarabine-based conditioning regimens. This conclusion is based on a retrospective analysis and should be validated in a prospective manner.

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Figure 1.
Overall survival according to treatment strategy.

TABLE I

Patients Characteristics

		Allo-SCT	HMA	<i>P</i> -value
Parameter		<i>N</i> = 53 (%)	<i>N</i> = 40 (%)	
Median age, years [range]		51 [20–62]	54 [38–79]	<0.001
Sex	Male	31 (58)	23 (57)	NS
	Female	22 (42)	17 (43)	
Median IPSS [range]		1.5 [0–3]	1.5 [0–3]	NS
IPSS CG	Good	15 (28)	10 (25)	NS
	Intermediate	5 (9)	4 (10)	
	Poor	33 (63)	23 (65)	
IPSS BM blasts	<5%	32 (60)	22 (55)	NS
	5–10%	17 (32)	15 (37)	
	11–20%	4 (8)	3 (8)	
Hemoglobin	<10 g/dL	29 (55)	22 (55)	NS
	>10 g/dL	24 (45)	18 (45)	
Platelets	>100 × 10 ⁹ /L	36 (68)	29 (72)	NS
	<100 × 10 ⁹ /L	17 (32)	11 (28)	
WBC	>5 × 10 ⁹ /L	49 (92)	34 (85)	NS
	<5 × 10 ⁹ /L	4 (8)	6 (15)	
Prior malignancy	Yes	28 (53)	21 (52)	NS
	No	25 (47)	19 (48)	

Allo-SCT, allogeneic stem cell transplantation; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; CG, cytogenetic; BM, bone marrow; WBC, white blood cells.

TABLE II**Outcome**

	Allo-SCT	HMA
Parameter	<i>N</i> = 53	<i>N</i> = 40
Median follow-up, months (range)	76 (5–210)	62 (40–98)
CR rate %	81	40
Median time to relapse, months (range)	9 (3–21)	15 (3–43)
Alive at last follow-up (%)	16 (30)	10 (25)
Median survival, months	26	25
4-year survival rate (%)	24	23

Allo-SCT, allogeneic stem cell transplantation; HMA, hypomethylating agent.

TABLE III

Subset Analysis of Outcomes

Parameter	N	CR	Early death	Median OS (months)
HMA				
Age (years)				
70	33	15 (45)		25
<70	7	5 (71)		15
P-value		0.21		0.04
IPSS				
Low	2	1 (50)		29
Int-1	14	5 (36)		26
Int-2	21	14 (67)		25
High	3	0		9
P-value		0.09		0.14
Allo-SCT				
Year				
2000	32	27 (84)	1 (3)	41
<2000	21	16 (76)	3 (14)	7
P-value		0.45		0.001
IPSS ^a				
Low	1	1 (100)		NR
Int-1	18	14 (78)	2 (11)	27
Int-2	28	23 (82)	3 (11)	26
High	4	3 (75)	1 (25)	9
P-value		0.93		0.43
Conditioning				
Flu/Bu	19	16 (84)	0	38
Others	34	27 (79)	4 (12)	11
P-value		0.67		0.04

CR, complete remission; Early death, 4-week mortality; OS, overall survival; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; Int, intermediate; Allo-SCT, allogeneic stem cell transplantation; NR, not reached; Flu/Bu, fludarabine/busulfan-based conditioning.

^aMissing data for two patients.