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Cytogenetics, Donor Type, and Use of Hypomethylating Agents in Myelodysplastic Syndrome with Allogeneic Stem Cell Transplantation

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A B S T R A C T

We investigated the impact of patient and disease characteristics, including cytogenetics, previous therapy, and depth of response, on the outcome of allogeneic hematopoietic stem cell transplantation (HSCT) for patients with myelodysplastic syndrome (MDS). We analyzed 256 MDS patients who underwent transplantation from a matched related (n = 133) or matched unrelated (n = 123) donor after 2001. Of the 256, 78 (30.5%) did not receive cytoreductive therapy before HSCT; 40 (15.6%) received chemotherapy, 122 (47.7%) received hypomethylating agents (HMA), and 16 (6.2%) received both (chemo+HMA). Disease status at HSCT defined by International Working Criteria was complete remission in 46 (18%) patients. There were significant differences between therapy groups: there were more therapy-related MDS and higher use of matched related donor in the untreated group. The chemotherapy group had higher serum ferritin levels at HSCT. Patients were older and had more high-risk disease by revised International Prognostic Scoring in the HMA group. Despite those differences, transplantation outcomes were similar in patients who were untreated and who received cytoreductive therapy before HSCT. Three-year event-free survival (EFS) was 44.2%, 30.6%, 34.2%, and 32.8% for untreated, chemotherapy, HMA, and chemo+HMA groups, respectively ($P = .50$). Multivariate analyses revealed that older age (hazard ratio [HR], 1.3; $P = .001$); high-risk histologic subtypes, including refractory anemia with excess blasts (HR, 1.5; $P = .05$) and chronic myelomonocytic leukemia (HR, 2.1; $P = .03$), high-risk cytogenetics with monosomal karyotype (MK) (HR, 4.0; $P < .0001$) and high serum ferritin level at HSCT (HR, 1.8; $P = .002$) were poor prognostic factors for EFS. Bone marrow blast count 5% or higher at HSCT (HR, 1.6; $P = .01$) and MK (HR, 4.2; $P < .0001$) were the only prognostic factors for increased relapse incidence after HSCT. Patients with MK represented a poor prognostic group, with 3-year EFS of 11.4% and relapse incidence of 60.9%. In this analysis, various therapy approaches before HSCT did not lead to different transplantation outcomes. Cytogenetics defined by MK was able to identify a very poor prognostic groups that innovative transplantation approaches to improve outcomes are urgently needed.

INTRODUCTION

Myelodysplastic syndromes (MDS) comprise a family of clonal hematopoietic diseases characterized by bone marrow failure and a predisposition to evolve into acute myeloid leukemia (AML) [1]. Despite major progress in understanding its pathophysiology and recent advances in treatment, particularly with hypomethylating agents (HMAs), MDS remains incurable with standard forms of treatment. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only therapeutic option that has the potential to produce long-term remission, with disease-free survival of 25% to 60%, depending on disease characteristics [2-4]. The major cause of treatment failure after HSCT in MDS is relapse of the disease. Cytogenetic abnormalities and the proportion of bone marrow myeloblasts are known to predict the risk of relapse after HSCT. Cytoreductive therapy is commonly used before referral for HSCT, with a goal of reducing risk of disease relapse after transplantation. The effectiveness of chemotherapy and/or HMA treatment before HSCT is not established.

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In the present analyses, we sought to determine the impact of disease characteristics at diagnosis and at HSCT, including pretransplantation MDS therapy and depth of response, cytogenetics, and donor type, on the outcome of HSCT.

METHODS

Patient Population

We retrospectively analyzed 256 patients, 18 years or older, who were diagnosed with MDS and underwent first HSCT at the University of Texas MD Anderson Cancer Center from January 1, 2001 to December 31, 2012. Histological subtypes were classified according to the World Health Organization definition [5]. Forty patients (15.6%) with refractory anemia (RA) or RA with ringed sideroblasts and 34 (13.7%) with refractory cytopenia with multilineage dysplasia were grouped as "low/intermediate risk" histology, whereas 45 (17.6%) with RA with excess blasts type 1 and 55 (21.5%) with RA with excess blasts type 2 were grouped as "high-risk" (Table 1). The histological subtype was MDS-unclassifiable (MDS-U) in 59 cases (23.2%), and 23 patients (9%) had chronic myelomonocytic leukemia (CMML). Cytogenetic findings were classified according to the 5-group classification recently described by Schanz et al. [6] and monosomal karyotype (MK) reported by Breems et al. [7]. Patients were categorized according to the revised International Prognostic Scoring System (IPSS-R) by disease characteristics at diagnosis [8]. CMML and therapy-related MDS (t-MDS) were not included in this risk scoring, per definition.

Prior Therapy for MDS and Response Evaluation

Of the 256 patients included in the study, 178 (69.5%) received treatment for MDS using chemotherapy and/or HMA before HSCT, whereas 78

Table 1
Patient and Disease Characteristic by MDS therapy before HSCT

Variable	Whole Cohort n = 256	Untreated n = 78	Chemo Only n = 40	HMA Only n = 122	Chemo+HMA n = 16	*P* Value
Age, median (IQR), yr	56 (48-62)	52 (45-57)	55 (44-60)	59 (53-64)	59 (56-60)	.0001
WHO histological subtype						
Low/intermediate	74 (28.9)	27 (34.6)	7 (17.5)	38 (31.2)	2 (12.5)	
High risk	100 (39.1)	13 (16.7)	26 (65.0)	51 (41.8)	10 (62.5)	
CMML	23 (9.0)	3 (3.8)	4 (10.0)	12 (9.8)	4 (25.0)	
MDS-U	59 (23.0)	35 (44.9)	3 (7.5)	21 (17.2)	0	<.001
T-MDS	92 (35.9)	43 (55.1)	12 (30.0)	37 (30.3)	0	<.001
Cytogenetics by 5-group risk	n = 254					
Very good/good	105 (41.3)	27 (35.1)	19 (47.5)	52 (43.0)	7 (43.7)	
Intermediate	32 (12.6)	9 (11.7)	6 (15.0)	13 (10.7)	4 (25.0)	
Poor	46 (18.1)	22 (28.4)	5 (12.5)	18 (14.9)	1 (6.3)	
Very poor	71 (28.0)	19 (24.7)	10 (25.0)	38 (31.4)	4 (25.0)	.20
MK	n = 254					
CN	102 (40.2)	27 (35.1)	17 (42.5)	51 (42.1)	7 (43.8)	
MK−	79 (31.1)	30 (39.0)	14 (35.0)	29 (24.0)	6 (37.5)	
MK+	73 (28.7)	20 (25.9)	9 (22.5)	41 (33.9)	3 (18.7)	.30
IPSS-R at diagnosis	n = 144					
Very low/low	40 (27.8)	11 (32.4)	2 (8.4)	23 (31.1)	4 (33.3)	
Intermediate	18 (12.5)	6 (21.8)	5 (20.8)	5 (6.8)	2 (16.7)	
High	22 (15.3)	6 (20.5)	6 (25.0)	9 (12.2)	1 (8.3)	
Very high	37 (25.7)	2 (14.1)	6 (25.0)	25 (33.8)	4 (33.3)	
Missing	27 (18.8)	9 (16.7)	5 (20.8)	12 (16.2)	1 (8.3)	.03
Morphological response by IWG*	n = 178					
CR	46 (25.8)		12 (30.0)	31 (25.4)	3 (18.8)	
AD	132 (74.2)		28 (70.0)	91 (74.6)	13 (81.2)	.70
Persistent karyotype abnormality at HSCT†	n = 106					
No	35 (33.0)		9 (37.5)	24 (33.3)	2 (20)	
Yes	71 (67.0)		15 (62.5)	48 (66.7)	8 (80)	.60
BM blast at HSCT, %						
<5	169 (66.0)	55 (70.5)	25 (62.5)	79 (64.8)	10 (62.5)	
≥5	87 (34.0)	23 (29.5)	15 (37.5)	43 (35.2)	6 (37.5)	.80
Ferritin level	n = 201	n = 47	n = 21	n = 118	n = 15	
Median, IQR	1131 (521-2246)	1077 (389-2637)	1555 (1100-2503)	997 (425-2010)	1748 (1002-3211)	.03
Stem cell source						
PB	169 (66.0)	56 (71.8)	22 (55.0)	78 (63.9)	13 (81.3)	
BM	87 (34.0)	22 (28.2)	18 (45.0)	44 (36.1)	3 (18.7)	.20
Donor source						
MRD	133 (52.0)	54 (69.2)	19 (47.5)	52 (42.6)	8 (50.0)	
MUD	123 (48.0)	24 (30.8)	21 (52.5)	70 (57.4)	8 (50.0)	.003
Conditioning regimen						
MAC	162 (63.3)	55 (70.5)	24 (60.0)	72 (59.0)	11 (68.8)	
RIC	94 (36.7)	23 (29.5)	16 (40.0)	50 (41.0)	5 (31.2)	.40
Time to HSCT from diagnosis, months						
Median, IQR	8 (5.2-15.3)	5.5 (3.4-12.5)	6.9 (5.5-12.3)	9.0 (6.0-16.8)	12.7 (6.8-32.9)	.0001
Transplantation yr						
Before 2005	62 (24.2)	36 (46.1)	26 (65.0)	0	0	
After 2005	194 (75.8)	42 (53.9)	14 (35.0)	122 (100)	16 (100)	<.001
Median follow-up of survivors, months						
Median, IQR	33.9 (17-63.4)	38.4 (18.1-73.4)	88.3 (51.6-125.1)	26.6 (15.5-45)	25.9 (16.6-58.5)	.01

HSCT indicates hematopoietic stem cell transplantation; WHO, World Health Organization; HMA, hypomethylating agents; IQR, interquartile range; CMML, chronic myelomonocytic leukemia, MDS-U, myelodysplastic syndrome unclassifiable; t-MDS, therapy-related MDS; MK, monosomal karyotype; IPSS-R; International Prognostic Scoring System-Revised; IWG, International Working Group; PB, peripheral blood; BM, bone marrow; MRD, matched related donor; MUD, matched unrelated donor; MAC, myeloablative conditioning; RIC, reduced intensity conditioning.
Data presented are n (%) unless otherwise indicated.
* Only patients who received MDS therapy before HSCT were included.
† Only patients with abnormal cytogenetics and who had cytogenetic evaluation at HSCT were included.