Biol Blood Marrow Transplant 26 (2020) 1021–1024

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Impact of Treatment Prior to Allogeneic Transplantation of Hematopoietic Stem Cells in Patients with Myelodysplastic Syndrome: Results of the Latin American Bone Marrow Transplant Registry

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Article history:
Received 14 September 2019
Accepted 21 January 2020

Key Words:
Myelodysplastic syndromes
Allogeneic hematopoietic stem cell transplantation
Treatment pre-HSCT
Overall survival

A B S T R A C T

It has been suggested that bridging therapy with intensive chemotherapy and/or hypomethylating agents followed by hematopoietic stem cell transplantation (HSCT) can be valuable in the treatment of patients with myelodysplastic syndromes (MDS). However, the influence of this approach on HSCT outcomes remains poorly defined. Therefore, our objective was to investigate the influence of treatment before HSCT in patients with MDS. We retrospectively analyzed data from the Latin American registry of 258 patients from 17 Latin American centers who underwent HSCT from 1988 to 2019. Our data showed that there was pre-HSCT. We detected no significant difference regarding the impact on overall survival of treated and untreated patients before HSCT. Despite these data, the type of previous treatment among treated patients showed a significant difference in overall survival. Treatment with hypomethylating agents together with pre-HSCT chemotherapy seems to result in better survival of the studied population. These data correspond to the first results obtained through cooperative work between various centers in Latin America comparing

Financial disclosure: See Acknowledgments on page 1024.
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https://doi.org/10.1016/j.bbmt.2020.01.030

the different approaches to patients and reflecting their reality and challenges. Therefore, the selection of pretransplant bridge therapy should be analyzed and focus given primarily to those approaches that result in better survival of patients with MDS.

The role of bridging therapy with intensive chemotherapy and/or hypomethylating agents followed by hematopoietic stem cell transplantation (HSCT) has been suggested, but there is some controversy regarding the influence of treatment response on transplant outcomes [1]. Considering this context, here we have investigated the influence of treatment prior to HSCT in patients with MDS.

MATERIALS AND METHODS

This is a multicenter retrospective study carried out in Brazil and Uruguay that assessed 258 adult and pediatric patients enrolled in the Latin American bone marrow transplant registry from 1988 to 2019. Data were collected from the database available at http://tmo.med.br/ (supplemental material). All eligible patients diagnosed with myelodysplastic syndromes (MDS) who underwent HSCT were included in the manuscript, while patients with MDS who did not undergo HSCT were excluded.

Overall survival was defined as the time between the date of initiation of pre-HSCT treatment and death or last follow-up. We aimed to compare outcomes of patients who were and were not treated before HSCT. In addition, patients were grouped by type of treatment (hypomethylating agents, chemotherapy, and both therapies) in the previously treated group. Patients were stratified according to the Revised International Prognostic Scoring System (IPSS-R). Conditioning regimen, graft-versus-host disease prophylaxis, and supportive treatment were performed according to the protocol of each institution. Patients were grouped per year of treatment (1989 to 1993, 1994 to 1998, 1999 to 2003, 2004 to 2008, 2009 to 2013, and 2014 to 2019).

Kaplan-Meier estimate was used for survival analyses. The log-rank test was used to compare the curves. The Student *t* test was used to evaluate categorical variables and the Mann-Whitney test for continuous variables. In the multivariate analysis, binary logistic regression was performed comparing the death outcome of the group that was pretreated versus the untreated group. The Cox risk coefficient was used to determine significance in multivariate analysis. A P value $<.05$ was considered statistically significant. Statistical tests were performed using the software SPSS (v.24; SPSS, Inc., Chicago, IL) and GraphPad Prism (v 5.0; GraphPad Software, La Jolla, CA).

RESULTS

Median age was 52 years (range, 2 to 79 years). In total, 162 (63%) were treated pre-HSCT, while 96 (37%) were not. Risk stratification according to IPSS-R is described in Table 1. Amongst treated patients, 63.6% received chemotherapy, 29.6% had hypomethylating drugs, and 6.8% received both therapies. Intravenous chemotherapy was more prevalent (88%), followed by oral chemotherapy (17%). Risk stratification according to the IPSS-R in the pre-HSCT therapy group is depicted in Figure 1.

Pre-HSCT chemotherapy consisted of acute myeloid leukemia induction with daunorubicin 45 mg/m^2 for 3 days and cytarabine 200 mg/m^2 for 7 days (n = 103). Six patients had 5q deletion and were treated with lenalidomide. Azacitidine was the most commonly used hypomethylating agent (88%), followed by decitabine (12%). In the group where both therapies were used before HSCT (11/162; 6.8%), 9 had a normal karyotype (82%), 1 patient had chromosome 8 trisomy (9%), and 1 had complex karyotype (9%).

The most commonly used myeloablative conditioning regimens (n = 203, 78.7%) were busulfan/fludarabine (n = 88, 43.34%), busulfan/cyclophosphamide (n = 70, 34.5%) and total body irradiation-based regimens (n = 18, 8.9%). The most commonly used reduced-intensity/nonmyeloablative regimens (n = 55, 21.3%) were busulfan/fludarabine (n = 25, 45.5%), fludarabine/melphalan (n = 25, 45.5%), and total body irradiation-based regimens (n = 4, 7.2%).

Table 1 describes patient and treatment characteristics. When comparing pre-HSCT treated and untreated patients, there was no statistical difference in overall survival (72.03% versus 62.49%; $P < .5228$) (Figure 1A). Multivariate analysis also showed survival to be independent of pre-HSCT treatment (hazard ratio, 0.72; 95% confidence interval [CI], 0.44 to 1.20; $P = .214$).

Evaluation of survival as a function of the type of previous treatment was limited to the time period from 2009 to 2019, since 2009 was the first year in which the combination was reported. There was an association between pre-HSCT combination treatment and a higher survival rate (83% [95% CI, 75.76% to 90.91%] versus 68% [95% CI, 61.70% to 68.09%] and 69% [95% CI, 62.88% to 70.62%]; $P< .001$) for those who received hypomethylating agents or chemotherapy alone, respectively. Median survivals for the 3 subgroups were 51, 34 and 45.7 months, respectively.

DISCUSSION

Our results are in line with the findings of Schroeder et al. [2]. Their retrospective single-center study included 165 patients with MDS with excess blasts (n = 126, 76%) and secondary acute myeloid leukemia (n = 39, 24%), of whom 67 patients (41%) underwent direct transplantation and 98 (49%) received pre-HSCT cytoreductive treatment (induction chemotherapy, n = 64; hypomethylating agent, n = 34). They reported that the induction chemotherapy group showed a higher complete remission rate (59% versus 18%, $P < .0001$) but no difference in survival rates. Use of pre-HSCT treatment showed no effect on overall survival, relapse-free survival, cumulative incidence of recurrence, and non-HSCT-related mortality.

Interestingly, our subgroup analysis showed improved survival with the pre-HSCT combination of chemotherapy and hypomethylating agents. Other studies have suggested a beneficial effect of cytotoxic chemotherapy [3,4], whereas others suggested no difference [5]. However, few studies have compared the various types of cytoreduction before HSCT. Gerds et al. [6] concluded that hypomethylating agents administered before HSCT yielded similar results to those with more intensive induction chemotherapy. A study by Damaj et al. [7] drew similar conclusions.

Our study is limited by the inability to obtain cytogenetics consistently, therefore preventing the use of the IPSS-R system to further stratify our patients [8].

The data presented here are the result of the cooperative work among several centers in Latin America. It reflects different approaches and challenges. The fundamental statistical limitation is that subjects who received chemotherapy and/or hypomethylating therapy and did not progress to transplantation (because of morbidity or mortality) are not included in this analysis. However, our outcomes are similar to those reported in the international literature and also indicate that the use of pre-HSCT therapy remains controversial, and a definitive answer awaits prospective study results.

Table 1
Characteristics of the Assessed Patients

	Treatment Pre-HSCT														
	1989-2019 (n = 258) (100%)		1989-1993 (n = 7) (2.7%)		1994-1998 (n = 17) (6.6%)		1998-2003 (n = 21) (8.2%)		2004-2008 (n = 31) (12%)		2009-2013 (n = 69) (26.7%)		2014-2019 (n = 113) (43.8%)		Total
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	
	162 (63)	96 (37)	6 (85.7)	1 (14.3)	12 (70.6)	5 (29.4)	7 (33.3)	14 (66.7)	17 (54.8)	14 (45.2)	47 (68.2)	22 (31.8)	73 (64.6)	40 (35.4)	258 (100)
Sex															
Female	70 (43.2)	43 (44.8)	3 (50)	1 (100)	2 (16.6)	1 (20)	3 (42.8)	8 (57.2)	7 (41.2)	6 (42.8)	23 (49)	9 (41)	32 (43.8)	18 (45)	113 (43.8)
Male	92 (56.8)	53 (55.2)	3 (50)	0 (0)	10 (88.4)	4 (80)	4 (57.2)	6 (42.8)	10 (58.8)	8 (57.2)	24 (51)	13 (59)	41 (56.2)	22 (55)	145 (56.2)
Age, yr															
Median	54	49	56.6	58	57.3	60	42	49.8	45.3	50.3	49	49	47.3	38.3	52
Interval	(2-79)	(2-70)	(54-63)	—	(40-73)	(44-67)	(10-55)	(36-62)	(16-70)	(21-69)	(11-74)	(17-68)	(9-79)	(2-70)	(2-79)
Type of donor															
Related	106 (65.4)	80 (83.3)	6 (100)	1 (100)	11 (91.6)	5 (100)	6 (85.7)	13 (92.8)	9 (53)	11 (79.6)	32 (68)	21 (95.5)	42 (57.5)	29 (72.5)	186 (72)
Unrelated	42 (26)	13 (13.5)	0 (0)	0 (0)	1 (8.4)	0 (0)	1 (14.3)	1 (7.2)	8 (47)	3 (21.4)	13 (27.8)	1 (4.5)	19 (26)	8 (20)	55 (21.4)
Haploidentical	14 (8.6)	3 (3.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4.2)	0 (0)	12 (16.5)	3 (7.5)	17 (6.6)
Type of cell source															
Peripheral blood	75 (46.3)	42 (43.7)	0 (0)	0 (0)	2 (16.6)	4 (80)	3 (42.8)	1 (7.2)	7 (41.2)	7 (50)	23 (49)	12 (54.5)	40 (54.8)	1 (45)	117 (45.3)
Bone marrow	83 (51.2)	53 (55.2)	6 (100)	1 (100)	10 (83.4)	1 (20)	4 (57.2)	13 (92.8)	8 (47)	6 (42.8)	22 (46.8)	10 (45.5)	33 (45.20	22 (55)	136 (52.7)
Cord blood	4 (2.5)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (11.8)	1 (7.2)	2 (4.2)	0 (0)	0 (0)	0 (0)	5 (2)
IPSS-R															
Very high risk	11 (6.8)	1 (1.04)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (11.8)	0 (0)	3 (63.8)	1 (4.5)	6 (8.3)	0 (0)	12 (4.6)
High risk	37 (22.8)	19 (19.8)	5 (83.4)	1 (100)	4 (33.4)	1 (20)	3 (42.8)	3 (21.4)	2 (11.8)	2 (14.3)	6 (12.8)	5 (22.7)	16 (22)	7 (17.5)	56 (21.7)
Intermediate	37 (22.8)	25 (26.04)	0 (0)	0 (0)	3 (25)	0 (0)	0 (0)	5 (35.7)	4 (23.6)	2 (14.3)	8 (17)	5 (22.7)	22 (30)	13 (32.5)	62 (24)
Low risk	17 (10.5)	12 (12.5)	1 (16.6)	0 (0)	3 (25)	0 (0)	0 (0)	5 (35.7)	3 (17.6)	0 (0)	6 (12.7)	2 (9)	4 (5.5)	5 (12.5)	29 (11.2)
Very low risk	2 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (21.3)	0 (0)	1 (1.4)	0 (0)	2 (0.77)
No record	58 (35.8)	39 (40.62)	0 (0)	0 (0)	2 (16.6)	4 (80)	4 (57.2)	1 (7.2)	6 (35.2)	10 (71.4)	22 (46.8)	9 (41)	24 (32.8)	15 (37.5)	97 (37.6)
Type of conditioning															
Myeloablative	120 (74)	83 (86.5)	6 (100)	1 (100)	12 (100)	5 (100)	7 (100)	13 (92.8)	14 (82.4)	13 (92.8)	39 (83)	18 (81.8)	42 (57.6)	33 (82.5)	203 (78.7)
Reduced intensity/ nonmyeloablative	42 (26)	13 (13.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.2)	3 (17.6)	1 (7.2)	8 (17)	4 (18)	31 (42.4)	7 (17.5)	55 (21.3)
Pre-HSCT treatment type															
Chemotherapy	103 (63.6)	—	6 (100)	—	12 (100)	—	6 (85.7)	—	17 (100)	—	33 (70.2)	—	29 (39.7)	—	103 (39.9)
Hypomethylating	48 (29.6)	—	0 (0)	—	0 (0)	—	1 (14.3)	—	0 (0)	—	10 (21.3)	—	37 (50.7)	—	48 (18.6)
Chemotherapy and hypomethylating	11 (6.8)	—	0 (0)	—	0 (0)	—	0 (0)	—	0 (0)	—	4 (8.5)	—	7 (9.6)	—	11 (4.2)

Values are number (%) unless otherwise defined.

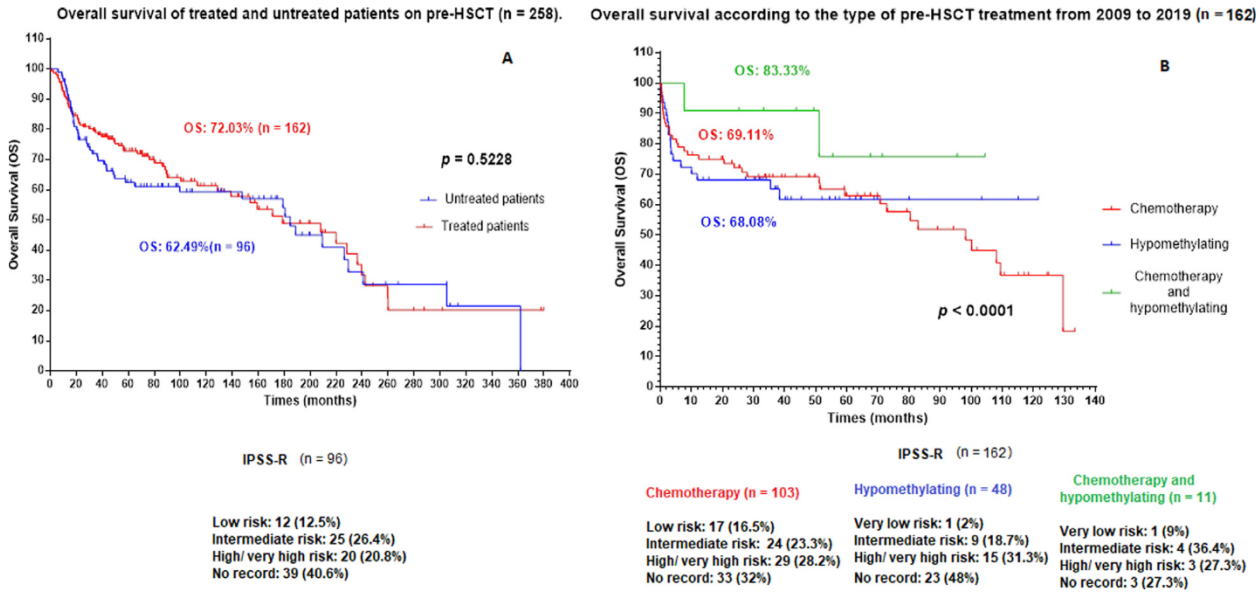

Figure 1. (A) Overall survival of treated (n = 162) and untreated (n = 96) pre-HSCT patients. (B) Overall patient survival according to pre-HSCT treatment. OS, overall survival. Absolute number of patients (n). Kaplan-Meier estimate was used for survival analyses. The log-rank test was used to compare the curves. The Student *t* test was used to evaluate categorical variables and the Mann-Whitney test for continuous variables. In the multivariate analysis, binary logistic regression was performed comparing the death outcome of the group that was pretreated versus the untreated group. The Cox risk coefficient was used to determine significance in multivariate analysis. A *P* value <.05 was considered statistically significant. Statistical tests were performed using the software SPSS (v. 24) and GraphPad Prism (v. 5.0).

ACKNOWLEDGMENTS

The authors thank all the centers that contributed data to the Latin American registry.

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2020.01.030.

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