Artigo / Article

Allogeneic hematopoietic stem cell transplantation for primary myelodysplastic syndrome

Transplante alogênico de células progenitoras hematopoiéticas para síndrome mielodisplásica primária

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*Characteristics and outcomes of 52 patients with myelodysplastic syndrome (MDS) who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) were analyzed. Median age was 30 years (range 2-61 years) and median time from diagnosis to allo-HSCT was 10 months (range 1-161 months). Thirty-six patients had advanced MDS or acute myeloid leukemia following MDS at transplant. Conditioning with busulfan and cyclophosphamide was administered to 73% of patients, and the median value of graft dose was 2.595 x 10^8 of total nucleated cells/kg. Overall survival and disease free survival at 4 years were 36% and 33%, respectively. Nineteen patients were alive, with a median follow-up of 3.8 years. Twelve patients relapsed and only one is alive, after donor lymphocyte infusion. Interval < 6 months between diagnosis and allo-HSCT decreased relapse (*P = *0.01). Mortality and relapse were significantly lower among patients with less advanced disease (*P = *0.03). Decreased mortality was also observed when transplant occurred after 1994, probably because more patients with less advanced disease received the procedure. Acute GVHD grades ≥ II occurred in 19 patients. Donor type (identical related versus non-related/partially matched related) influenced the incidence of acute GVHD (*P = *0.03). Eleven patients developed chronic GVHD and previous acute GVHD was a risk factor (*P = *0.03). Thirty-three patients died, 22 (67%) secondary to transplant-related complications. Patients with MDS should undergo allo-HSCT earlier, mainly if they have a compatible donor and are young. Rev. bras. hematol. hemoter. 2004;**26**(2):71-77.*

Key words: *Myelodysplastic syndrome, allogeneic hematopoietic stem cell transplantation, acute myeloid leukemia.*

Introduction

The main characteristic of myelodysplastic syndrome (MDS) is the development of peripheral blood cytopenias, with bone marrow usually hyper or normocellular, reflecting impaired maturation of hematopoietic cells. Another typical feature of MDS is dysplasia of at least one bone marrow cell lineage (erythroid, myeloid, or megakaryocytic) such as ringed sideroblasts, neutrophils with hypogranulation, pseudo-

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Pelger anomaly, hypo- or hypersegmented nuclei, and micromegakaryocytes. MDS has a tendency to progress into acute myeloid leukemia (AML) in approximately 20% of cases.[1-5]

In clinical aspects, MDS is a heterogeneous group with different forms of presentation and progression. The French, American and British (FAB) group has provided a classification with prognostic utility,[6] as has the European Association of Hematopathologists and the Society for Hematopathology, which developed the World Health Organization (WHO) classification.[7]

Besides hematopoietic stem cell transplantation (HSCT), the current treatments of MDS include supportive care (transfusional support and antimicrobial therapy), chemotherapy, immunosuppressive therapy, differentiating and cytoprotective agents, recombinant growth factors and inhibitors of angiogenesis.[8] Although chemotherapy provides long-term survival in a few patients, the unique curative treatment for MDS is allogeneic HSCT (allo-HSCT).[3]

In this study, we retrospectively evaluated the results of allo-HSCT in MDS patients, analyzing the possible factors associated with the outcome. This is the first Brazilian report about this issue.

Patients and Methods

Patients

From April 1988 to March 2001, fifty-two patients with primary MDS underwent T-cell repleted allo-HSCT and were included in this analysis. No patient had been treated with chemo- or radiation therapy prior to the procedure, and the main characteristics of patients, disease and allo-HSCT are shown in Table 1.

Methods

Patients were isolated in single or double bed rooms with highly efficiency particulate air (HEPA). When ABO incompatibility was present, red blood cells or plasma were removed by starch sedimentation. Conditioning regimes were Busulfan (Bu) (16 mg/kg for adults or 640 mg/m^2 for children less than 20 kg via oral) plus Cyclophosphamide (Cy) (120 mg/kg intravenously); Bu, Cy plus Melphalan (140 mg/m^2 intravenously); Bu, Cy plus Etoposide (60 mg/kg intravenously) and Cy plus Total Body Irradiation (1200 to 1440 rads) (see Table 1). Prophylaxis for herpes virus and *Pneumocystis carinii* were Acyclovir and Trimetropim-sulfamethoxazole, respectively, along with Ketokonazol or Fluconazol for fungus. Graft-versus-host disease (GVHD) prophylaxis was with Cyclosporine A (CsA) and Methotrexate (MTX) according to the Seattle protocol,[9] or CsA, MTX and Methylprednisolone.[10] Myeloid engraftment was assessed with an absolute neutrophil count (ANC) > 0.5 x 10^9/L for three consecutive days, and platelet engraftment with platelet count > 20 x 10^9/L without transfusion for seven consecutive days. Patients were assessed for engraftment if they survived at least 28 days; those surviving more than 15 days and 100 days post allo-HSCT with engraftment were considered at risk for acute and chronic GVHD, respectively. Published criteria defined and graded acute[11] and chronic[12] GVHD, hepatic veno-occlusive disease (VOD)[13] and mucositis.[14] Transplant related mortality (TRM) was outlined as all causes of non-relapse deaths. As stated by the FAB classification, we considered refractory anemia (RA) and RA with ringed sideroblasts (RARS) as less advanced MDS; RA with excess blasts (RAEB), RA with excess blasts in transformation (RAEB-T), chronic myelomonocytic leukemia (CMML) and AML following MDS were considered advanced MDS. Chromosomal analysis characterized three risk groups of patients: low risk when normal, -Y alone, del (5q) alone, and del (20q) alone; high risk when ≥ 3 abnormalities or anomalies of chromosome 7; and intermediate risk for others abnormalities.[15]

Statistical methods

The last follow-up date was June 30th 2001. The overall and disease free survival (OS and DFS) curves after transplantation (starting point) were calculated by the Kaplan-Meier method. The impact of age at allo-HSCT, time from diagnosis to allo-HSCT, disease presentation, chromosomal analysis, year of transplant, donor compatibility, conditioning regimen and total nucleated cells infused (TNC) on clinical outcome, as well as OS and DFS were tested by univariate analysis. The Mann-Whitney test was used to compare median differences and χ^2 test for the categorical variables. The Kruskal-Wallis test compared three unpaired groups. A *P* value of < 0.05 was considered significant. Cut-off of number of TNC was calculated based on median value. The multivariate analysis test used was the MANOVA test, and a *P* value of < 0.1 was considered significant.

Results

From 52 patients, 12 (23%) had RA, 3 (5.7%) RARS, 4 (7.6%) CMML, 7 (13.4%) RAEB, 6 (11.5%) RAEB-T, 19 (36.5%) AML and one (1.9%) a non-classifiable disease. Chromosomal analysis was assessable in 39 patients, and 27 (69%) had abnormalities.

Survival

As of July 2001, nineteen patients were alive. Kaplan-Meier OS and DFS were 36% and 33% at 4 years (Figure 1), with a median follow-up of 3.8 years or 1410 days (range 12-4832 days). Less advanced disease patients had an advantage in OS and DFS (both 60%) when compared to

Table 1
Demographic and clinical characteristics of patients

Nº of patients	**52**
Median follow-up, days (range)	1410 (12-4832)
Patients	
Age (years) at allo-HSCT, median (range)	30 (2-61)
Gender, male/female	28/24
Months from diagnosis to allo-HSCT, median (range)	10 (1-161)
Disease morphology	
Less advanced MDS	15 (28.8%)
Advanced MDS or AML	36 (69.2%)
Unclassifiable	1 (1.9%)
Karyotype risk (IPSS)	
Low	13 (25%)
Intermediate	19 (36.5%)
High	7 (13.5%)
Not accessible	13 (25%)
Conditioning	
Bu/Cy	38 (73%)
Bu/Cy/VP16	7 (13.4%)
Bu/Cy/Mel	2 (3.8%)
Cy/TBI	5 (9.6%)
Hematopoietic value of the graft	
TNC x 10^8/kg, median (range)	2.595 (0.47-15.35)
Stem cell source (related/unrelated)	
Bone marrow	48 (43/5)
Cord blood	3 (2/1)
Peripheral blood	1 (1/0)
Donor	
HLA-identical sibling	43 (82.6%)
Partially matched family member	3 (5.7%)
Unrelated donor	6 (11.5%)
GVHD prophylaxis	
CsA + MTX	30 (57.9%)
CsA + MTX + CTC	10 (19.2%)
CsA + CTC	7 (13.4%)
CsA	5 (9.6%)

Allo-HSCT, allogeneic hematopoietic stem cell transplantation; Bu; busulfan; CsA, cyclosporine; Cy, cyclophosphamide; CTC, corticosteroid; Mel, melphalan; MTX, methotrexate; TBI, total body irradiation; TNC, total nucleated cells; VP16, etoposide.

Table 2
Acute GVHD according to donor, conditioning and prophylaxis

	Acute GVHD grades > II (%)	*P*
Donor		
HLA-identical sibling16 (37.2)0.03		
Non-related or partially matched family member	6 (66.6)	
Conditioning		
Bu/Cy	17 (44.7)	0.55
Others	5 (35.7)	
GVHD prophylaxis		
CsA + MTX	13 (43.3)	0.73
CsA + MTX + CTC	3 (30)	
CsA + CTC	4 (57.1)	
CsA	2 (40)	

patients with advanced disease (27% and 23%, respectively) (Figures 2 and 3).

Engraftment

Forty-five patients were assessable for engraftment analysis; forty-three patients fulfilled the criteria for myeloid (range 11-36 days, median 23 days) and 41 patients for platelet engraftment (range 14-83 days, median 25 days). TNC (< 2.56 or > 2.56 x 10^8/kg) had no influence on engraftment time.

Transplant-related toxicity

Mucositis grades ≥ II was the most frequent toxicity, present in 45 patients (86.5%); in 21 cases (40.3%) it was grade IV. We did not detect factors influencing incidence and severity of mucositis.

Nineteen of 44 assessable patients (43%) developed acute GVHD grade ≥ II, and 8 (18%) had grade III or IV. Donor compatibility (HLA-identical sibling *vs.* non-related or partially matched family members) influenced the incidence of acute GVHD ($P = 0.03$) (Table 2). Chronic GVHD occurred in 11 of 37 assessable patients (30%). Extensive mild to severe disease developed in 9 patients and limited disease was documented in 2 patients. In univariate analysis, previous acute GVHD was a risk factor for development of chronic GVHD ($P = 0.03$). Older patients had a higher incidence of chronic GVHD (18%, 30% and 50% for patients < 21, 21-39 and > 39 years, respectively) although it was not significant ($P = 0.39$).

Causes of death, transplantation-related mortality (TRM) and relapses

Thirty-three patients died, fourteen up to day +100 post allo-HSCT, with twenty-two patients from TRM, with infection being responsible for ~25% of these deaths. Twelve patients relapsed between 122 and 1.760 days post allo-HSCT (median 183 days) (see Table 4). Six relapsed patients received donor lymphocyte infusion and one is alive, seven years after allo-HSCT and 3.5 years after relapse. Mortality was lower among patients with less advanced disease (Figure 2) and transplanted after 1994, when compared to patients with advanced disease ($P = 0.03$)

or transplanted before 1994 (P = 0.04), respectively. Patients with less than six months from diagnosis to allo-HSCT and less advanced disease also had lower relapse rate when compared to other patients in their groups (P = 0.01 and P = 0.03) (Figure 3). Multivariate statistical analysis confirmed the results. Among patients with non-related or partially matched family members, there is a trend also suggesting lower relapse rate, when compared to HLA-compatible donor (P = 0.07). Details are in Table 3.

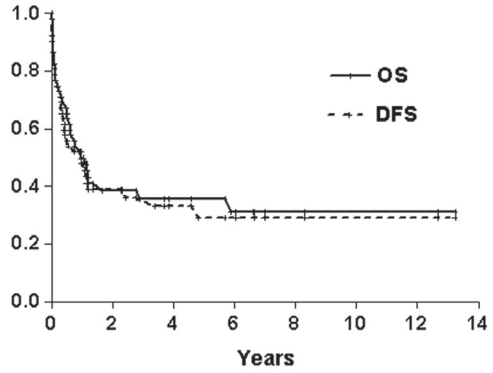

***Fig. 1** – Kaplan Meier estimates of OS and DFS*

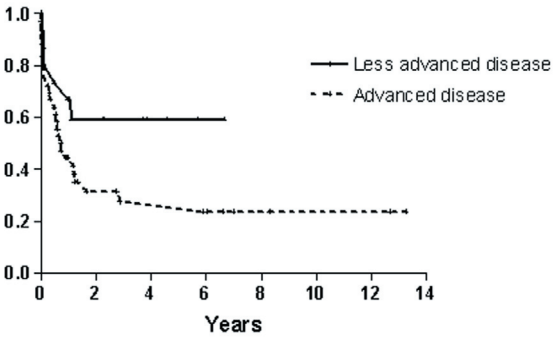

***Fig. 2** – Kaplan-Meier estimates of OS among patients with advanced and less advanced disease*

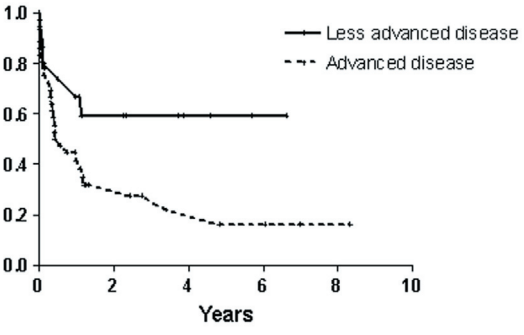

***Fig. 3** – Kaplan-Meier estimates of DFS among patients with advanced and less advanced disease*

Discussion

On average MDS is diagnosed in the seventh decade of life. Elderly patients maintained with hemoglobin level > 9.5 g/dL, neutrophil count > $0.5x10^9$/L and platelets count > $20x10^9$/L may have a good quality of life, just with regular follow-ups, as reported by Germing et al after a retrospective analysis of 1.600 patients.[16] However, as patients with MDS have their normal hematopoietic stem cell pool declining with time, those with long-lasting disease probably have no more normal residual stem cells left. So, younger patients needed another therapeutic approach, and allo-HSCT is the potentially curative option. Our results showed OS and DFS of 36% and 33% at four years, similar to recent reports in literature where OS and DFS varied from 26 to 47% and from 23% to 36%, respectively.[3,4,8,17-19] This inferior outcome of MDS patients is largely due to high post-transplant relapse and unexpected high TRM. Our patients transplanted with less advanced disease had lower relapse rate and consequently better survival, especially when the procedure occurred in the first six months of diagnosis. Anderson[3] and Deeg et al[4] also reported less advanced disease as an factor associated with better survival, while patients transplanted with advanced disease had inferior outcome and higher relapse rates.[17]

TRM has remained unexpectedly high among MDS patients, and in most trials it is around 40%.1[7,18] This particularly high rate mortality in MDS patients, when compared to patients with other malignant diseases, has been associated to complications like previous bacterial and fungal colonization and infection, and iron overload and sensitization as a result of transfusion of blood products. Oral mucositis, present in 86% of our patients, is the most obvious manifestation of damage elsewhere, particularly in the gut. The gut injury that develops after HSCT has been linked to acute GVHD, VOD, systemic infections and increased systemic levels of lipopolysaccharides and TNF-α, both probably correlated with idiopathic pneumonia syndrome.[20,21] Copelan et al[19] reported 100% of oral toxicity among their patients, and TRM was 36%. We lost 22 of our 52 patients (42%) from TRM, fourteen before day +100. However, less advanced disease favorably influenced survival in our group, a fact reported by others.[3,4] Our analysis also showed decrease in the mortality rate among patients transplanted after 1994, maybe secondary to a specific factor: indication of transplant to more patients with less advanced disease. We also observed that more intensive conditioning

regimens are probably inefficient, not improving survival (Table 3). GVHD is another important cause of morbidity and mortality following allo-HSCT, and acute GVHD is the most important risk factor for development of chronic GVHD.[22] Acute GVHD ≥ grade II and chronic GVHD were diagnosed in 43% and 30% of our patients, respectively, similar to others reports.[3,18] When the donor was other than an HLA identical sibling, a higher rate of acute GVHD

Table 3
Univariate analysis of patients, disease and allo-HSCT characteristics.

Characteristic	Deaths n (%)	P	Relapse n (%)	P	DFS Median (range)	P	OS Median (range)	P
All patients (n=52)	33 (63.4)		12 (23)		353 (12-4832)		353 (12-4832)	
Age at allo-HSCT								
<21 years (n=16)	11 (68.7)	**.25**	4 (25)	**.59**	284 (19-4621)	**.45**	390 (19-4621)	**.4**
21-39 years (n=28)	19 (67.8)		5 (17.8)		314 (12-4832)		314 (12-4832)	
>39 years (n=8)	3 (37.5)		3 (37.5)		457 (20-1674)		457 (20-2416)	
Months from diagnosis to allo-HSCT								
< 6 (n=14)	8 (57.1)	**.39**	1 (7.1)	**.01**	242 (12-2210)	**.58**	308 (12-2210)	**.56**
6 - 12 (n=17)	13 (76.4)		8 (47)		161 (17-4832)		226 (17-4832)	
> 12 (n=21)	12 (57.1)		3 (14.2)		418 (17-4621)		423 (17-4621)	
Disease morphology*								
Less advanced (n= 15)	6 (40)	**.03**	0	**.03**	423 (19-2423)	**.17**	423 (19-2423)	**.3**
Advanced (n= 36)	26 (72.2)		12 (33.3)		188 (12-4832)		278 (12-4832)	
Karyotype risk								
Low (n= 13)	10 (76.9)	**.51**	4 (30.7)	**.13**	158 (12-1009)	**.35**	217 (12-1009)	**.39**
Intermediate (n= 19)	11 (57.8)		1 (5.2)		359 (17-2324)		359 (17-2324)	
High (n= 7)	5 (71.4)		2 (28.5)		445 (20-4621)		445 (20-4621)	
Transplant year								
1988-1993 (n= 17)	14 (82.3)	**.04**	5 (29.4)	**.44**	150 (12-4832)	**.21**	192 (12-4832)	**.2**
1994-2001 (n= 35)	19 (54.2)		7 (20)		386 (17-2553)		423 (17-2553)	
Donor								
HLA-identical sibling (n=43)	28 (65.1)	**.58**	12 (27.9)	**.07**	359 (12-4832)	**.79**	359 (12-4832)	**.6**
Non-related or partially matched family member (n=9)	5 (55.5)		0		189 (17-1674)		189 (17-1674)	
Conditioning								
Bu/Cy (n=38)	22 (57.8)	**.16**	9 (23.6)	**.86**	362 (12-4832)	**.19**	373 (12-4832)	**.16**
Others** (n=14)	11 (78.5)		3 (21.4)		142 (17-1674)		204 (17-1674)	
TNC (x108/kg)								
< 2.595 (n=26)	17 (65.3)	**.77**	5 (19.2)	**.51**	221 (12-3039)	**.36**	278 (12-3039)	**.39**
> 2.595 (n=26)	16 (61.5)		7 (26.9)		359 (17-4832)		359 (17-4832)	

**One patient with unclassifiable disease.*
***Others: Bu/Cy/Mel = 2; Bu/Cy/VP16 = 7; Cy/TBI = 5.*

Table 4
Causes of deaths

	Nº cases
Relapse of MDS/AML	11
TRM causes	22
Infection	8
Bacteria	3
Aspergillus	2
Virus	1
Indeterminate	2
Acute GVHD	5
Chronic GVHD	3
Hepatic VOD	2
Hemorrhage	2
Primary graft failure	1
Multiorgan failure	1
Total	**33**

was noticed, as previously described,[3] with no influence in survival or relapse. In our univariate analysis, acute GVHD was an important risk factor for development of chronic GVHD.

We believe that allo-HSCT is the treatment of choice for MDS patients with an HLA-compatible donor and younger age, preferentially when performed in the first 6 months after diagnosis. If a full-match related donor is unavailable, procurement of a mismatch related or an unrelated donor is mandatory. When established that the patient is able to receive the allo-HSCT, reduction of TRM must be the major goal. The use of peripheral blood stem cells (G-PBSC) or bone marrow cells (G-BM) harvested after stimulation with growth factors may diminish the risk of bacterial and fungal infection. Recent reports showed that recovery of granulocytes and platelets occur around 16 and 14 days post allo-HSCT, respectively, utilizing G-PBSC or G-BM.[23] Also, the use of cytoprotective agents like amifostine concomitantly with conditioning regimen should be tested in a trial, in an endeavor to decrease mucosal injury and its complications, including the activation of the mucosal-lung axis.[24] Another goal is reduction of relapse. Early detection of increasing mixed chimerism (autologous marrow repopulation) post-transplant through molecular methods is a clear evidence of relapse. Withdrawal of immunosuppression (if still in use) followed by donor infusion lymphocytes as adoptive immunotherapy are capable of reestablishing complete chimerism and maintenance of continuous complete remission, mainly because MDS is a category of malignancy with intermediate sensitivity to GVL effects.[25]

Tailoring the treatment to MDS patients, in an attempt to define the optimal timing to transplant and to reduce TRM and relapse, undoubtedly will improve the results of the procedure.

Resumo

*Características e resultados de 52 pacientes com síndrome mielodisplásica (MDS) submetidos a transplante alogênico de células progenitoras hematopoiéticas (TCPH) foram analisados. A idade mediana foi de 30 anos (variação de 2-61 anos) e o tempo mediano entre o diagnóstico e transplante foi de dez meses (variação de 1-161 meses). Trinta e seis pacientes tinham MDS avançada ou leucemia mielóide aguda secundária a MDS ao transplante. O condicionamento com busulfano e ciclofosfamida foi recebido por 73% dos pacientes, e a dose celular mediana do enxerto foi de 2.56 x 10^8 células nucleadas/kg. A sobrevida global e a sobrevida livre de doença aos quatro anos foi de 36% e 33%, respectivamente. Dezenove pacientes estavam vivos, com um seguimento mediano de 3,8 anos. Doze pacientes recaíram e apenas um deles está vivo, após infusão de linfócitos do doador. Intervalo menor que 6 meses entre o diagnóstico e o transplante reduziu a ocorrência de recaída (P = 0.01). Mortalidade e recaída foram significativamente mais baixas entre os pacientes com doença menos avançada (P = 0.03). Mortalidade mais baixa também foi observada quando o transplante ocorreu após 1994, provavelmente porque mais pacientes com doença menos avançada foram transplantados. Doença do enxerto-contra-hospedeiro (DECH) aguda graus ≥ II ocorreu em 19 pacientes, e sua incidência foi influenciada pela compatibilidade entre doador e paciente (aparentado idêntico versus não-aparentado/aparentado parcialmente compatível) (P = 0.03). Onze pacientes desenvolveram DECH crônica que teve como fator de risco DECH aguda (P = 0.03). Trinta e três pacientes morreram, sendo 22 (67%) de complicações do transplante. Estes dados sugerem que pacientes com MDS devem ser submetidos ao TCPH precocemente, principalmente se são jovens e possuem doador compatível. Rev. bras. hematol. hemoter. 2004;**26**(2):71-77.*

Palavras-chave: *Síndrome mielodisplásica; transplante alogênico de células progenitoras hematopoiéticas; leucemia mielóide aguda.*

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