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Article

Hematopoietic stem cell transplantation in children and adolescents with acute leukemia. Experience of two Brazilian institutions

Juliane Morando[1]
Marcos Augusto Mauad[2]
Sérgio Costa Fortier[1]
Flavia Zattar Piazera[1]
Mair Pedro de Souza[2]
Claudia Oliveira[2]
Clarisse Machado[2]
Ederson Matos[2]
Wellington Moraes Azevedo[2]
Lisandro Lima Ribeiro[1]
Elenaide Coutinho Nunes[1]
Marco Antonio Bitencourt[1]
Daniela Cariranha Setúbal[1]
Vaneuza Moreira Funke[1]
Michel Michels de Oliveira[1]
Larissa Alessandra Medeiros[1]
Samir Kanaan Nabhan[1]
Gisele Loth[1]
Caroline Bonamim Santos Sola[1]
Adriana Koliski[1]
Ricardo Pasquini[1]
José Zanis Neto[1]
Vergilio Antonio Rensi Colturato[2]
Carmem Maria Sales Bonfim[1]

Hematopoietic Stem Cell transplantation (HSCT) is the treatment of choice for patients with high-risk leukemia. In spite of this, relapse remains a major cause of death of these patients. Our objective was to analyze the outcomes of patients with acute leukemia submitted to hematopoietic stem cell transplantation in two Brazilian institutions. A retrospective study of 208 patients transplanted between 1990 and 2007 with a median age of 9 years (range: 1-18 years) was made. One hundred and nineteen patients had acute lymphocytic leukemia (ALL) and 89 had acute myeloid leukemia (AML). Early disease was considered for CR1 and CR2 cases and advanced disease >CR3 and refractory and relapse disease. Ninety patients are alive between 258 and 6068 days after hematopoietic stem cell transplantation (M: 1438 days). The overall survival (OS) was 45% (3 years) and event free survival (EFS) was 39% (3 years). Primary graft failure occurred in 14/195 patients (8%). There were no differences in the overall survival and event free survival between patients with acute lymphocytic leukemia and acute myeloid leukemia, between sources of cells used or between those who developed acute or chronic graft-versus-host disease (GVHD). When comparing transplants from related and unrelated donors, there was no difference in the overall survival. Patients with acute lymphocytic leukemia receiving the total body irradiation (TBI) conditioning regimen had better overall survival and event free survival ($p<0.001$). One hundred and eighteen patients died between 0 and 1654 days after hematopoietic stem cell transplantation (M:160 days). Transplantation-related-mortality (TRM) at D+100 was 16% and cumulative incidence of relapse was 40% (3 years). Patients with advanced disease had lower 3-year overall survival and event free survival ($p<0.001$). Multivariate analysis showed that disease status was the most significant factor associated with higher event free survival and overall survival. Our results show that children and adolescents transplanted with early disease can achieve considerable overall survival and also highlights the inefficacy of hematopoietic stem cell transplantation for patients with advanced disease.

Key words: *Hematopoietic stem cell transplantation; Leukemia, Myeloid, Acute/therapy; Precursos cell lymphoblastic leukemia-lymphoma; Graft vs Host Disease; Bone marrow transplantation; Humans; Child, Preschool; Child; Adolescent*

Hospital de Clínicas, Universidade Federal do Paraná (UFPR), Curitiba (PR), Brasil; Hospital Amaral Carvalho, Jaú (SP), Brasil.

[1]Bone Marrow Transplant Service, Hospital de Clínicas, Universidade Federal do Paraná (UFPR), Curitiba (PR), Brazil
[2]Bone Marrow Transplant Service, Hospital Amaral Carvalho, Jaú (SP), Brazil

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Correspondence: *Juliane Morando*
Serviço de Transplante de Medula Óssea do Hospital de Clínicas da UFPR
Rua General Carneiro, 181, 15º andar – Bairro Alto da Glória
80060-900 – Curitiba (PR), Brasil
Tel.: 55 41 3360-1000
E-mail: julimorando@terra.com.br

Introduction

Acute leukemias, accounting for approximately 30% of cancer in under 15-year-old patients, are the most frequent neoplasms in childhood.[1] Despite the high remission rate achieved in these patients, 20% to 30% relapse, usually within five years of treatment.[2] Even with the improvements in treatment regimens and supportive measures, the expected disease-free survival is still between 35% and 60%.

Hematopoietic stem cell transplantation (HSCT) remains the best therapeutic option for patients with high-risk leukemia at diagnosis and for most patients that relapse.[3] The results of different studies suggest that allogeneic HSCT can cure from 50 to 60% of recipients who would not attain such an outcome with chemotherapy alone.[4] Unfortunately, only 30% of patients referred for transplantation have a compatible related donor which means alternative donors are necessary.[5] Despite the increase in volunteer donors and cord blood banks, the probability of finding a fully compatible donor for Brazilian patients is not high and mismatched transplants are associated with a higher number of complications, in particular graft versus host disease (GvHD) and rejection.[6]

In Brazil there are few studies that show the results of transplants performed in children and adolescents with acute leukemia. As local knowledge can assist in understanding and choosing the best therapeutic options, this study aims to evaluate the results of HSCT performed in children and adolescents with acute leukemia in two large Brazilian centers.

Methods

Two hundred and eight under 19-year-old patients, who were submitted to HSCT for acute leukemia during the period April 1990 to December 2007, were included in this study. Of the total, 145 patients were transplanted in the Hospital de Clínicas, UFPR, Curitiba and 63 patients in Hospital Amaral Carvalho, Jau.

The patients' ages ranged from 1 to 18 years with a median of 9 years. Seventy-four patients were female and 137 were male. Other characteristics of the patients are shown in Table 1.

HLA compatibility was evaluated based on the characterization of the major histocompatibility complex antigens belonging to classes I and II of the A, B and DR loci. Patients and donors were considered fully compatible when they had similar antigens in all 6 loci, i.e. 6/6 compatibility.

The 26 patients transplanted using peripheral stem cells (PSC) were fully compatible (6/6). Of the 138 patients who received bone marrow (BM), 19 (13%) had a single mismatch (5/6) and the other 119 (87%) were fully compatible (6/6). Among patients who received transplants with umbilical cord blood (UCB), 15 (34%) had two mismatches (4/6), 12 (27%) had a single mismatch (5/6) and the remaining 17 patients (39%) were fully compatible (6/6).

At the time of transplantation, 20 patients had acute lymphoblastic leukemia (ALL) in first clinical remission (CR1). Of these, 12 had high-risk cytogenetics [t(9;22), t(4;11) or hypodiploid] and another two patients had poor responses to induction using corticosteroids. The remaining patients transplanted in CR1 had high-risk disease with hypercellularity at diagnosis and two had high-risk T-ALL. Fifty and 49 patients underwent a second transplantation with disease in second clinical remission (CR2) and with advanced disease (in third remission - CR3 or higher, relapse or refractory disease), respectively.

Table 1: Characteristics of the entire group of patients and ALL and AML subgroups

	Total patients (%)	ALL patients nº (%)	AML patients nº (%)	p-value
Age				
< 10 anos	111 (53)	65 (55)	46 (52)	n/s
≥ 10 anos	97 (47)	54 (45)	43 (48)	
Donor type				
Related	139 (67)	69 (58)	70 (79)	0.02
Non-related	69 (33)	50 (42)	19 (21)	
Hematopoietic stem cell source				
Bone marrow	138 (66)	74 (62)	64 (72)	n/s
Umbilical cord blood	44 (21)	29 (24)	15 (17)	
Peripheral blood	26 (13)	16 (14)	10 (11)	
Status at time of HSCT				
Early disease (CR1/CR2)	131 (62)	70 (59)	61 (68)	n/s
Advanced disease ≥ CR3/refractory or relapse disease	77 (38)	49 (41)	28 (32)	
Conditioning				
BU+CPA+ATG	77 (37)	20 (17)	57 (64)	n/s
CPA+TBI+ATG	102 (49)	87 (73)	15 (17)	
Other regimens without TBI (BU+FLU/BU+CPA+VP16)	29 (14)	11 (10)	17 (19)	
GvHD prophylaxis				
Csn ± corticoid	46 (22)	28 (24)	18 (20)	N/s
Csn + Mtx ± corticoid	162 (78)	91 (76)	71 (80)	
Year of transplant				
1990 to 1999	73 (35)	34 (29)	39 (44)	0.02
2000 to 2007	135 (65)	85 (71)	50 (56)	
Total	208 (100)	119 (100)	89 (100)	

HSCT = Hematopoietic stem cell transplantation; BU = busulfan; CPA = cyclophosphamide; ATG = antithymocyte globulin; TBI = total body irradiation; FLU = Fludarabine; VP16 = Etoposide; Csn = Cyclosporin A; Mtx = Methotrexate

Of the 89 patients with acute myeloid leukemia (AML), eight were transplanted in first relapse without receiving chemotherapy before conditioning, 37 in CR1, 24 in CR2 and 20 had advanced disease.

Patients in CR1 and CR2 were characterized as patients in early disease and patients in = CR3 and those with refractory disease or relapse were classified as having advanced disease.

During conditioning, patients received drugs commonly used during HSCT depending on the underlying disease, the type of donor, the stem cell source and the presence of HLA incompatibilities. The choice of the prophylactic regimen for chronic GvHD also took into consideration these factors.

The conditioning regimen used for most ALL patients was cyclophosphamide and total body irradiation (TBI), and for AML patients, it was busulfan and cyclophosphamide. The immunoprophylaxis schedule most often used for patients who were submitted to HSCT using bone marrow and peripheral blood was cyclosporine and methotrexate and for patients who received UCB cells, it was cyclosporine and corticosteroids (Table 1).

Neutrophil engraftment was evaluated in patients who survived for more than thirty days after transplant and who had an absolute neutrophil count exceeding 0.5 x 10^9 cells/L for three consecutive days without using growth factors. Platelet recovery was defined for patients who had counts above 50,000 x 10^9 cells/L for three consecutive days and remained for seven days without transfusions. Patients who only had neutrophil engraftment were considered as having partial response. Patients who had autologous recovery according to chimerism analysis and those who did not meet criteria for neutrophil engraftment and platelet recovery were considered as having primary graft failure.

Only patients who had partial or complete engraftment were assessed for acute GvHD, and only patients who survived for more than one hundred days with engraftment were assessed for chronic GvHD.

Acute GvHD was defined according to published clinical and laboratory criteria[7] and categorized by grade (I-IV). Chronic GvHD was classified as limited or extensive according to the classification criteria proposed by some authors.[8]

Death within the first hundred days after transplantation for any cause other than relapse was regarded as transplant-related mortality (TRM).

Relapse was evaluated by clinical symptoms associated with the detection of leukemic cells at the site of the lumbar puncture, in the cerebrospinal fluid or at biopsy.

Overall survival (OS) was calculated from the day of transplantation until death or the last contact with the patient and event-free survival (EFS) was calculated from the day of transplantation until relapse, death or the last contact.

The Kaplan-Meier method was used to analyze the OS and EFS. The log-rank test was used for univariate analysis and Cox regression for multivariate analysis, which included all variables with p-values < 0.2 in the univariate analysis. Death was used as a competitive risk factor in the analysis of the cumulative incidence of transplant success and relapse. Death due to relapse was used as a competitive risk factor in cumulative transplant-related mortality.

A level of significance of 5% (p-value < 0.05) was adopted and the SPSS computer software (Statistical Package for the Social Sciences) was used for statistical analysis.

Results

Of all the patients who participated in this study, ninety are alive with a median follow up of 1438 days (Range: 258-6068 days). The 3-year OS was 45% (Figure 1) and the EFS was 39%.

Of the 208 patients, 195 survived more than thirty days after HSCT and were evaluated for engraftment with a cumulative incidence of 88%. Eight patients (4%) only had neutrophil engraftment and 13 patients (8%) had primary graft failure.

The survival of patients with primary graft failure or just neutrophil engraftment was very bad. Only four patients are living (14%): three have autologous engraftment and one was submitted to a second transplant. The main causes of death in this group of patients were infection in ten patients, residual disease in four, acute GvHD in three and hemorrhage in two.

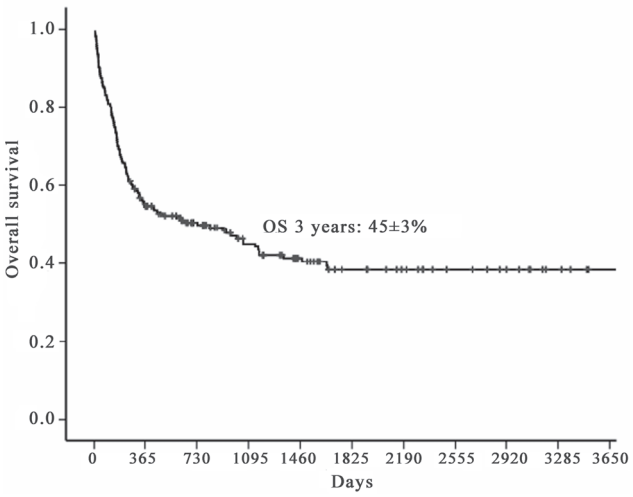

Figure 1. Overall survival of the entire group of patients

The main complications after HSCT are summarized in Table 2.

The cumulative incidence of TRM was 16% at one hundred days (Figure 2) with the most common causes of death being infection in 15 patients, GvHD in eight, engraftment failure in three and veno-occlusive disease in three.

By univariate analysis, TRM was significantly higher in the following groups: unrelated transplants ($p < 0.001$), advanced disease at time of transplant ($p < 0.001$), age over 10 years ($p < 0.001$), transplantation with mismatches ($p < 0.001$), patients with acute GvHD, ($p = 0.04$) and transplant performed with UCB cells ($p = 0.03$). In multivariate analysis, the only significant risk factor for MRT was advanced disease at the time of transplant ($p = 0.009$).

No significant difference was observed in OS and EFS of patients who developed acute or chronic GvHD regardless of the severity of the disease.

The cumulative incidence of relapse after transplantation was 40% at three years (Figure 3) and the median time of relapse was 163 days (range: 22 to 1468 days) after transplant.

No statistically significant differences were identified when the OS and EFS were compared between ALL and AML patients. There were also no significant differences in the OS and EFS between over and under 10-year-old patients, patients who received transplants from related or unrelated donors, transplants with or without HLA mismatches, or between HSCT using different cells sources.

Patients who underwent a conditioning regimen involving TBI showed a trend toward better 3-year OS ($p = 0.06$) and EFS ($p = 0.06$). There was also a lower incidence of relapse among patients who received this conditioning ($p = 0.001$). However no association was seen between TRM and the conditioning regimen.

Table 2. Complications after HSCT of the entire group of patients and AML and ALL subgroups

Complications	Nº cases/ total patients (%)	Nº cases/ ALL patients (%)	Nº cases/ AML patients (%)
Acute GvHD	7/181 (37)	39/100 (39)	28/81 (34)
GI-II	41 (23)	27 (27)	14 (17)
GIII-IV	26 (14)	12 (12)	14 (17)
Chronic GvHD	28/158 (18)	15/83 (18)	13/75 (17)
Limited	8 (5)	7 (8.5)	1 (1.5)
Extensive	20 (13)	8 (9.5)	12 (16)
Relapse	78/208 (3.5)	42/119 (35)	36/89 (40)
TRM	34/208 (16)	24/119 (20)	10/89 (11)

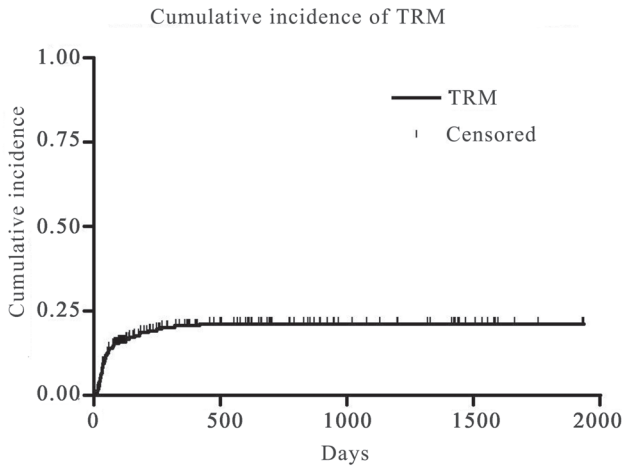

Figure 2. Cumulative incidence of transplant-related mortality on day + 100

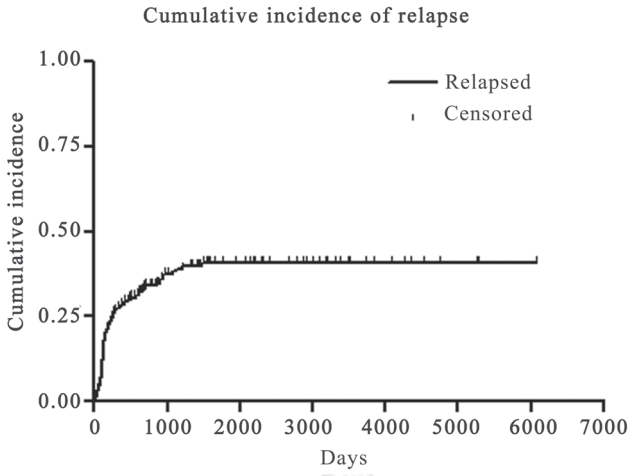

Figure 3. Cumulative incidence of relapse after HSCT - 40% in three years

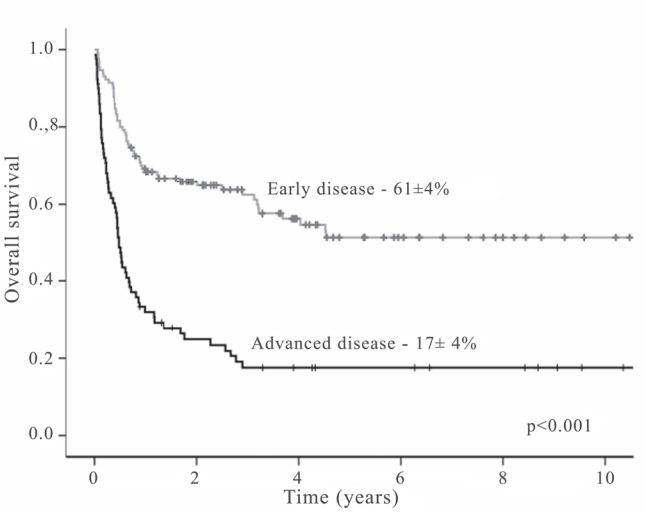

Figure 4. Comparison of survival at 3 years among patients in early disease and advanced disease at HSCT

Patients submitted to transplant before 1995 had a worse OS compared to patients transplanted after 1995 (p = 0.01). Transplant patients in early disease had a better 3-year OS at than those undergoing HSCT in advanced disease (Figure 4). The 3-year EFS rate was also significantly higher in the group transplanted in early disease (46% vs. 13%; p < 0.001).

In the multivariate analysis, the only factor that had an impact on the OS and EFS was disease status (early disease or advanced disease) at the time of transplantation (Table 3).

Table 3.: Variables included in the univariate and multivariate analyses and the respective p-values

	Univariate p-value	Multivariate p-value
Diagnosis LLA LMA	0.468	-
Transplant Related Non-related	0.636	-
HLA Match (6/6) With mismatches (4/6 or 5/6)	0.310	-
Stem cell source Umbilical cord blood Bone marrow Peripheral blood	0.860	-
Year of HSCT Up to 1995 After 1995	0.012	0.069
Age at HSCT Under 10 years Over 10 years	0.442	-
Conditioning With TBI Without TBI	0.054	0.081
Acute GvHD Yes No	0.517	-
DECH crônica Yes No	0.282	-
Status of the disease Early disease Advanced disease	<0.001	<0.001

HSCT = hematopoietic stem cell transplantation: TBI = total body irradiation

Acute Lymphoblastic Leukemia

The 3-year OS and EFS of ALL patients were 43% and 38%, respectively. The incidence of engraftment failure was 7% and TRM was 20%.

Relapse of disease occurred in 42 patients (35%), 31 (73%) of whom had advanced disease at the time of HSCT.

ALL Patients who received TBI in the conditioning regimen had better 3-year OS and EFS than patients who received other regimens (p < 0.001). In addition, transplant patients conditioned with TBI had a lower incidence of relapse (p < 0.001).

Patients who were transplanted in CR1 had a better OS rate, followed by those in CR2 and CR3. Patients transplanted with active disease (relapse or refractory) showed disappointing results (Figure 5).

The OS and EFS were significantly better in patients in early disease at the time of transplantation (p <0.001).

In the multivariate analysis, disease status at the time of HSCT and the use of TBI in the conditioning regimen were the only factors associated with better survival of ALL patients.

Acute Myeloid Leukemia

The 3-year OS and EFS of AML patients were 44% and 40%, respectively. The incidence of engraftment failure was 6% and the TRM was 11%. Relapse occurred in 36 patients (40%); of these 26 (72%) had advanced disease at the time of HSCT.

When only AML patients were evaluated, those transplanted in CR1 had a better 3-year OS, followed by patients transplanted in first relapse and patients in CR2 (Figure 6).

Patients transplanted with active disease had a 3-year OS of 5% (only one of 20 patients is alive).

Patients in early disease showed better 3-year OS and EFS than those patients transplanted in advanced disease (p = 0.002).

In the multivariate analysis, the only factor related to better OS and EFS of AML patients was the disease status at the time of HSCT.

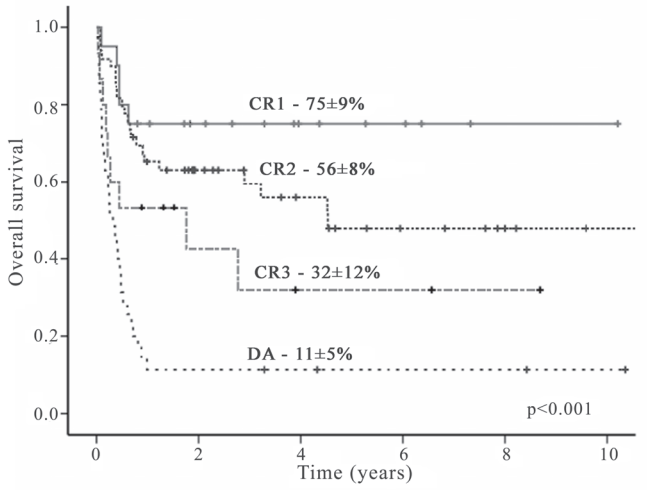

Figure 5. Three-year overall survival of ALL patients according to disease status at HSCT

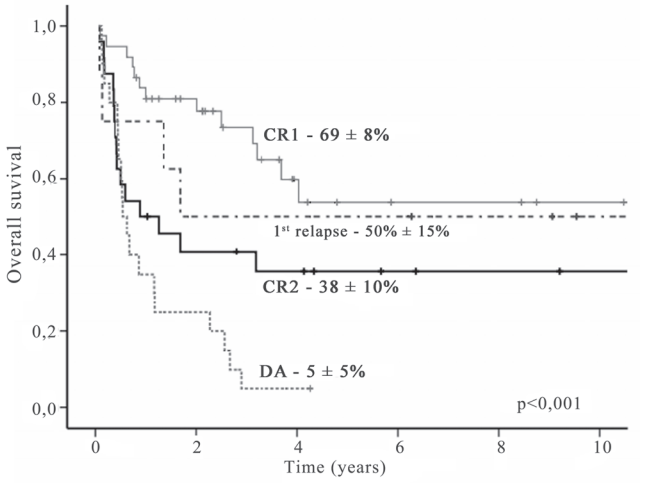

Figure 6. Three-year overall survival of AML patients according to disease status at HSCT

Discussion

This, similar to other published studies, shows that good results in the OS of patients transplanted in the early stages of leukemia can be achieved; in fact the main factor related to patient survival is the status of disease at the time of transplantation.[9,10]

Patients who underwent transplantation when they were in CR1 had better OS and EFS, but it is well known that transplantation is only indicated in this situation when patients present a high-risk condition such as the presence of cytogenetic alterations at diagnosis which is associated to poor prognosis or failure to respond to induction chemotherapy.[9-11] Both ALL and AML patients in CR2 have well-defined indications for HSCT and present with good OS and EFS.[12,13] In this study, patients transplanted in CR1 and CR2 (early disease) had very good survival rates comparable to those reported in the literature.[5,9,10]

Results of transplants with unrelated donors have improved significantly and achieved results very similar to those using matched relatives.[14,15] These results were confirmed in our study; even so a higher TRM was observed in patients receiving HSCT from unrelated donors.

No significant difference in patient survival was identified between the different sources of stem cells, however, the number of transplants performed using stem cells from peripheral blood and UCB remains small.[15]

In addition, there were no significant differences in the OS or EFS of patients transplanted with fully matched donors compared to those with some mismatch. These data differ from those reported in the literature[16,17] probably due to the small sample size and the impossibility of comparing HLA typing between the different periods analyzed; in recent years, there have been improvements in HLA typing which have resulted in a better selection of bone marrow donors and a reduction in the TRM. Patients transplanted more recently with matched donors and in early disease stage had an excellent survival rate.

The TRM was similar to that reported in the literature and was influenced by well-known factors such as the type of donor (related vs. unrelated), presence of HLA mismatches, the source of stem cells, disease status and incidence of acute GvHD.[18]

Interestingly, patients transplanted before 2000 showed no difference in the TRM, probably because, at that time, many transplants were performed with mismatches or stem cell sources other than bone marrow. The survival rate was lower in patients transplanted before 1995, possibly because the supportive care was worse at the time. Studies have shown that ALL patients benefit from conditioning using TBI, with better survival rates free of leukemia and less TRM.[19] In the current study patients who received TBI had better OS and EFS.

A total of 41% of ALL patients (49/119) and 22% of AML patients (20/89) were referred for transplantation in advanced disease (≥ 3rd remission, relapse or refractory disease). We know that the results achieved with transplantation in patients in advanced disease are very bad and a reflection, at least in part, of the different problems faced by transplant services in Brazil. These problems include the difficulty of adequate initial patient staging, the lack of chemotherapy in some Brazilian cities and there is the difficulty of arranging a hospital bed to transplant the patient at the best time after remission in the case of patients who have suitable related donors.

The biggest obstacle today in unrelated transplants is the lack of available beds as the cost is high and public agencies do not provide adequate financial support. With the growing number of volunteer donors in Brazil, the possibility of finding a compatible donor is increasing.

Even within the high-risk group, it is well know that there are subgroups of patients who really benefit from transplantation. Thus early identification of these groups is essential in order to begin the search for a donor and arrange a hospital bed. Moreover, the demand for new conditioning regimens and changes in effective transplantation strategies, such as haploidentical transplants, may assist other patients. Haploidentical HSCT is becoming a viable alternative for these patients, mainly because virtually all people have a haploidentical and easily accessible donor available (father, mother, brother).[20,21] Additionally, these transplants have a greater potential for graft versus leukemia effect, even though they appear to be related to a higher incidence of severe GvHD and delayed engraftment and hence a higher rate of TRM.[22]

The creation of cooperative groups is of fundamental importance in the evaluation of the results obtained especially with regards to the treatment of high-risk patients. The statistical analysis has greater significance when the larger number of patients of cooperative groups is analyzed together. This allows a better understanding of the main factors affecting the outcomes of transplants performed in children and adolescents with acute leukemia in Brazil.

This work provides an opportunity to evaluate the results in two important Brazilian institutions and highlights the need for improvements in diagnosis, staging and treatment of leukemia. Although the results are comparable with the literature, many patients in advanced disease were sent for HSCT and thus as expected the results are poor when compared to patients transplanted at an early stage of the disease.

Resumo

O transplante de células-tronco hematopoéticas (TCTH) é o tratamento de escolha para leucemias agudas de alto risco. Apesar da melhora na sobrevida destes pacientes, a recidiva continua sendo a maior causa de óbito pós-transplante de células-tronco hematopoéticas. O objetivo deste trabalho foi analisar os resultados dos transplantes realizados em crianças com leucemia aguda em duas instituições brasileiras. Realizou-se estudo retrospectivo de 208 pacientes transplantados entre 1990-2007. Mediana de idade: 9 anos; 119 pacientes com leucemia linfoide aguda (LLA) e 89 com leucemia mieloide aguda (LMA). Doença precoce: CR1 e CR2. Doença avançada: > CR3, doença refratária ou recidivada. Noventa pacientes vivos entre 258-6.068 dias (M:1.438), com sobrevida global (SG) de 45% (3 anos) e a sobrevida livre de recaída (SLR) 39% (três anos). 14/195 pacientes tiveram falha primária de pega (8%). Não houve diferença na sobrevida global e sobrevida livre de recaída entre pacientes com leucemia linfoide aguda e leucemia mieloide aguda, entre transplantes aparentados e não aparentados, tampouco entre as fontes de células utilizadas. O desenvolvimento da doença do enxerto contra hospedeiro (DECH) aguda ou crônica também não influenciou a sobrevida global e sobrevida livre de recaída. Pacientes com leucemia linfoide aguda condicionados com irradiação corporal total (TBI) apresentaram melhor sobrevida global e sobrevida livre de recaída (p<0,001). Cento e dezoito pacientes morreram entre 1-1.654 dias pós-transplante de células-tronco hematopoéticas (M:160). Mortalidade relacionada a transplante (MRT) (dia+100): 16%. Incidência cumulativa de recaída: 40% (3 anos). Pacientes com doença avançada tiveram menor sobrevida global e sobrevida livre de recaída (três anos)(p<0,001). Na análise multivariada, o status da doença foi o principal fator associado ao aumento da sobrevida global e sobrevida livre de recaída. Nossos resultados mostram que é possível se atingir uma boa sobrevida para pacientes com doença precoce e também mostram a baixa eficácia naqueles com doença avançada.

Descritores: *Transplante de células-tronco hematopoéticas; Leucemia mieloide aguda/terapia; Leucemia-linfoma linfoblástico de células precursoras; Doenças enxerto-hospedeiro; Transplante de medula óssea; Humanos; Criança; Pré-escolar; Adolescente*

References

1. Linet MS, Ries LA, Smith MA, Tarone RE, Devesa SS. Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. J Natl Cancer Inst. 1999. 91(12):1051-8.
2. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med. 2006;354(2):166-78.
3. MacMillan ML, Davies SM, Nelson GO, Chitphakdithai P, Confer DL, King RJ, et al. Twenty years of unrelated donor bone marrow transplantation for pediatric acute leukemia facilitated by the National Marrow Donor Program. Biol Blood Marrow Transplant. 2008;14(9 Suppl):16-22.
4. Thomas ED, Blume KG, Forman SJ. Hematopoietic cell transplantation. 2nd ed. Boston: Blackwell Science; 1999.
5. Rocha V, Cornish J, Sievers EL, Filipovich A, Locatelli F, Peters C, et al. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. Blood. 2001;97(10):2962-71.
6. Grewal SS, Barker JN, Davies SM, Wagner JE. Unrelated donor hematopoietic cell transplantation: marrow or umbilical cord blood? Blood. 2003;101(11):4233-44.
7. Flowers ME, Kansu E, Sullivan KM. Pathophysiology and treatment of graft-versus-host disease. Hematol Oncol Clin North Am. 1999;13(5):1091-112.viii-ix.
8. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, et al. Chronic graft versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med. 1980;69(2):204-17.
9. Lodewick T, Cornelissen JJ. Allogeneic stem cell transplantation in acute myeloid leukemia: a risk-adapted approach. Blood Rev. 2008;22(6):293-302.
10. Mehta PA, Davies SM. Allogeneic transplantation for childhood ALL. Bone Marrow Transplant. 2007;41(2):133-9.

11. Bunin NJ, Davies SM, Aplenc R, Camitta BM, DeSantes KB, Goyal RK, et al. Unrelated donor bone marrow transplantation for children with acute myeloid leukemia beyond first remission or refractory to chemotherapy. J Clin Oncol. 2008;26(26): 4326-32.

12. Bunin N, Carston M, Wall D, Adams R, Casper J, Kamani N, King R; National Marrow Donor Program Working Group. Unrelated marrow transplantation for children with acute lymphoblastic leukemia in second remission. Blood. 2002; 99(9):3151-7.

13. Fagioli F, Zecca M, Locatelli F, Lanino E, Uderzo C, Di Bartolomeo P, Berger M, Favre C, Rondelli R, Pession A, Messina C; AIEOP-HSCT group. Allogeneic stem cell transplantation for children with acute myeloid leukemia in second complete remission. J Pediatr Hematol Oncol. 2008;30 (8):575-83.

14. Locatelli F, Zecca M, Messina C, Rondelli R, Lanino E, Sacchi N, et al. Improvement over time in outcome for children with acute lymphoblastic leukemia in second remission given hematopoietic stem cell transplantation from unrelated donors. Leukemia. 2002;16(11):2228-37.

15. Eapen M, Rubinstein P, Zhang MJ, Stevens C, Kurtzberg J, Scaradavou A, et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. Lancet. 2007;369 (9577):1947-54. Comment in: Lancet. 2007;369(9577): 1906-8.

16. Dehn J, Arora M, Spellman S, Setterholm M, Horowitz M, Confer D, et al. Unrelated donor hematopoietic cell transplantation: factors associated with a better HLA match. Biol Blood Marrow Transplant. 2008;14(12):1334-40.

17. Anasetti C. What are the most important donor and recipient factors affecting the outcome of related and unrelated allogeneic transplantation? Best Pract Res Clin Haematol. 2008;21(4): 691-7.

18. Bacigalupo A, Sormani MP, Lamparelli T, Gualandi F, Occhini D, Bregante S, et al. Reducing transplant-related mortality after allogeneic hematopoietic stem cell transplantation. Haematologica. 2004;89(10):1238-47.

19. Davies SM, Ramsay NK, Klein JP, Weisdorf DJ, Bolwell B, Cahn JY, et al. Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia. J Clin Oncol. 2000; 18(2):340-7.

20. Aversa F, Terenzi A, Tabilio A, Falzetti F, Carotti A, Ballanti S, et al. Full haplotype-mismatched hematopoietic stem-cell transplantation: a phase II study in patients with acute leukemia at high risk of relapse. J Clin Oncol. 2005;23(15):3447-54.

21. Huang XJ. Current status of haploidentical stem cell transplantation for leukemia. J Hematol Oncol. 2008;1:27.

22. Aversa F, Reisner Y, Martelli MF. The haploidentical option for high-risk haematological malignancies. Blood Cells Mol Dis. 2008;40(1):8-12.

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