Results of syngeneic hematopoietic stem cell transplantation for acute leukemia: risk factors for outcomes of adults transplanted in first complete remission

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ABSTRACT

Background

The possibility of performing syngeneic hematopoietic stem cell transplantation is rare and there are concerns about the absence of a graft-versus-leukemia effect following such a strategy. We report the outcomes of a large series of adult patients who underwent syngeneic hematopoietic stem cell transplantation for acute myeloblastic leukemia or acute lymphoblastic leukemia.

Design and Methods

The outcomes of all syngeneic transplants for acute myeloblastic or lymphoblastic leukemia reported to the European Group for Blood and Marrow Transplantation registry were analyzed; a study of prognostic factors was performed for those transplanted in first complete remission.

Results

One hundred and sixty-two patients, 109 with acute myeloblastic leukemia and 53 with acute lymphoblastic leukemia, were identified; 116 were in first complete remission. Most of the patients did not receive prophylaxis against graft-versus-host disease. Nineteen patients developed acute graft-versus-host disease and only three patients developed chronic graft-versus-host disease. The median follow-up was 60 months. At 5 years the non-relapse mortality was 8±5%, the relapse incidence 49±8% and the leukemia-free survival 43±3%. The corresponding figures for patients in first complete remission were 7±2%, 40±4% and 53±5% at 5 years. Analysis of patients in first complete remission showed that the number of courses of chemotherapy required to induce first complete remission was the main risk factor: the leukemia-free survival at 5 years was 66±6% when first complete remission was reached after one induction course of chemotherapy and was only 20±9% when first complete remission was reached after at least two induction courses of chemotherapy (p=0.0001); the relapse incidence was 30±6% and 54±10%, respectively (p=0.007).

Conclusions

Outcomes were better for patients transplanted in first complete remission than in second complete remission or a more advanced phase of the disease. When a syngeneic donor is available for patients with high risk acute leukemia, allotransplantation should be performed as soon as the first complete remission has been achieved, ideally with one course of chemotherapy.

Key words: acute leukemia, syngeneic transplantation.

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Introduction

Treatment of acute leukemia includes allogeneic hematopoietic stem cell transplantation (HSCT) from a family member or an unrelated donor. The possibility of performing HSCT from an identical twin donor, i.e., a syngeneic donor, is rare. Indeed the last 2005 activity survey of the European Group for Blood and Marrow Transplantation (EBMT) on HSCT indicated that, of a total of 8890 allogeneic transplants, 4702 were done from a related HLA identical donor, 514 from a related HLA non-identical donor, 3617 from an unrelated donor and only 57 (0.64%) from a twin donor.[1] It was previously reported that syngeneic HSCT was associated with a low non-relapse mortality but with a high relapse incidence.[2,3] This was corroborated by an International Bone Marrow Transplantation Registry (IBMTR) comparative study showing that after allogeneic bone marrow transplantation for early leukemia the highest relapse incidence was observed after syngeneic transplants and the lowest after unmanipulated bone marrow transplants when graft-versus-host disease (GVHD) was diagnosed.[4] These observations were the demonstration of an immunological effect after allogeneic bone marrow transplants but were not in favor of a possible graft-versus-leukemia effect after syngeneic HSCT. However, proven GVHD is observed after approximately 10% of syngeneic HSCT, indicating that a syngeneic graft-versus-leukemia effect may exist. Indeed, efforts have been made to identify factors that could influence the occurrence of a syngeneic graft-versus-leukemia effect such as nucleated cell dose in the graft[5] and parity.[6]

In this study we report the largest series of syngeneic HSCT for acute myeloblastic leukemia (AML) and lymphoblastic leukemia (ALL) in adults, all reported to the EBMT registry by European teams.

Design and Methods

Patients

Adult patients (over 16 years old) undergoing HSCT from a syngeneic identical twin for AML or ALL were selected from the Acute Leukaemia Working Party registry of the EBMT over a period of 30 years from January 1975 to December 2003 (median year: 1994); 72% of patients were transplanted after January 1990. The selected patients were reported to the EBMT by 86 European teams. All patients had *de novo* acute leukemia. A total of 162 eligible patients who received a syngeneic HSCT were selected for the study. All patients received a myeloablative conditioning regimen.

Statistical analysis and end-points

A descriptive analysis was performed for all patients and patients transplanted in first complete remission. Prognostic analyses were restricted to the subgroup of adult patients transplanted in first complete remission, constituting the only homogeneous subgroup with a number of patients (n=116) sufficient for a multivariate analysis.

The primary end-point of the study was to determine the outcome defined as time to death or relapse, non-relapse mortality and leukemia-free survival. Variables considered were recipient age, sex, disease characteristics (type of leukemia, cytogenetics, white blood cell count at diagnosis, cytomegalovirus serology), donor characteristics (cytomegalovirus serology), time from diagnosis to first remission, number of induction courses to reach first remission, disease status at transplant (first complete remission, second complete remission or more advanced disease); transplant characteristics (source of stem cells, dose of nucleated cells infused, conditioning regimen including total body irradiation or not, GVHD prophylaxis and year of transplant)

Cumulative incidence curves were used in a competing risk setting, since death and relapse are competing events.[7] Probabilities of leukemia-free survival were calculated using the Kaplan-Meier estimate; the log-rank test was used for univariate comparisons.

In the population of patients allografted in first remission, associations of graft characteristics with outcomes were evaluated in multivariate analyses, using Cox proportional hazards for leukemia-free survival and survival, and the proportional sub-distribution hazard regression model of Fine and Gray for other outcomes.[8] A stepwise backward procedure was used to construct a set of independent predictors for each end-point. All predictors with a p value below 0.10 were considered, and sequentially removed if the p value in the multiple model was above 0.05. All tests were two-sided. The type I error rate was fixed at 0.05 for determination of factors associated with time to event outcomes. Statistical analyses were performed with SPSS (Inc., Chicago) and Splus (MathSoft, Inc, Seattle) software packages.

Results

Disease and patient characteristics

Table 1 lists the disease, patient and transplant characteristics. Overall 162 patients were analyzed: 109 with AML and 53 with ALL. The median age of the whole population was 36 years old (range, 16-68 years old). One hundred and sixteen patients were transplanted in first complete remission, 21 in second complete remission and 25 in a more advanced stage of disease. Information on cytogenetics at diagnosis was available for 78/162 patients comprising 59 with AML and 25 with ALL. According to the South-Western Oncology Group (SWOG) classification,[9] eight AML patients were in the favorable prognostic group, 47 patients were in the intermediate group and four patients were in the unfavorable group. Among the ALL group no abnormality was observed in 16 patients, whereas cytogenetic abnormalities were reported for nine patients: two patients with t(4;11) and seven with t(9;22). One patient had a detectable bcr-abl transcript fusion without a detectable t(9;22).

Disease and patient characteristics of patients with acute leukemia transplanted in first complete remission

One hundred and sixteen patients were transplanted in first complete remission. Table 1 lists the disease, patient and transplant characteristics. Eighty-two patients had AML and 34 ALL. The median age was 36 years old (range, 16-62 years old). The median time from diagnosis to first complete remission was 43 days (range, 14-196), the median time from first complete remission to transplantation 107 days (range, 13-321 days) and the median time from diagnosis to transplantation 162 days (range, 49-358 days). The number of lines of induction chemotherapy to reach first complete remission was one for 68% of the patients, two for 21% of patients, and over two for 11% of the patients. Seven patients received a syngeneic transplant more than 6 months after achieving first complete remission.

Table 1. Disease, patient and transplant characteristics of all 162 adults patients with acute leukemia and of 116 patients transplanted in first complete remission (CR1).

	All patients (n=162)	*Patients in CR1 (n=116)*
Variables	N. (%) or median (range)	N. (%) or median (range)
Age	36 (16-68)	36 (16-62)
Gender		
Male	85 (52%)	59 (51%)
Female	77 (48%)	57 (49%)
Leukocyte count at diagnosis	12x10^9/L (1-590x10^9/L)	11.75x10^9/L (0.9-590x10^9/L)
Disease type		
Acute myeloid leukemia	109 (67%)	82 (71%)
Acute lymphoblastic leukemia	53 (33%)	34 (29%)
Disease status at transplant		
First complete remission	116 (71.5%)	116 (100%)
Second complete remission	21 (13%)	
Advanced disease	25 (15.5%)	
Median days from diagnosis to CR1		43 (14-196)
Median days from diagnosis to transplantation		162 (49-358)
Median days from CR1 to transplantation		107 (13-321)
Number of induction chemotherapy courses to reach CR1 (90/116)		
One		61 (68%)
Two		19 (21%)
More than two		10 (11%)
Cytomegalovirus status		
Patient positive	60% (47 missing)	60% (31 missing)
Donor positive	55% (59 missing)	57% (39 missing)
Donor/recipient negative	32% (59 missing)	31% (39 missing)
Source of stem cells		
Bone marrow	112 (70%)	79 (68%)
Peripheral blood	48 (29%)	35 (30%)
Both	2 (1%)	2 (2%)
Median dose of nucleated cells infused		
Bone marrow (range)	2.6x10^8/kg (0.2-273)	2.8 x10^8/kg (0.2-27)
Peripheral blood (range)	10x10^8/kg (0.2-229)	10.97x10^8/kg (0.2-229)
Conditioning regimen		
With total body irradiation	93 (58%)	67 (58%)
High dose chemotherapy alone	65 (40%)	47 (41%)
Missing	4 (2%)	2 (1%)
Graft-versus-host disease prophylaxis		
No	140 (86.5%)	98 (84.5%)
Yes	22 (13.5%)	18 (15.5%)
Cyclosporine alone	17	14
Methotrexate alone	3	2
Ex vivo T-cell depletion	2	2

Transplant characteristics of all patients

All patients received a myeloablative conditioning regimen which included total body irradiation in 58% of the patients overall, in 49% of those with AML and in 79% of the ALL patients. The source of stem cells was bone marrow for 70% of the patients, peripheral blood for 29%, and 1% received both bone marrow and peripheral blood. The majority of patients (86.5%) did not receive any GVHD prophylaxis, whereas the remaining (13.5%) did receive prophylaxis. Information on parity of female patients and recipients was partially retrieved (62.5% of syngeneic transplantations). Twenty-two female patients were nulliparous and 21 parous, 19 female donors were nulliparous and 20 parous.

Transplant characteristics of patients transplanted in first complete remission

All patients received a myeloablative conditioning regimen, which included total body irradiation in 58% of them. The source of stem cells was bone marrow for 68% of the patients. No GVHD prophylaxis was given to 84.5% of this group of patients. Serology for cytomegalovirus was negative for both donor and recipient in 31% of the transplants.

Engraftment

Engraftment was defined as the time to reach a neutrophil count of 0.5×10^9/L and a platelet count of 0.5×10^9/L. All patients but one engrafted. For bone marrow transplantation the median time to reach 0.5×10^9/L neutrophils, calculated from the day of the transplant, was 15 days (range, 10-51 days) and the median time to reach a platelet count of 0.5×10^9/L was 24 days (range, 12-247 days). For peripheral blood transplantation the median time to reach neutrophil engraftment was 12 days (range, 8-42 days), and the time to reach a platelet count of 0.5×10^9/L was 16 days (range, 8-73 days).

Acute and chronic GVHD

Nineteen patients developed acute GVHD: 13 grade I, four grade II, and two grade III-IV. For six patients the diagnosis of acute GVHD was proven by a biopsy; five of these six patients were confirmed to be monozygotic twins either serologically (n=3) or by molecular biology (n=2). Eight patients out of 22 patients given GVHD prophylaxis developed acute GVHD. Only three patients developed chronic GVHD

which was limited in two patients and extensive in one patient. One patient died from acute GVHD.

Outcome

The median follow-up for survivors was 60 months (range 1-275 months). A total of 69/162 patients died. The original disease was the cause of death for 49 patients. The remaining 20 patients died from GVHD (n=1), cardiac toxicity (n=2), hemorrhages (n=2), graft failure (n=1), infections (n=6), interstitial pneumonitis (n=4), secondary malignancy (n=1), and other non-relapse-related causes (n=3). The outcome at 5 years for all patients showed a leukemia-free survival of 43±3%, a relapse incidence of 49±8% and a non-relapse mortality rate of 8±5%. Patients in first complete remission showed leukemia-free survival, relapse incidence and non-relapse mortality rates at 5 years of 53±5%, 40±4% and 7±2%, respectively (Figure 1). At 1 year the leukemia-free survival was 40±45% and 42±17% for patients with AML (n=10) or ALL (n=11), respectively, transplanted in second complete remission. At 3 years the leukemia-free survival, relapse incidence and non-relapse mortality rates in the whole group of patients transplanted in second complete remission were 28±11%, 62±10% and 10±7%, respectively, and the corresponding figures in patients transplanted in a more advanced stage of disease were 27±9%, 69±7% and 4±4% at 3 years.

Outcome of patients with Philadelphia-positive ALL transplanted in first complete remission

The t(9; 22) Philadelphia chromosome was detected, by cytogenetics, in five patients and one further patient had the bcr/abl rearrangement detected by molecular biology, with a normal karyotype. Of these six paients, two died from relapse at 865 days and 778 days after transplantation. The remaining four patients were alive, one in relapse with a follow-up of 234 days, and the three in complete remission with follow-ups of 636 days, 632 days and 138 days.

Analyses of risk factors associated with outcomes after syngeneic HSCT for patients with acute leukemia transplanted in first complete remission

Cytomegalovirus status, source of stem cells, year of transplant, type of acute leukemia (AML or ALL), and total body irradiation in the conditioning regimen were not statistically significantly associated with outcomes (Table 2). The numbers of courses of chemotherapy to induce first complete remission was an important factor associated with leukemia-free survival, relapse incidence and non-relapse mortality. Leukemia-free survival at 5 years was 66±6% when first complete remission was reached after one course of induction chemotherapy and was only 20±9% when first complete remission was reached after at least two courses of induction chemotherapy (p=0.0001). The relapse incidence was 30±6% and 64±10%, respectively (p=0.007), and the non-relapse mortality rate 4±3% and 15±8%, respectively (p=0.052) (Figure 2). Recipient age (below 36 years old) was also associated with increased leukemia-free survival.

In multivariate analysis the only variable that was still statistically significant was one induction course of chemotherapy to reach first complete remission. This variable was associated with a higher leukemia-free survival (p=0.0007, RR: 0.33, 95% CI: 0.18-0.63) and a lower relapse incidence (p=0.015, RR: 2.4, 95% CI: 1.2-4.8).

Discussion

Syngeneic HSCT is a rare event. We report here the largest series of syngeneic transplants performed for acute leukemia in adults. The objectives of this study were to describe the outcomes of patients receiving such transplants and to analyze prognostic factors in adult patients who underwent syngeneic HSCT in first complete remission.

We found that leukemia-free survival at 5 years was 53% for patients transplanted in first complete remission, and 66% when the first complete remission was obtained after one induction course. These results are comparable to those previously reported after

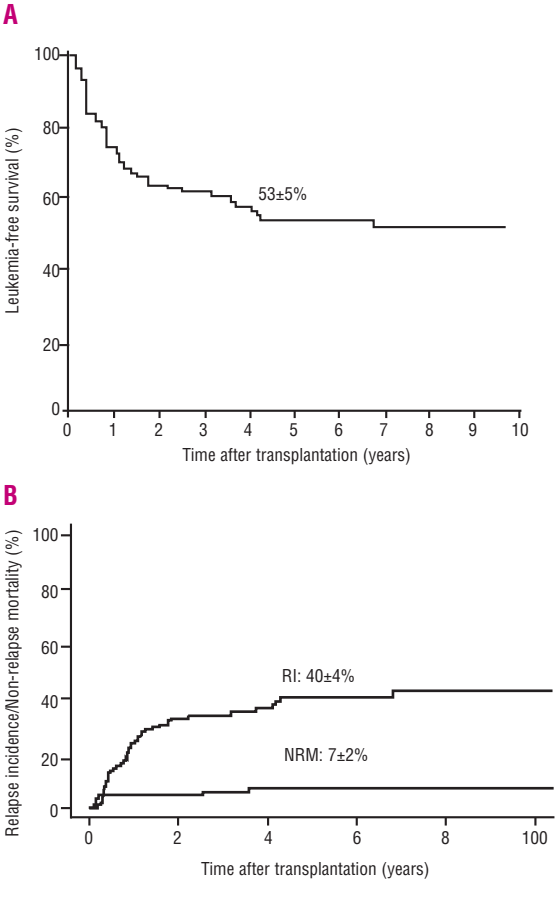

Figure 1. Leukemia-free survival, relapse incidence and non-relapse mortality of patients with acute leukemia after syngeneic hematopoietic stem cell transplantation in first complete remission. (A) Leukemia-free survival probability. The percentage shown is the 5-year probability. (B) Relapse incidence (RI) and non-relapse mortality (NRM) probability. The percentage shown are for the 5-year timepoint.

genoidentical HSCT for acute leukemia with leukemia free survival being 48% at 5 years and 66% at 3 years,[10,11,12] and those reported in the last EBMT survey on acute leukemia (*www.ebmt.org*) which showed that adult patients transplanted with a graft from an HLA identical donor had an overall survival at 5 years of 57% when transplanted in first complete remission (n=8549), 41% when transplanted in second complete remission (n=2046) and 18% when transplanted in a more advanced stage of disease (n=3202). These sur-

Table 2. Univariate analysis for outcomes after syngeneic HSCT for adults with acute leukemia.

Variables	*Leukemia-free survival (%)*	*Relapse incidence (%)*	*Non-relapse mortality (%)*
Median age (36 years)			
<median	65±7	31±6	3±2
>median	42±7	49±7	9±4
p value	0.03	0.09	0.29
Patient/recipient sex			
Male	49±7	48±7	3±2
Female	57±7	33±7	10±4
p value	0.37	0.13	0.24
Median year of HSCT (1994)			
< median	49±6	41±5	10±3
> median	60±8	38±8	2±2
p value	0.29	0.78	0.12
Type of disease			
Acute myeloid leukemia	50± 6	41±6	8±3
Acute lymphoblastic leukemia	52± 10	39±9	3±3
p value	0.67	0.99	0.40
Median time from diagnosis to CR1 (43 days)			
< median	58±8	36±8	6±4
> median	46±8	45±8	9±4
p value	0.08	0.25	0.36
Median time from CR1 to syngeneic HSCT (107 days)			
< median	42±8	48±8	10±5
> median	63±8	32±8	5±4
p value	0.08	0.18	0.42
Number of induction courses to reach CR1			
1	66±6	30±6	4±3
>1	20±9	64±10	15±8
p value	0.0001	0.007	0.05
Source of stem cells			
Bone marrow	52±6	40±5	8±3
Peripheral blood	47±12	50±2	3±2
p value	0.77	0.92	0.44
TBI in conditioning regimen			
No	51±8	45±8	3±3
Yes	53±7	37±6	9±9
p value	0.59	0.73	0.13
Patient CMV serostatus			
Negative	71±8	23±8	6±4
Positive	41±8	49±9	10±4
p value	0.09	0.08	0.78
Donor CMV serostatus			
Negative	49±10	40±9	10±6
Positive	50±8	43±8	8±4
p value	0.83	0.63	0.7

HSCT: hematopoietic stem cell transplantation; CR1: first complete remission; CMV: cytomegalovirus; TBI: total body irradiation.

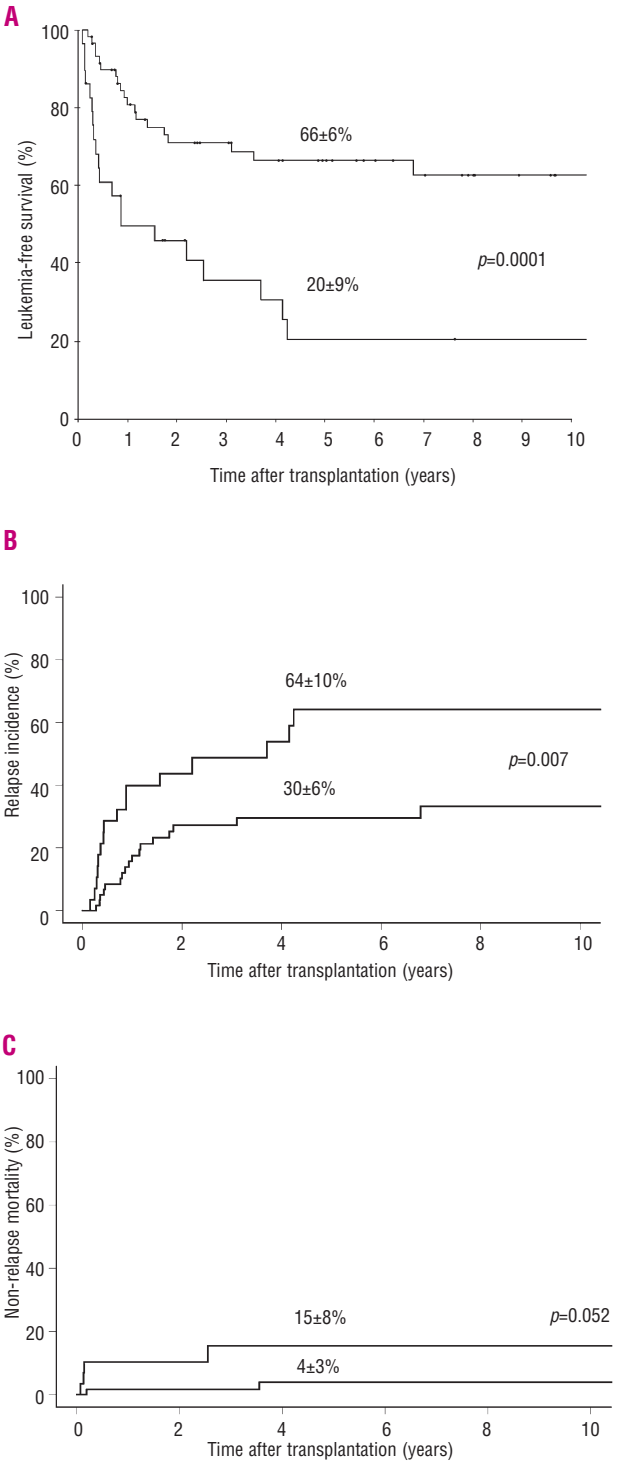

Figure 2. Leukemia-free survival, relapse incidence and non-relapse mortality of patients with acute leukemia after syngeneic hematopoietic stem cell transplantation during first complete remission (CR1) according to the number of induction chemotherapy courses needed to reach CR1. (A) Leukemia-free survival. Upper curve: one induction course to reach CR1. Lower curve: more than one induction course to reach CR1. The percentages shown are for the 5-year timepoint. (B) Relapse incidence. Lower curve: one induction course to reach CR1. Upper curve: more than one induction course to reach CR1. The percentages shown are for the 5-year timepoint. (C) Non-relapse mortality. Lower curve: one induction course to reach CR1. Upper curve: more than one induction course to reach CR1. The percentages shown are for the 5-year timepoint.

vival rates are essentially the same as those in our study. This is mainly explained by the very low non-relapse mortality usually found after syngeneic HSCT. However we also found that the relapse incidence at 5 years was only 40% among patients transplanted in first complete remission and only 30% when the first complete remission was reached with one induction course. This last observation indicates that the combination of a low non-relapse mortality rate and a possible syngeneic graft-versus-leukemia effect resulted in a good survival. Indeed, a syngeneic graft-versus-leukemia effect has already been suggested by retrospective studies comparing syngeneic HSCT to HLA-identical sibling HSCT in acute leukemia, chronic myeloid leukemia[3] and multiple myeloma.[13] In these studies the leukemia-free survival of patients given the two types of transplants was not statistically different. Furthermore authentic cases of acute and chronic GVHD were reported after syngeneic transplants.[14-16] In our study, acute GVHD occurred in only 19 patients (11%) and chronic GVHD in only three patients (1.8%). Acute GVHD was histologically proven in six patients who were all, except one, confirmed as monozygotic twins, thus excluding the possiblity that the GVHD had occured in non-twin transplants. Given the low incidence of acute and chronic GVHD in our study, it was not possible to analyze any associations of GVHD with outcomes, particulary relapse.

Some authors have tried to identify parameters that could influence the occurrence of GVHD and the graft-versus-leukemia effect after syngeneic HSCT. In an IBMTR study the dose of syngeneic nucleated cells infused was shown to have an effect on survival.[5] The outcome was improved when more than 3×10^8 nucleated cells/kg were transplanted: a lower relapse rate was associated with a higher dose of nucleated cells.

A more recent study identified risk factors for GVHD in 126 consecutive cases of syngeneic HSCT.[6] In this study the cumulative incidence of GVHD was 18%. GVHD was more frequent when the donor was parous than when the donor was nulliparous or male, and when the recipient was parous than when the recipient was nulliparous. Other risk factors for syngeneic GVHD included age, busulfan/melphalan/thiotepa in the conditioning regimen, post-transplant interleukin 2, HLA-A26, and more recent transplantation year. However, it was pointed out that many of the risk factors in syngeneic GVHD were the same as those in allogeneic HSCT. In our study the main prognostic factor that influenced outcome, according to both univariate and multivariate analyses, was the number of induction courses to reach first complete remission. This factor has already been recognized as a major prognostic factor in all transplants for acute leukemia.[17,18] Neither our study nor previous studies have been able to identify peculiar factors that could influence the occurrence of syngeneic GVHD and a syngeneic graft-versus-leukemia effect.

In summary, this study showed that syngeneic HSCT for acute leukemia can lead to a high survival rate among adult patients transplanted in first complete remission. This was mainly due to a low non-relapse mortality rate but also to a possible syngeneic graft-versus-leukemia effect. Since the results of syngeneic transplantation were better when the transplant was performed in first complete remission obtained after one course of induction, it remains questionable whether a search for an alternative donor is necessary in other patients.

Appendix

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Authorship and Disclosures

LC, AG, EG , FF, RP, RW, EM, DB, AIA, JS, MS, N-CG and VR: acquisition of data, revision and approval of the article; LF, in addition: design of the study, interpretation and drafting the article; ML:analysis of data. The authors reported no potential conflicts of interest.

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