Pediatric Hematology and Oncology, 22:597–608, 2005

ISSN: 0888-0018 print / 1521-0669 online
DOI: 10.1080/08880010500198871

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STEM CELL TRANSPLANTATION AS CONSOLIDATION THERAPY FOR CHILDREN IN FIRST-REMISSION AML: A Single-Center Report

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□ *A large number of patients affected by acute myeloid leukemia (AML) achieve complete remission following induction chemotherapy based on high-dose aracytin and anthracyclines. However, a postremission consolidation treatment appears to be essential to maintain the remission status. Sixteen patients with newly diagnosed AML received induction chemotherapy according to the AIEOP LAM 92P/Mod protocol. All patients were HLA-typed, and if no donor was identified within the family, patients underwent autologous stem cell transplantation (autoSCT) with mafosfamide-purged bone marrow. Patients with very high-risk AML (cytogenetics with t(9;22), hyperleukocytosis (540 × 10^9/L), and AML-M7 with trilineage myelodysplasia) underwent unrelated donor transplantation. One patient relapsed before autoSCT. Eleven patients underwent autoSCT with purged bone marrow, 3 patients underwent unrelated donor transplantation (UD), and 1 patient underwent HLA-identical, matched familiar donor transplantation (MFD). All patients achieved complete remission following one course. No treatment-related deaths occurred during first-line treatment. The median interval between diagnosis and transplant was 175 days (129–277). Three patients relapsed following autoSCT; none relapsed after alloSCT. Taking stem cell transplantation as the starting point, overall survival was 93%, disease-free survival (according to the chosen treatment) was 80%, the relapse rate was 20%, and transplant-related mortality was 0%.*

Keywords acute myeloid leukemia, children, stem cell transplantation

The prognosis of childhood acute myeloid leukemia (AML) has improved over the last 4 decades. Nowadays, more than 80% of children having AML achieve remission and in half of these cases remission is maintained and long-term cure achieved [1]. Aggressive induction chemotherapy protocols have improved the achievement of complete remission [2–4]. For children in remission with a sibling donor the therapy of choice is allogeneic stem cell transplantation (alloSCT) [5, 6]. However, an HLA-identical

Received 11 December 2004; accepted 7 June 2005.
We thank Andrew Martin Garvey for critically reviewing our manuscript.
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family donor is available to less than one-third of patients. In the absence of a suitable HLA-matched family donor (MFD), treatment options include chemotherapy, autologous (autoSCT), or unrelated donor (UD) transplantation [7]. The results of randomized clinical trials for AML in children seem to suggest equivalent outcomes after intensive chemotherapy and autoSCT in first remission [8], but no conclusive data are available since there are limited data in children [9]. In particular, in the few studies [1, 5, 10, 11] focusing on pediatric patients, only one [1], in which autoSCT transplantation was compared with no further therapy, showed an advantage in terms of lukemia-free survival (LFS) for patients who underwent stem cell transplantation (SCT), whereas the remaining did not show any advantage in the probability of survival for patients who underwent transplantation.

In view of the above considerations, we carried out a single-institution retrospective study aimed at analyzing our results on leukemia-free survival of children with AML in first remission who underwent SCT. All patients were HLA-typed, and if no donor was identified within the family, patients underwent autoSCT with mafosfamide-purged bone marrow [12]. Three out of 16 patients were considered as very high risk for relapse because of poor cytogenetics t(9;22) [13], hyperleukocytosis (540×10^9/L) [14], and acute megakaryoblastic leukemia with trilineage myelodysplasia [15–18], and, finally, they underwent UD transplantation.

Here, we report the outcome of patients affected by AML enrolled in our center who underwent SCT in first remission following intensive induction chemotherapy with bone marrow as the stem cell source.

PATIENTS AND METHODS

First-Line Treatment

Between March 1998 and August 2002, 16 children were enrolled in the AIEOP LAM 92 P/Modified Protocol (Italian Paediatric Haematology and Oncology Association–Acute Myeloid Leukaemia Protocol). The clinical details are outlined in Table 1. All children achieved first remission following 1 course. This was achieved following induction chemotherapy with high-dose aracytin (100 mg/m^2 daily iv on days 1–10, total dose 1000 mg/m^2), etoposide (100 mg/m^2 on days 1–5, total dose 500 mg/m^2), and idarubicin (10 mg/m^2 on days 1–3, total dose 30 mg/m^2). Two postremission courses were also based on aracytin (100 mg/m^2 on days 1–7, total dose 700 mg/m^2), etoposide (100 mg/m^2 on days 1–3, total dose 300 mg/m^2), and idarubicin (10 mg/m^2 on days 1 and 2, total dose 20 mg/m^2). No G-CSF was administrated to accelerate the leukocyte reconstitution. Patients with no family donor and autoSCT candidates underwent bone marrow harvest followed by 2 courses of daunomycin (60 mg/m^2 iv), aracytin (60 mg/m^2 3 times daily sc on days 1–5, total dose 900 mg/m^2), and 6-thioguanine

TABLE 1 Clinical Details of Patients Entered in the Study

Characteristics	No. of patients	Median
Age (years)		5.8 (1.7–15.3)
Sex (male/female)	8/8	
FAB classification		
M0	1	
M2	9	
M3v	1	
M4	3	
M5	1	
M7	1	
WBC count at diagnosis ($\times 10^9$/L)		19.08 (1.98–540)
BM blasts (%)		73 (33–95)
Cytogenetic characteristics		
Normal karyotype	8	
t(8;21)	3	
Inv 16	1	
43-46 XY, t(11;?)(p13;?)	1	
45 XY del(9); del(20)	1	
t(9;22)	1	
t(1;11)	1	
No. of days to achieve first CR		33 (26–66)
Interval between diagnosis and autoSCT (months)		5.8 (4.3–9.2)
Interval between first CR and autoSCT (months)		4.6 (3.4–9)
Interval between diagnosis and alloSCT (months)		5.5 (4.1–6.1)
Interval between first CR and alloSCT (months)		3.9 (3.2–4)
Graft characteristics (autoSCT)		
No. of cells infused ($\times 10^8$/kg)		1.45 (0.38–17.22)
No. of $CD34^+$ cells infused ($\times 10^6$/kg)		6.2 (0.14–28.7)
No. of CFU-GM infused ($\times 10^4$/kg)		0.15 (0–6.27)
Graft characteristics (alloSCT)		
No. of cells infused ($\times 10^8$/kg)		6.59
No. of $CD34^+$ cells infused ($\times 10^6$/kg)		10.2
No. of CFU-GM infused ($\times 10^4$/kg)		10.4
Growth factors after SCT		
None	6	
G-CSF	9	

Note. CR, complete remission; autoSCT, autologous stem cell transplantation; alloSCT, allogeneic stem cell transplantation; CFU-GM, colony forming unit—granulocyte-monocyte; G-CSF, granulocyte colony-stimulating factor.

(70 mg/m^2 3 times daily p.o. on days 1–5, total dose 1050 mg/m^2). Three patients affected by AML with t(9;22), hyperleukocytosis (540×10^9/L), and AML M7 with trilineage myelodysplasia underwent UD transplantation with no further chemotherapy courses. Platelets were given if less than 20×10^9/L or bleeding occurred, while packed red cells were given if hemoglobin was lower than 8 g/dL. During the aplastic phase, and if fever occurred, the children received empirical large-spectrum antibiotics. Vancomycin was added if fever persisted for 72 h. Neutrophil recovery was defined as the first of 3 consecutive days of absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/L, while platelet recovery was defined as the first of 3 consecutive days of an

unsupported platelet count $\geq 50 \times 10^9$/L. Toxicity due to anti-neoplastic agents was graded according to Bearman score [19].

Monitoring the Leukemia Response

Following each course of chemotherapy and following transplant, all patients underwent bone marrow examination. The marrow aspirate was examined for morphology, by immunophenotyping and, if possible, by cytogenetic or molecular biology if a cytogenetical or molecular marker was identified at diagnosis. In case of autografting, the harvested marrow was also evaluated.

Bone Marrow Purging

All children who underwent autoSCT received marrow purged in vitro with an active cyclophosphamide derivative. The cell suspension (2×10^7 cells/mL), obtained after centrifugation and resuspension in medium 199 with autologous plasma, was exposed to 4-hydroxazaphosphorine (mafosfamide) at a final concentration of 100 μg/mL (50 μg/1×10^7 cells) for 30 min at 37°C. The cells were then immediately cooled with ice for 2 min and centrifuged at 4°C to block the drug action abruptly. After 2 washes the cells were resuspended in fresh medium and cryopreserved with 10% dimethylsulfoxide (DMSO) until reinfusion [20].

Preparative Regimen

Children who underwent autoSCT were conditioned with total body irradiation (TBI) (200 cGy/dose 2 times daily for 3 days, total dose 1200 cGy) over days −4 to −2, and melphalan (140 mg/m^2 iv) on day −1. On day 0 the thawed stem cell graft was infused through a central line. The unrelated donor recipients received TBI (200 cGy/dose 2 times daily for 3 days; total dose 1200 cGy) on days −7 to −5, thiotepa (10 mg/kg iv) on day −4, cyclophosphamide (60 mg/kg once daily for 2 days iv, total dose 120 mg/kg) on days −3 and −2, and rabbit anti-thymocyte (3.5 mg/kg once daily for 3 days, total dose 10.5 mg/kg) on days −4 to −2 (IMTX, SangStat, Milan, Italy). The MFD recipient received busulfan (4 mg/kg p.o. in divided doses daily for 4 days, total dose 16 mg/kg) on days −7 to −4, cyclophosphamide (60 mg/kg once daily for 2 days iv, total dose 120 mg/kg) on days −3 and −2, and melphalan (140 mg/m^2 iv) on day −1. The graft-versus-host disease (GvHD) prophylaxis was cyclosporine (CyA) 3 mg/kg iv from day −7 for unrelated donor recipients and 3 mg/kg iv from day −1 for the MFD recipient. Short MTX (10 mg/m^2 on day +1, 8 mg/m^2 on days +3 and 8 mg/m^2 on day +6) was also given to unrelated donor recipients. According to the clinical status, CyA was administrated per os as early as possible.

Viruses and Fungal Prophylaxis

From day −5 acyclovir 250 or 500 mg/m^2 was administered 3 times daily iv to all recipients if CMV IgG was negative or positive, respectively. AlloSCT patients received acyclovir 500 mg/m^2 3 times daily iv if the donor or recipient was CMV IgG positive. Lyposomal amphotericin B 1 mg/kg/day iv from day −1 for autologous recipients or MFD recipients or from day −7 for unrelated donor recipient until day +30 and following this itraconazole 6 mg/kg p.o. were given as fungal prophylaxes until day +100. Aerosolized amphotericin B was administrated twice a day from day −5 as a topical fungal prophylaxis until discharge from the BMT unit. To prevent *Pneumocystis carinii* infection aerosolized pentamidine (300 mg or 150 mg according to patient weight) was administered every 3 weeks starting from day −5, followed by trimethoprim sulfamethoxazole until day +180 from transplant or when CD4$^+$ lymphocytes were >200/μL. Azithromycin (10 mg/kg p.o.) was also given 1 day per week as a gram-positive cocci prophylaxis from days +100 to +365. Afterward, an antipneumococcical vaccination was performed.

Engraftment

Myeloid engraftment was defined as the first of 3 consecutive days when the neutrophil count $\geq 0.5 \times 10^9$/L, and platelet engraftment was defined as the first of 3 consecutive days of unsupported platelet count $\geq 50 \times 10^9$/L. Chimerism was evaluated by fluorescent in situ hybridization (FISH) if the recipient and donor were sex mismatched, or by microsatellite molecular biology if the recipient and donor were sex matched. The GvHD grading was performed according to established criteria [21, 22]. The Bearman score was utilized for the preparative regimen toxicity.

Long-Term Side Effects

To evaluate the long-term sequelae of the preparative regimen, starting 6 months from transplantation and with 6-month intervals, all patients underwent endocrinological (serum dosage of TSH, fT4, fT3, LH, FSH, cortisol, ACTH, and somatomedin and physical examination), cardiac (ECG and echocardiogram), and pulmonary function tests (PFTs), including ventilatory capacity, lung volumes, and diffusion capacity for carbon monoxide (DLCO). The patients also had an ophthalmological evaluation to assess the toxicity of the treatment.

Statistical Analysis

Data up to May 2004 were analyzed. Event-free survival (EFS), transplant-related mortality (TRM), relapse rate (RR), and neutrophil and platelet engraftment curves after transplantation (starting point) were calculated by

the Kaplan-Meier method [23] and compared using the log-rank test [24]. In the EFS analysis, both relapse and death in remission due to any cause were considered treatment failures, whereas in the RR analysis, only disease relapse was considered a failure. In the TRM analysis, all deaths not due to leukemia recurrence were considered failures. Results were expressed as a probability (%).

RESULTS

Clinical and Hematological Parameters Following First-Line Therapy

All children achieved first remission following one course. No death or life-threatening complication occurred following induction chemotherapy. Neutrophil reconstitution, following first, second, and third courses, occurred on day 23 (18–36), day 16 (4–20), and day 20 (10–33), respectively. Platelet reconstitution, following the first, second, and third courses, occurred on day 26 (11–39), day 10 (4–23), and day 17 (5–35), respectively. Regimen-related toxicity was moderate and largely restricted to fever. No grade III organ toxicities were documented.

Transplant-Related Toxicities

Transplant-related toxicity was assessed according to Bearman score. Toxicity was moderate with no grade III organ toxicities (Table 2).

Leukemia Response Before SCT

All patients achieved morphological and immunophenotypical complete remission following the first course of chemotherapy. The biological remission varied according to disease for patients in whom a cytogenetic

TABLE 2 Engraftment- and Transplant-Related Toxicities According to Bearman Score Following Autologous and Allogeneic SCT

	autoSCT	alloSCT
PMN $\geq 0.5 \geq 10^9$/L	20 (15–49)	15 (8–22)
PLT $\geq 50 \geq 10^9$/L	51 (22–210)	16 (11–31)
Mucosae	Grade 3 = 0 pts	Grade 3 = 0 pts
Gastrointestinal	Grade 3 = 0 pts	Grade 3 = 0 pts
Kidney	Grade 3 = 0 pts	Grade 3 = 0 pts
Hemorragic	Grade 3 = 0 pts	Grade 3 = 0 pts
Liver	Grade 3 = 0 pts	Grade 3 = 0 pts
Heart	Grade 3 = 0 pts	Grade 3 = 0 pts
CNS	Grade 3 = 0 pts	Grade 3 = 0 pts
Bladder	Grade 3 = 0 pts	Grade 3 = 0 pts
Lung	Grade 3 = 0 pts	Grade 3 = 0 pts
Skin	Grade 3 = 0 pts	Grade 3 = 0 pts

TABLE 3 Monitoring of the Acute Myeloid Leukemia-Specific Marker by Molecular Biology

UPN	Molecular marker	1st course	2nd course	3rd course	BM harvest prepurging	+30 days	+60 days	+90 days	+180 days	+365 days	Last follow-up
206	CBFB/MYH11	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Neg	Neg	Neg +66 months
217	AML1/ETO	Pos	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg +65 months
321	AML1/ETO	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg +30 months
348	AML1/ETO	Pos	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg	Neg +24 months

or molecular marker was found. Three out of 4 patients who had a molecular leukemia marker did not reach biological remission before SCT. Two patients with good risk AML t(8;21) and 1 patient with inv16 underwent autoSCT with an unclarified leukemia specific marker (Table 3). One patient with AML M3v relapsed before autoSCT. This patient underwent salvage chemotherapy with 2 courses of fludarabine, aracytin, and G-CSF (FLAG) and then successfully allografted in a second complete remission with an unrelated cord blood unit.

Engraftment

All patients but one (who failed platelet engraftment and finally relapsed) achieved complete hemopoietic engraftment, and the median time to achieve neutrophil recovery was 18 days (11–55 days).The median time to obtain a self-sustained platelet count more than 50×10^9/L was 43 days (21–210). For purged autoSCT the neutrophil and platelet engraftment was achieved on days +20 and 51, respectively. For alloSCT recipients neutrophil and platelet engraftment was achieved on days +15 and 16, respectively ($p =$ NS for neutrophil and platelet engraftment). Among alloSCT recipients, only UPN 354 developed aGvHD grade III, which required rabbit anti-thymocyte treatment; no patients developed cGvHD.

Patient Outcome

Overall survival was 93% and event-free survival according to the treatment was 80% (Figure 1) with a median follow-up of 40 months (15–80). One patient experienced relapse before SCT on day 206 from diagnosis and was considered only when assessing first-line therapy toxicity. The EFS for alloSCT recipients was 100%, while for autoSCT recipients it was 73% (Figure 2). Three patients (20%) experienced leukemia relapse at a median time of 70 days after autoSCT (range 31–291 days). One of the 3 patients who relapsed died from disease progression in a few days. The remaining 2 patients were treated to obtain a second complete remission and then allografted (one patient received an unrelated cord blood transplantation and the other an UD bone marrow transplantation). Both patients are alive and disease-free at 11 and 35 months following the second graft. In the autoSCT population, the EFS probability, according to autografting before or after

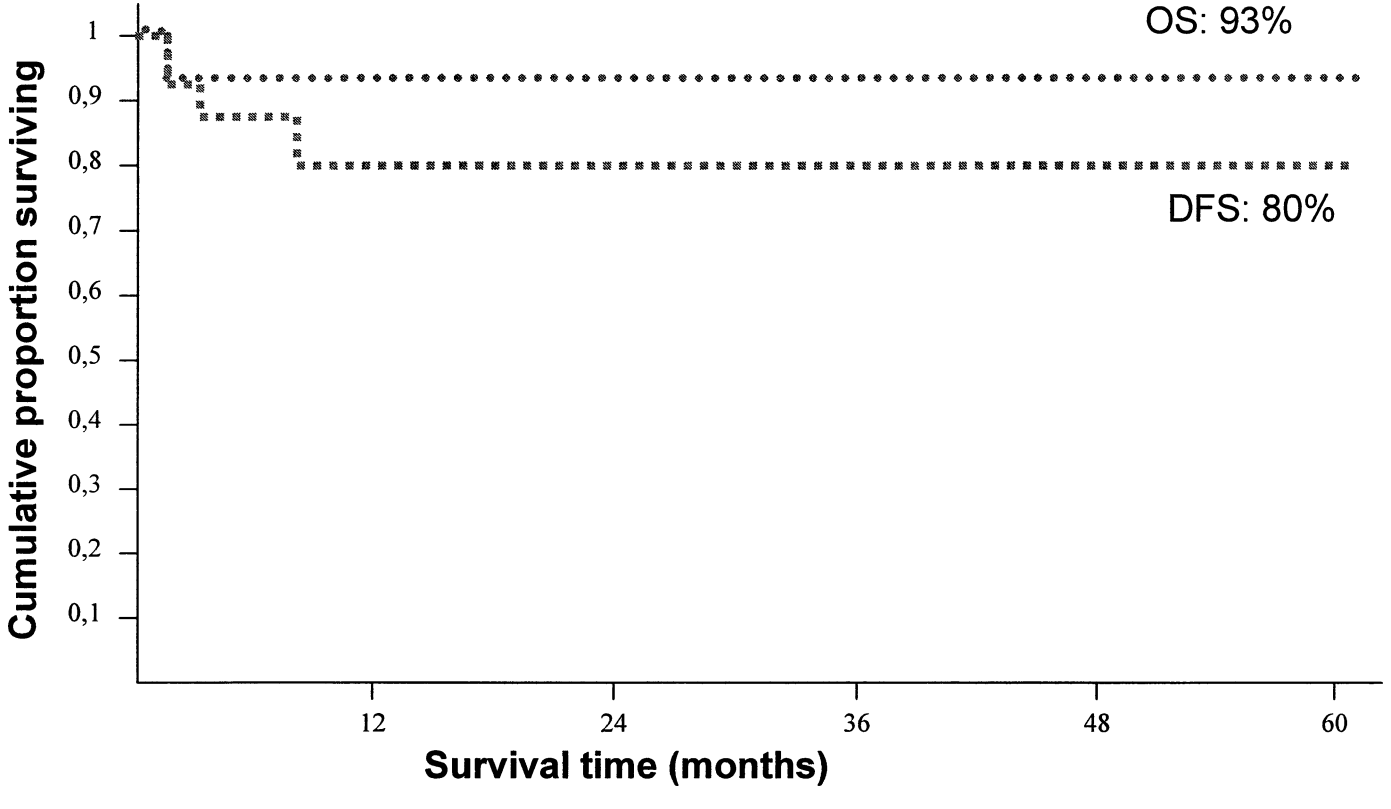

FIGURE 1 Overall and disease-free survival for children with AML who underwent stem cell transplantation in first remission.

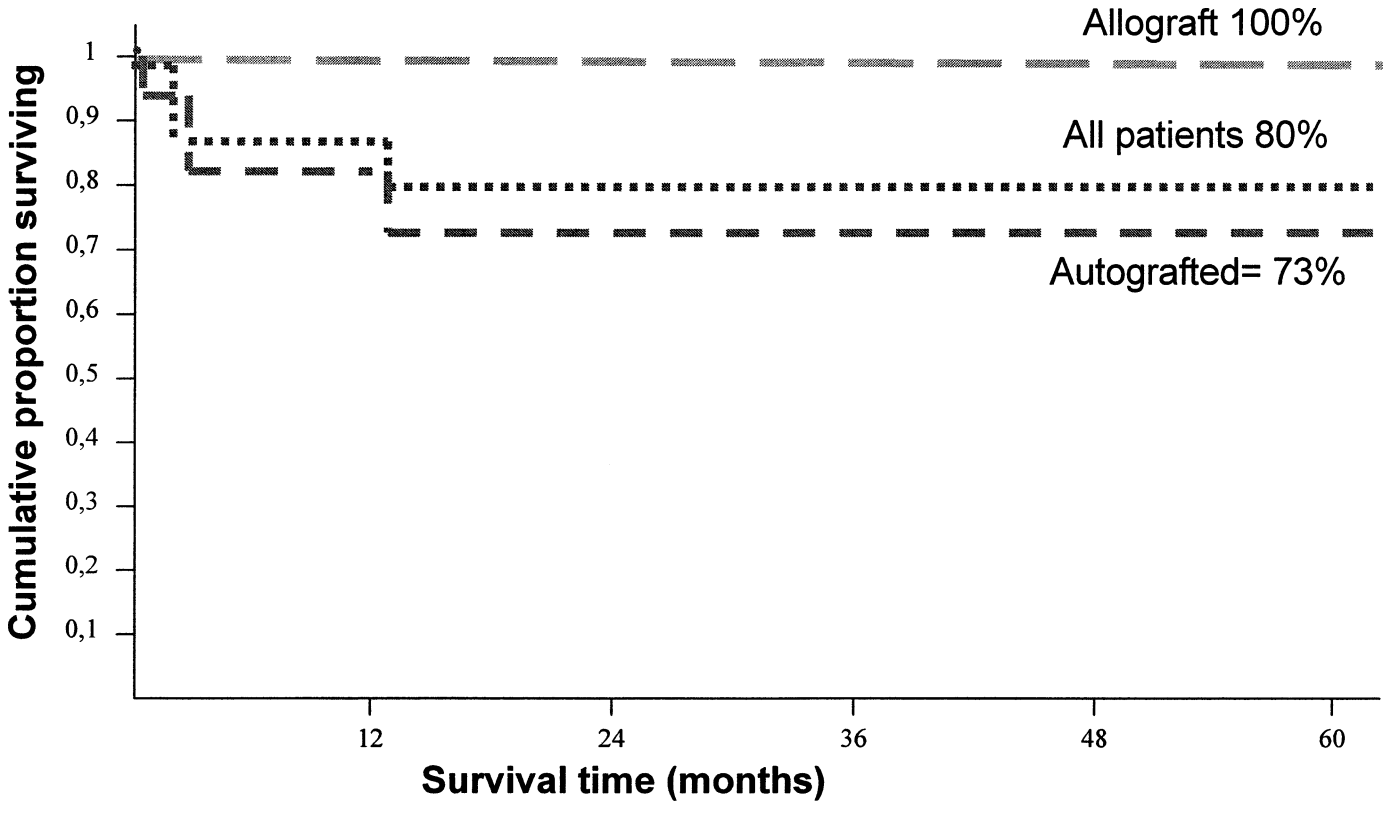

FIGURE 2 Disease-free survival in children who underwent stem cell transplantation according to donor type.

day 90 (90 days being the median time between first remission and harvest), was 67 and 80%, respectively ($p = .2$), while for patients who underwent autografting before or after day 45 (45 days being the median time between harvest and grafting) it was 80 and 66%, respectively ($p = .72$).

Long-Term Side Effects

Eight of the 12 patients, with a follow-up of more than 24 months (median follow up 40 months [range 25–74]), were evaluated for the occurrence of long-term side effects of the transplant procedure. The predominant long-term complication was seen in the endocrinological system (8% hypothyroidism, 17% hypogonadism, and 42% growth impairment). Despite the short follow-up none of the patients developed cataracts, leukoencephalopathy, secondary malignancies, or cardiac and pulmonary deficiency.

DISCUSSION

Aggressive induction protocols have improved the remission rate of patients affected by AML. Adequate postremission therapy remains essential to reduce the risk of leukemia relapse and to obtain a definitive cure for children with AML [7, 25, 26], but low-dose maintenance chemotherapy has not improved outcomes [27]. Although some authors have found that autoSCT offered little overall survival advantage over intensive chemotherapy, especially in children [1], other experiences have shown that SCT represents a milestone in the successful treatment of children with AML [12]. Several randomized studies in children with AML in first remission, which compared intensive chemotherapy with autoSCT, have shown no differences in overall survival [5]. Allogeneic stem cell transplantation is the best choice if a sibling donor is available, because of the lower TRM incidence and higher probability of leukemia-free survival [6]. If no HLA-identical donor is found within the family, the transplant procedures may be conducted using either autologous stem cell rescue or unrelated donor transplantation as alternatives.

In this series, 11 out of 16 patients underwent autoSCT in first remission. To prevent the risk of a post-transplant relapse because of leukemia cells collected with the autologous graft, all grafts in vitro were purged with standard-dose mafosfamide [12, 28]. Despite the high rate of EFS reported, it has to be stressed that the chance to obtain a second complete remission in 2 out of 3 of the relapsed patients was not affected by a previous graft. In particular, the successful use of allogeneic bone marrow or umbilical cord blood transplantation indicates that the toxicity associated to our protocol does not preclude a successful subsequent allograft, which is considered a very high risk procedure for patients who relapsed following autoSCT (TRM 40–85%) [29].

No TRM or relapses occurred with alloSCT, confirming that alloSCT is today the most effective procedure for high-risk AML patients such as t(9;22) or t(1;11). Despite the short follow-up, another encouraging result of this TBI-based preparative regimen is the mild to moderate organ-specific toxicity observed and late side effects are limited to growth impairment, hypothyroidism, and hypogonadism.

In conclusion, despite the low number of patients reported and the short follow-up, our data suggest that induction chemotherapy with high-dose aracytin, etoposide, and idarubicin is a safe and effective approach to obtain complete remission in patients with AML and the consolidation given by SCT produced encouraging results on the feasibility of this approach with very high-risk AML children.

ACKNOWLEDGEMENT

This work was supported by AIRC, Compagniadi San Paolo and ADISCO-Sezione Piemonte.

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