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# Favorable Outcome for Infant Acute Lymphoblastic Leukemia after Hematopoietic Stem Cell Transplantation

*David A. Jacobsohn, Brad Hewlett, Elaine Morgan, William Tse, Reggie E. Duerst, Morris Kletzel*

Northwestern University, The Feinberg School of Medicine, Children's Memorial Hospital, Chicago, Illinois

Correspondence and reprint requests: David A. Jacobsohn, MD, 2300 Children's Plaza, Box 30, Chicago, IL 60614 (e-mail: djacobsohn@childrensmemorial.org).

## ABSTRACT

Infants with acute lymphoblastic leukemia (ALL) have a poor prognosis when treated with standard chemotherapy. A subset of these infants, particularly those with mixed-lineage leukemia (*MLL*) rearrangements, has a high likelihood of relapse. Hematopoietic stem cell transplantation (HSCT) performed early in first remission may improve outcome. We present the results of 16 patients with infant ALL who were treated with HSCT in first remission. Six patients were ≤6 months of age at diagnosis, 11 had an initial white blood cell count of >50 000/μL, and all patients with determinable cytogenetics had a high-risk karyotype [t(4:11) abnormality or other *MLL* rearrangement]. All patients received 150 cGy of total body irradiation for 8 doses (1200 cGy). Fifteen of 16 patients received etoposide at 1000 mg/m² as a continuous infusion over 24 hours and cyclophosphamide at 60 mg/kg/d for 3 days. Eight patients received HSCT from an HLA-identical sibling, and 8, from unrelated cord blood. Twelve (75%) patients remain long-term survivors (median follow-up, 4.7 years). Two patients, 1 of whom had minimal residual disease at HSCT, died after relapse following HSCT. Two patients died of transplant-related causes. The HSCT was well tolerated; 15 patients achieved neutrophil engraftment at a median of 16 days. Acute and chronic graft-versus-host disease were minimal in these patients. These results support the use of HSCT in the treatment of infant ALL, especially when used as consolidation in first remission. The risk of relapse seems to be decreased with this approach. Further work is being performed to determine the long-term effects from this therapy.
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## KEY WORDS

Pediatric  •  Infant ALL  •  Leukemia  •  Stem cell transplant

## INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) for infant acute lymphoblastic leukemia (ALL) remains controversial [1], even though infant ALL seems to be biologically distinct from other leukemias and is usually associated with a poor prognosis. Biologically, these leukemic cells often have 11q23 translocations or myeloid/lymphoid or mixed-lineage leukemia (*MLL*) rearrangements and lack the common acute lymphoblastic leukemia antigen or CD10 antigen on their surface [2,3]. Among those with 11q23 translocations, it seems that infants with a 4:11 trans-

location have an even worse prognosis and usually die of progressive disease [4,5]. Other poor-prognostic markers in addition to the *MLL* gene and a lack of CD10 are age <6 months at diagnosis and a high white blood cell count at diagnosis [6]. Results of 59 infants treated on the ALL-Berlin-Frankfurt-Munich 90 trial, in which all patients received intensive chemotherapy and few received allogeneic HSCT in first complete remission [CR1; only if a matched sibling was available and if ultra-high-risk characteristics were present, such as a t(4:11) abnormality combined with a poor prednisone response], have been published [7]. The 6-year event-free survival (EFS) in this series was 50%. When combining data from ALL-BFM 86 and ALL-BFM 90, the 10-year EFS for 90 infants was 46% [8]. Furthermore, 23 infants with ALL treated

with intensive therapy on the Dana-Farber Cancer Institute consortium protocols had an EFS of 54%. It is interesting to note that of the 7 infants found to have a rearranged *MLL* gene, only 3 remained in CR1 [9]. Clearly, infant ALL is a high-risk subgroup in which even more intense therapy needs to be studied.

Recent reports of myeloablative HSCT for infants with ALL have demonstrated EFS in the 64% to 76% range when HSCT is performed in CR1 [10-12]. Survival is compromised when HSCT is performed beyond CR1 and is dismal when performed in relapse. Our approach at Children's Memorial Hospital has been to perform HSCT in patients with infant ALL early in CR1 whenever possible. In 1999, we reported a small case series of these patients [13]. Given these results, we opted to continue our intensive approach and are now updating our results. We present the results, including transplant-related toxicities and survival, of 16 infants with ALL who underwent HSCT in CR1.

## PATIENTS AND METHODS

### Patients

Beginning in 1992, a standard cytoreduction regimen was used for transplantation in patients with hematologic malignant disease regardless of stem cell source. Prophylaxis of infections and graft-versus-host disease (GVHD) was also comparable. Requirements included complete hematologic remission (histopathologic analysis of bone marrow and cerebrospinal fluid [CSF]) within 2 weeks of HSCT and a Lansky performance status >90. Pretransplantation evaluation of organs also needed to be satisfactory, with bilirubin and creatinine <1.5 times the upper limit of normal and aspartate aminotransferase and alanine aminotransferase both <2.5 times the upper limit of normal. Also, the shortening fraction was required to be >27% on echocardiogram and pulse oximetry had to be >94% in room air with no evidence of dyspnea. Matched related donors were used whenever available; otherwise, infants received an unrelated cord blood transplant (CBT). All transplantation protocols were approved by the Children's Memorial Hospital institutional review board, and parents gave consent for transplantation and associated therapeutic procedures and interventions.

### Treatment

All patients were initially treated with intensive multidrug chemotherapy. Chemotherapy received before transplantation was composed of either Pediatric Oncology Group (POG) 9407 or POG 9107 in all but 1 patient, who was treated on the Children's Cancer Study Group 1961 protocol (Table 1). Most patients quickly went to HSCT after the induction and inten-

**Table 1.** *Characteristics and Outcome of HSCT in 16 Patients with Infant ALL*

| Age (mo) | Sex | WBC (×10⁹/L) | Karyotype* | Prior Chemotherapy† | HSCT Type | Status | HLA | Time (mo)‡ | Conditioning Regimen | GVHD Prophylaxis | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | M | 61 | High risk | POG 9407 | RBMT | CR1 | 6/6 | 7 | TVC | CSA/MTX | CCR |
| 4 | M | 29 | High risk | POG 9107 | RBMT | CR1 | 6/6 | 14 | TVC | CSA/MTX | CCR |
| 6 | M | 400 | High risk | POG 9407 | UCBT | CR1 | 5/6 | 4 | TVC | CSA/MTX/ATG | TRM |
| 7 | F | 4 | Undeterm | POG 9107 | UCBT | CR1 | 5/6 | 10 | TVCT | CSA/MTX/ATG | CCR |
| 15 | F | 546 | High risk | CCG 1961 | UCBT | CR1 | 6/6 | 8 | TVC | CSA/MTX/ATG | CCR |
| 4 | F | 700 | Undeterm | POG 9407 | UCBT | CR1 | 4/6 | 4 | TVCT | CSA/MTX/ATG | TRM |
| 8 | M | 750 | High risk | POG 9407 | UCBT | CR1 | 5/6 | 4 | TAC | CSA/MTX/ATG | CCR |
| 8 | M | 212 | Undeterm | POG 9407 | RPBSCT | CR1 | 6/6 | 3 | TVC | CSA/MTX | CCR |
| 7 | F | 410 | Undeterm | POG 9407 | RBMT | CR1 | 6/6 | 3 | TVC | CSA/MTX | CCR |
| 4 | M | 63 | High risk | POG 9107 | RBMT | CR1 | 6/6 | 3 | TVC | CSA/MTX | CCR |
| 6 | M | 42 | High risk | POG 9107 | RBMT | CR1 | 6/6 | 2 | TVC | CSA/MTX | Rel§ |
| 8 | F | 564 | Undeterm | POG 9407 | UCBT | CR1 | 4/6 | 4 | TVC | CSA/MTX/ATG | CCR |
| 2 | F | 1000 | High risk | POG 9407 | UCBT | CR1/MRD | 4/6 | 5 | TVC | CSA/MTX/ATG | Rel§ |
| 8 | M | 37 | High risk | POG 9407 | RBMT | CR1 | 6/6 | 3 | TVC | CSA/MTX | CCR |
| 9 | M | 360 | High risk | POG 9407 | UCBT | CR1 | 4/6 | 5 | TVC | CSA/MTX/ATG | CCR |
| 8 | M | 36 | High risk | POG 9407 | RBMT | CR1 | 6/6 | 4 | TVC | CSA/MTX | Rel |

RBMT indicates related bone marrow transplant; UCBT, unrelated cord blood transplant; RPBSCT, related peripheral blood stem cell transplant; TVC, TBI/etoposide/cyclophosphamide; MRD, minimum residual disease at transplantation; TVCT, TBI/etoposide/cyclophosphamide/thiotepa; TAC, TBI/cytarabine/cyclophosphamide; TRM, transplant-related mortality; CCG, Children's Cancer Study Group; CCR, continuous complete remission; Rel, relapse; CSA, cyclosporin A; MTX, methotrexate; WBC, white blood cell count; ATG, antithymocyte globulin.

*High risk signifies t(4:11) or *MLL* gene rearrangement. "Undeterm" represents an undeterminable karyotype.

†Most patients completed induction and intensification (POG 9407) or induction and a partial first cycle of postinduction (POG 9107).

‡Time from diagnosis to HSCT.

§Death due to disease progression after single transplantation.

sification phases of chemotherapy and documentation of morphologic CR. Two patients, 1 on POG 9407 and 1 on POG 9107, continued on their protocol through consolidation before they received HSCT.

All patients received 150 cGy of total body irradiation (TBI) for 8 doses (total, 1200 cGy) on days −9, −8, −7, and −6. Fifteen of 16 patients received etoposide 1000 mg/m$^2$ as a continuous infusion on days −5 and −4 and cyclophosphamide 60 mg/kg/d on days −4, −3, and −2, with mesna uroprophylaxis. One patient, enrolled in a POG protocol, received cytarabine 100 mg/kg per dose every 12 hours for 4 days instead of etoposide, and the cyclophosphamide dosing was different (45 mg/kg/d on days −7 and −6). From 1996 to 1999, unrelated CBT recipients (n = 2) also received 1 dose of thiotepa 5 mg/kg on day −5. Patients with negative CSF cytology at all times before HSCT received triple intrathecal therapy (methotrexate, hydrocortisone, and cytarabine) monthly for 6 months after HSCT if <1 year of age. Patients with a history of positive CSF cytology at any time before HSCT received an additional 1200-cGy cranial boost before HSCT. All boys received an additional 400-cGy boost to the testes.

HLA typing was performed by serologic methods for class I antigens with confirmation of class II antigens by molecular analysis for all recipients and matched-sibling donors. Hematopoietic stem cells were not T-cell depleted or purged. Acute GVHD prophylaxis for matched related transplants consisted of cyclosporine (CSA) 1.5 mg/kg per dose intravenously every 12 hours and methotrexate on days 1 (15 mg/m$^2$), 3 (10 mg/m$^2$), and 6 (10 mg/m$^2$). CSA was changed to the oral route once the patient was tolerating oral intake. Unrelated CBT recipients received continuous-infusion CSA (5 mg/kg/d), which was changed to the oral route when they tolerated oral intake; short-course methotrexate, as described previously; and equine antithymocyte globulin (Upjohn, Columbus, OH) 20 mg/kg (premedicated with methylprednisolone 2 mg/kg per dose) on days 1, 3, 5, and 7.

All patients were cared for in positive-pressure laminar flow rooms. Additional supportive care included prophylactic fluconazole 3 to 5 mg/kg/d and oral acyclovir 250 mg/m$^2$ twice daily through day +180. Intravenous immunoglobulin (250 mg/kg) or cytomegalovirus immune globulin (100 mg/kg; in the case of a cytomegalovirus-positive patient or donor) was administered weekly until day +100 and then monthly until 6 months after HSCT. Pentamidine (4 mg/kg intravenously) was given monthly for *Pneumocystis carinii* prophylaxis. Beginning in 1995, all patients received granulocyte colony-stimulating factor 5 to 10 μg/kg starting at day +7. Broad-spectrum antibiotics were started empirically for fever and neutropenia. In general, for clinical grade II or greater acute GVHD, documented histologically, initial treatment was with methylprednisolone 2 mg/kg/d. Progression or no response after 1 week usually led to additional immunosuppressive therapy with agents such as antithymocyte globulin, infliximab, or daclizumab, or switching calcineurin inhibitor. Acute GVHD was graded at least weekly according to the Keystone criteria, and chronic GVHD was defined as limited or extensive [14,15].

Engraftment of neutrophils was defined as achievement of a peripheral neutrophil count >500/μL for 3 consecutive days. Engraftment of platelets was defined as a platelet count >20 000/μL without transfusions for at least the preceding 7 days. Patients were not considered eligible for platelet engraftment if they died and did not have an unsupported platelet count >20 000/μL before day 180. Donor engraftment was determined by polymerase chain reaction assay of genomic DNA for variable number tandem repeat polymorphisms [16] after the year 2000 and by restriction fragment length polymorphism before then.

### Statistical Methods

Patient characteristics, including transplant- and disease-related variables, were described by using medians and frequencies for continuous and categorical variables, respectively. The duration for transplant-related outcomes used July 1, 2005, as the date of last follow-up, and, hence, observations are right-censored. Kaplan-Meier analysis was used to assess relapse, overall survival, and EFS and to obtain estimates of median survival at 1 and 3 years. Days to neutrophil and platelet recovery are described by using medians with ranges. Median neutrophil recovery was calculated for patients whose neutrophils recovered by day 60, and median platelet recovery was calculated for patients whose platelets recovered by day 180. Incidences of acute and chronic GVHD were calculated with confidence intervals (CIs). The data were complete, and 5% was used as the level of significance. Statistical analyses were conducted with Stata 6.0 (StataCorp LP, College Station, TX).

### RESULTS

### Patient Characteristics at Diagnosis and Transplantation

Tables 1 and 2 list the patient characteristics at diagnosis and at transplantation. The median age at transplantation was 11.5 months (range, 6-22 months), and the median time from diagnosis to transplantation was 4 months (range, 2-14 months). The median age at diagnosis for this group of patients was 7 months (range, 2-15 months). All patients except 1 were <1 year of age at diagnosis. The 15-month-old was included in this series given the presence of *MLL* gene rearrangement and a white blood cell count >500 000/μL at diagnosis, which suggested that this

**Table 2.** *Presenting Characteristics and Initial Outcome in 16 Patients with Infant ALL*

| Feature | Data |
| --- | --- |
| **Sex, n (%)** | |
| Male | 10 (63%) |
| Female | 6 (37%) |
| **CD10 antigen, n (%)** | |
| Positive | 3 (19%) |
| Negative | 12 (75%) |
| Unknown | 1 (6%) |
| **Age at diagnosis (mo)** | |
| Median | 7.2 |
| Range | 2-15 |
| **WBC ($\times 10^9$/L)** | |
| Median | 286 |
| Range | 4.3-1000 |
| **Extramedullary disease at diagnosis, n (%)** | |
| CNS | 4 (25%) |
| None | 12 (75%) |
| **Karyotype, n (%)** | |
| t(4:11) | 10 (62%) |
| Other *MLL* | 1 (6%) |
| Undeterminable | 5 (32%) |
| **Outcome, n (%)** | |
| Relapse (death) | 2 (13%) |
| Relapse (alive in CR2) | 1 (6%) |
| TRM | 2 (13%) |
| CCR | 11 (69%) |

WBC indicates white blood cell count; CNS, central nervous system; TRM, transplant-related mortality; CCR, continuous complete remission since transplantation.

child's ALL had infant-type biology. Six patients (38%) were ≤6 months of age at diagnosis, 11 (69%) had an initial white blood cell count >50 000/μL, and all 11 patients with determinable cytogenetics had a high-risk karyotype [a t(4:11) abnormality or other *MLL* gene rearrangement]. Twelve (75%) patients were negative for CD10 antigen expression on their leukemic blasts. Central nervous system disease was present in 4 (25%) patients. At transplantation, all patients were in morphologic CR; however, 1 patient had evidence of persistent minimal residual disease given the presence of a karyotype abnormality.

The transplantation regimen included TBI, cyclophosphamide, and etoposide in all patients except 1, who received cytosine arabinoside instead of etoposide (as part of a POG protocol). Donors were 8 HLA-identical siblings (7 bone marrow and 1 peripheral blood stem cells) and 8 unrelated cord blood donors, of which 4 were 4/6 HLA matched, 3 were 5/6 HLA matched, and 1 was a 6/6 HLA match. The median cell dose infused was $3.6 \times 10^8$ total nucleated cells per kilogram (range, 2.6-4.8) for HLA-identical siblings and $1.2 \times 10^8$ total nucleated cells per kilogram (range, 0.9-2.4) for unrelated CBT. All recipients and donors were cytomegalovirus seronegative.

### Engraftment

Fifteen of the 16 patients achieved a neutrophil count >$0.5 \times 10^8$/L. The median time was 16 days (range, 11-25 days). Fourteen patients achieved an unsupported platelet count >20 000/μL at a median of 36 days (range, 12-82 days). The patients who did not achieve neutrophil engraftment and platelet engraftment received unrelated CBT. Patients who received transplants from a matched sibling donor achieved neutrophil engraftment an average of 6 days faster ($P = .01$) and platelet engraftment an average of 20 days faster ($P = .006$) than those who received transplants from an unrelated cord blood source. There were no cases of graft rejection.

### GVHD and Transplant-Related Toxicities

Three (19%; 95% CI, 4%-45%) of 16 patients developed grade II or III acute GVHD; there were no cases of grade IV acute GVHD (Table 3). These 3 patients all received unrelated CBT. Of 12 evaluable patients, 4 (33%; 95% CI, 9%-65%) developed chronic GVHD. Three cases were limited (from an unrelated CBT), and 1 was extensive (from a matched sibling). There were no cases of veno-occlusive disease and no cases of fungal infection. Eight patients had documented bacteremia with fever, but there were no cases of death due to sepsis. All patients experienced mucositis, which resolved. Long-term sequelae are currently being assessed and will be the subject of a future article. Briefly, no surviving patient has any prohibitive complications. The main observation has been growth impairment.

### Nonrelapse Mortality, Relapse, and Survival

Two patients (12%; 95% CI, 1%-38%) died of nonrelapse causes on days 36 and 42. Both of these patients received unrelated CBT. Causes of death were pulmonary hemorrhage in 1 and respiratory distress syndrome with parainfluenza infection in the other.

Two of 14 evaluable patients relapsed at 48 and 129 days and died of progressive disease. One had received bone marrow from a matched sibling, and 1 had received unrelated CBT. The patient who relapsed at day 48 was the 1 patient with a persistent cytogenetic abnormality at transplantation. Finally, 1 patient who had received a matched-sibling transplant relapsed in the testes and bone marrow 210 days after transplantation. He is currently in remission after salvage induction chemotherapy and will undergo a reduced-intensity transplant.

To summarize, 12 (75%; 95% CI, 47%-92%) of 16 patients survive with a median follow-up of 4.7 years (range, 0.6-12.6 years). The estimated probability of EFS at 1 year is 64% (95% CI, 40%-88%). The estimated overall survival at 1 and 3 years is 75% (95% CI, 47%-92%) (Figure 1). Given the small numbers, no meaningful comparison can be made of survival between matched sibling and unrelated CBT.

**Table 3.** *Toxicities Associated with HSCT*

| Variable | n |
|---|---|
| **Causes of death (n = 4)** | |
|   **Relapse** | 2 |
|   **Transplant-related mortality** | 2 |
|     **Pulmonary hemorrhage** | 1 |
|     **Parainfluenza (RDS)** | 1 |
| **Complications other than TRMs** | |
|   **Acute GVHD** | 10 |
|     **Grade I** | 7 |
|     **Grades II-III** | 3 |
|   **Chronic GVHD** | 4 |
|     **Limited** | 3 |
|     **Extensive** | 1 |
|   **Mucositis** | 16 |
|   **Fever and neutropenia** | 15 |
|   **Documented bacteremia** | 5 |

RDS indicates respiratory distress syndrome; GVHD, graft-versus-host disease.

## DISCUSSION

Controversy remains regarding the most appropriate therapy for infants with ALL. The results of patients treated with chemotherapy alone demonstrate survival in the 20% to 40% range, with particularly dismal survival in patients with *MLL* gene rearrangements, CD10 negativity, or both [17-20]. We describe excellent outcomes with allogeneic HSCT for infant ALL when it is performed as consolidation therapy early and in CR1. Of 16 infants treated with this approach, 12 remain long-term survivors.

Stem cell transplantation may be an attractive option for improving EFS in infants with ALL. In addition to delivery of high doses of chemotherapy, radiotherapy, or both, there is a graft-versus-leukemia effect associated with transplantation that may play a role in infant ALL. However, some of the concerns with HSCT are morbidity and mortality from the preparative regimen and a potential increase in late effects given the delivery of high-dose radiation, chemotherapy, or both at such a young age. Given the rarity of infant ALL, all reports of HSCT for this disease have a small number as their main limitation.

Marco et al. [10] performed HSCT in 26 patients with either lymphoblastic or myeloid infant leukemia. Of the 10 ALL patients, 6 received autologous and 4 allogeneic HSCT. The conditioning regimen for all patients was busulfan based and did not include radiation. Within the ALL patients, there was a 5-year EFS of 56%. Improved survival was noted in patients who received HSCT within 4 months of achieving CR1. Key differences as compared with our study are that more than half of the patients received autologous cells and that the preparative regimen did not contain TBI. Possible concerns with using autologous cells are, obviously, the reinfusion of cells with minimal residual disease and the lack of a graft-versus-leukemia effect from an allogeneic transplant.

Kosaka et al. [11] recently reported their results of 41 infant ALL patients with *MLL* positivity and the absence of CD10 expression. Thirty-eight patients underwent allogeneic HSCT with a 3-year EFS of 54%. Survival was clearly better for those who underwent transplantation in CR1 (64% for 29 patients) as opposed to CR2 or greater (22% for 9 patients). Most patients in this report received unrelated cord blood as their source of stem cells. The conditioning regimen was not uniform (either TBI based or busulfan based), and GVHD prophylaxis also varied. Sanders et al. [12] recently reported on 40 infants, most with *MLL* gene rearrangements, who received allogeneic HSCT. Most patients received a TBI/cyclophosphamide regimen. The main predictor of survival was phase of disease. EFS was 76% for 17 patients in CR1, 45% for 7 in CR2, and 8% for 16 in relapse. Both of these reports suggest that consolidation with transplantation soon after achievement of CR1 improves survival in ALL.

Since the inception of the transplantation program in 1992, it has been the philosophy at Children's Memorial Hospital to submit all patients with infant ALL to HSCT. Selection bias is possible in that some patients may have died before getting to HSCT, although the intent was that all patients with infant ALL would receive HSCT. Our patients represent a very high-risk group (Table 2), consistent with the publications described previously. Most notably, all 11 evaluable patients had an *MLL* gene rearrangement, which seems to be the most important poor-risk factor in these patients.

Our report represents one of the largest cohorts of infants with ALL who have undergone HSCT in CR1 by using a uniform transplantation regimen. Our treatment protocol is different from and more intensive than others [11,12] in that in addition to TBI, the dose of cyclophosphamide is 180 mg/kg (instead of 120 mg/kg), and the regimen also includes etoposide.
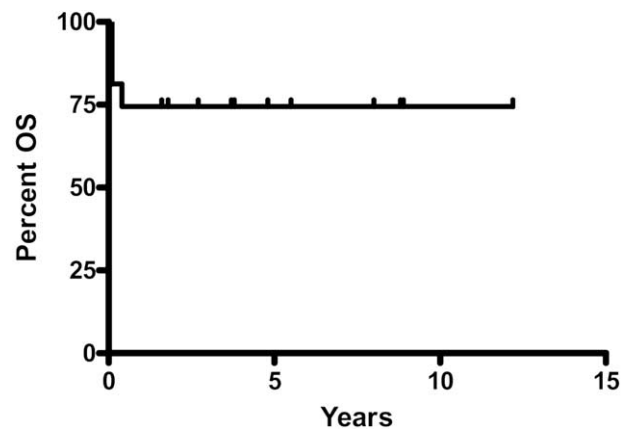


**Figure 1.** Overall survival (OS) in 16 infants with acute lymphoblastic leukemia who underwent hematopoietic stem cell transplantation in morphologic complete remission.

The median time from diagnosis to transplantation was 4 months, which is similar that reported by Sanders et al. [12] and Kosaka et al. [11]. Although we are unable to analyze outcome according to time from diagnosis to transplantation, our results do suggest, especially when viewed in the context of the 2 other studies, that early transplantation in CR1 yields excellent survival in these high-risk patients. Of 16 patients, only 2 relapsed, well within 1 year from transplantation. It is worthwhile to note that although all patients were in a morphologic remission, 1 had definite evidence of minimal residual disease, given the presence of abnormal cytogenetics at transplantation. One may conclude that this patient had chemorefractory disease, and this further underscores the importance of a true remission for transplantation to have a positive effect.

In our experience, engraftment was good, and toxicities were low and very manageable. The excellent engraftment, despite our use of unrelated cord blood in many patients, may be due to the immaturity of the infants' immune systems and the large number of cells per kilogram achieved given their low weight. Furthermore, the rates of severe acute GVHD and extensive chronic GVHD are very low, which may be due not only to the immature immune system, but also to the fact that these patients were not heavily pretreated, which can be associated with increased GVHD. The transplant-related mortality of 12% is also quite favorable, once again highlighting the importance of a good performance before transplantation. Other than these 2 deaths, there were no major complications, such as fungal infection or veno-occlusive disease. The fact that there were no late deaths suggests good immune reconstitution and minimal chronic GVHD.

Clearly, concern exists regarding late sequelae with TBI in infants. Growth impairment is more pronounced in infants who have undergone HSCT with TBI as opposed to chemotherapy-only regimens [21]. Leung et al. [22] recently analyzed a small group of infant ALL survivors and found that if they had been treated with transplantation and radiation, as opposed to chemotherapy only, there was an increased rate of late sequelae. The main late effects his group found were growth impairment, learning impairment, hypothyroidism, and delay of pubertal development. In addition to these late effects, Sanders and colleagues' [12] recent publication also highlights osteopenia and cataracts. It is interesting to note that there were no severe neurocognitive delays in 16 patients who had testing after HSCT. This is in clear contrast to the high rate of neurocognitive delays reported by Leung et al. [22]. Our group is currently in the process of finalizing neuropsychiatric testing in the surviving infants, and these data will form part of a follow-up article documenting late effects in these infants.

The risks and benefits, therefore, need to be clearly weighed before infants with ALL are submitted to HSCT. From our experience and that of a few others, it does seem that infants with very-high-risk leukemia, mainly those with *MLL* gene rearrangements, benefit from high-intensity allogeneic HSCT. Twelve (75%) of our 16 patients are long-term survivors. The benefit seems to be most evident when HSCT is performed in CR1, within months from diagnosis. Certainly work remains to be performed to determine whether the bulk of the effect is from the high-dose therapy or from an allogeneic (graft-versus-leukemia) effect. If an allogeneic effect does seem to play a role in this setting, then some of the long-term toxicities could be avoided by using reduced-intensity conditioning. This area deserves future investigation.

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