No Disadvantage in Outcome of Using Matched Unrelated Donors as Compared With Matched Sibling Donors for Bone Marrow Transplantation in Children With Acute Lymphoblastic Leukemia in Second Remission

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Purpose: **We evaluated the outcome of children with acute lymphoblastic leukemia (ALL) in second remission (2CR), comparing bone marrow transplantation (BMT) using either matched sibling donors or unrelated donors (URDs).**

Patients and Methods: **A total of 65 patients, aged 2 months to 20 years at BMT, with ALL in 2CR underwent allogeneic BMT at seven Nordic centers during 1990 to 1997. Of the first relapses, 85% were in bone marrow; 46% occurred on therapy, and 54%, off therapy. The preparative regimens were cyclophosphamide plus total-body irradiation ± antithymocyte/antilymphocyte globulin, busulfan plus cyclophosphamide ± antithymocyte/antilymphocyte globulin, or cytarabine plus total-body irradiation. Of the allografts, 37 were from HLA-matched siblings and 28 were from URDs.**

Results: **In the sibling versus URD graft recipient groups, the posttransplantation 5-year event-free survival was 39% versus 54% (*P* = .4), the estimated posttransplantation relapse rate was 76% versus 40% (*P* = not significant [NS]), and the toxic death rate was 19% versus 11% (*P* = NS). The incidence of significant (grade 2 to 4) acute graft-versus-host disease (GVHD) was 38% versus 64% (*P* < .05) and was 14% versus 32% (*P* < .10) for severe (grade 3 to 4) acute GVHD; the incidence of chronic GVHD was 26% versus 57% (*P* < .05) and was 13% versus 22% (*P* = NS) for extensive chronic GVHD in the sibling and URD groups.**

Conclusion: **BMT with matched URD allografts offers at least equal survival for children with ALL in 2CR, as compared with allografts from matched sibling donors. URD allografts were not associated with a higher toxic mortality rate, although both acute and chronic GVHD were more frequent with URD. Indications for using matched URD allografts in ALL 2CR can be considered the same as for using matched sibling donors.**

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IN CHILDHOOD ACUTE lymphoblastic leukemia (ALL), modern multiagent chemotherapy results in approximately 70% to 80% prolonged disease-free survival or cure rate.[1-3] The Nordic results give an event-free survival (EFS) rate of 77% for patients diagnosed in the 1990s.[4] Although the outcome for childhood ALL accordingly is good, approximately 25% of children with ALL will experience a relapse, and the long-term prognosis after relapse still remains poor: only approximately 25% to 30% of children who experience relapse achieve a lasting second remission (2CR), according to Nordic studies.[5] Extensive measures are needed to control the disease in relapsed ALL.

Bone marrow transplantation (BMT) has been widely used as salvage therapy for children with ALL in 2CR, particularly after on-therapy or early relapses. According to multiple studies,[6-12] allogeneic BMT with HLA-identical sibling donors offers a better prognosis for children with ALL in 2CR than chemotherapy alone, resulting in 30% to 60% long-term disease-free survival. Nordic results are along the same line, with a 40% EFS for the BMT group as compared with 23% for the chemotherapy group.[13] However, only approximately one fifth of BMT candidates have access to an HLA-identical sibling donor. The use of other family members, usually partially matched, has been limited.

Unrelated donors (URDs) from national and international marrow donor registries have emerged as a valuable source of alternative donors. In the Nordic countries, the use of URDs started in the early 1990s and was based on the

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access to both national and international marrow donor registries. Today at least 50% of all pediatric transplantations in the Nordic countries use URDs.

The initial experience with URDs was not altogether encouraging because of a high toxic mortality rate and a high incidence of severe graft-versus-host disease.[14,15] With genomic typing of HLA class II antigens, more accurate matching has been achieved, which is translating into a better outcome with the use of unrelated donors.[16] In children who have undergone URD transplantation, the transplantation-related mortality rate has been approximately 30% to 50% using nonmanipulated grafts,[17,18] and 20% to 40% with T-cell–depleted grafts.[19-21] The majority of the toxic deaths have been early, ie, within the first 100 days posttransplantation. Emphasis on the toxic mortality involved in URD transplantation has in practice led to different transplantation indications depending on the donor available, with a lower threshold for transplantations using HLA-identical sibling donors.

In the Nordic countries, we had the opportunity to compare BMT using URDs versus HLA-identical sibling donors in a population-based study of uniformly treated pediatric patients with ALL. We studied children with ALL in 2CR, and in the present article we document that BMT using URDs is not inferior to BMT with matched sibling donors in terms of EFS or toxic mortality rate.

PATIENTS AND METHODS

Patients

All children in the five Nordic countries were included who underwent allogeneic BMT for ALL in 2CR during July 1, 1990, through December 31, 1997, and who had either an HLA-identical sibling or an unrelated volunteer register donor. A total of 65 children, 42 male and 23 female, were included. The median follow-up time of the survivors in 2CR was 4.5 years (range, 2 to 9 years) at December 31, 1999. The children who underwent transplantation represent 16.1% of all relapsed ALL patients.

The ALL 2CR status was based on morphologic bone marrow examination. Patients with isolated extramedullary relapse were also included. Those patients who had experienced relapsed in the form of acute myelogenous leukemia or myelodysplastic syndrome were not included.

The patients underwent transplantation at seven Nordic centers, located in four countries (Copenhagen, Denmark, n = 14; Helsinki, Finland, n = 15; Oslo, Norway, n = 6; Huddinge, Sweden, n = 19; Uppsala, Sweden, n = 5; Göteborg, Sweden, n = 3; and Lund, Sweden, n = 3).

Study Groups

Of the patients, 37 had an HLA-identical sibling donor (Allosib group), and 28 had an unrelated volunteer donor (URD group). The male/female distribution was 70%/30% in the Allosib group, and 57%/43% in the URD group. The age at the initial diagnosis was 2 months to 15 years, and at BMT 11 months to 20 years. The age distributions of the study groups were not significantly different, although there were more teenagers in the Allosib group and one infant in the URD group.

Table 1. Period of Initial ALL Diagnosis and the Nordic Society of Pediatric Hematology and Oncology–ALL Risk Category[4] at Initial Diagnosis

	% of Patients		
	Allosib (n = 37)	URD (n = 28)	Total (n = 65)
7/81 to 6/86	—	4	2
7/86 to 12/91	76	25	54
1/92 to 12/97	24	71	45
Standard risk	22	18	20
Intermediate risk	35	29	32
High risk	43	42	43
Infants	—	11	5

Therapy for ALL

All patients were treated uniformly according to common Nordic ALL protocols.[4] During July 1981 to June 1986, there was a common protocol for standard risk (SR) ALL, during July 1986 to December 1991 for both SR and intermediate risk (IR) ALL, and during January 1992 to December 1997 for three risk categories: SR, IR, and high risk (HR). These three risk categories included all ALL patients except for infants and those with B-cell (Burkitt's) ALL. When a common Nordic protocol was not available, mainly Berlin-Frankfurt-Münster protocols were used. The distribution of the study group patients among the three time periods for separate generations of Nordic protocols is indicated in Table 1. Most study patients were diagnosed during the two latest eras, and only one was diagnosed before 1986. The skew of Allosib BMT to the earlier time period and overrepresentation of URD in the later period is most likely due to the development of marrow donor registries and international search and the consequently better access to URDs in the more recent years. The distribution of the study patients among the original risk categories is given in Table 1. Almost half of the patients had initially high-risk ALL.

First ALL Relapse

The first ALL relapse occurred in bone marrow in 85% of the patients, whereas 15% had isolated extramedullary relapses. There were no major differences between the study groups (Table 2).

Of the first relapses, 46% occurred on therapy and 54% occurred off therapy (Table 3). The study groups were quite similar regarding the

Table 2. Site of First ALL Relapse

	Allosib (n = 37)	URD (n = 28)	Total (n = 65)
BM, total	32	23	55 (85%)
BM, isolated	26	16	42
BM, combined	6	7	13
Extramedullary isolated, total	5	5	10 (15%)
CNS	2	4	6
Testis	2	—	2
CNS + testis	—	1	1
Other	1	—	1

Abbreviation: BM, bone marrow.

Table 3. Time of the First ALL Relapse

	% of Patients		
	Allosib (n = 37)	URD (n = 28)	Total (n = 65)
On therapy	43	50	46
Off therapy	57	50	54
On therapy, within 24 months from diagnosis	32	39	35
On therapy or within 6 months of therapy discontinuation	59*	82*	69
After 6 months from therapy discontinuation	41*	18*	31

*$P < .05$ (χ^2 test).

time of the first relapse, except that late relapses were overrepresented in the Allosib group. The induction therapy for relapse mostly used Berlin-Frankfurt-Münster relapse protocols[22] or the Nordic HR-ALL protocol.[4]

Time From Relapse to BMT

The mean (± SD) time from documentation of the first relapse until the BMT was 148 ± 62 days in the Allosib group and 174 ± 72 days in the URD group (P = .12). Accordingly, the donor search and planning of stem-cell collection took 26 days longer in the URD group. Correction was not attempted for this source of potential bias.

The need to wait the additional month for BMT can be translated in how many children experienced relapse during this waiting time. Between days 148 and 174 after first relapse, five children experienced a second relapse (1.3% of all who had entered 2CR). Choosing any month within 130 to 200 days after first relapse, the number of children who experienced relapse per month was in the same order of magnitude.

Preparative Regimens

The preparative regimens varied somewhat by center (Table 4). Total-body irradiation (TBI) was not administered to any child younger than 1 year of age and was administered only to a few at 1 to 3 years of age, whereas most children 4 years of age or older received TBI of 10 to 14 Gy. TBI was given in a single fraction to 27% and in three to seven fractions to 73%. Most children (82%) received cyclophosphamide (Cy) in standard preparative doses. Busulfan (Bu) together with Cy, without TBI, was given to the youngest patients. High-dose cytarabine (HD-ARA-C) with TBI was used at two centers. Antithymocyte globulin (ATG), in varying preparations and dosages, was given to 64% of the URD group patients at three centers for 3 to 5 days pretransplantation.[23] Approximately 60% of the patients received four to six posttransplantation doses of intrathecal methotrexate.

The frequencies of the preparative regimen components given did not differ very much between the Allosib group and URD group: TBI, 68% versus 79%; Cy, 78% versus 86%; Bu, 38% versus 18%; ARA-C, 22% versus 14%. The only major difference was the ATG, which was administered to URD patients only.

Table 4. Preparative Regimens

	No. of Patients		
	Allosib (n = 37)	URD (n = 28)	Total (n = 65)
Cy^1 + TBI	13	2	15
Cy^1 + TBI + ATG	—	16	16
Bu + Cy^1 or Cy^2	12	2	14
Bu + Cy^2 + ATG	—	3	3
ARA-C + TBI	8	4	12
Other combinations*	3	1	4

Abbreviations: Cy^1, cyclophosphamide 60 mg/kg/d × 2 days; Cy^2, cyclophosphamide 50 mg/kg/d × 4 days; Bu, busulfan 4 mg/kg/d × 4 days; ARA-C, cytarabine 3 g/m^2 every 12 hours × 12, total 36 g/m^2; ATG, antithymocyte/antilymphocyte globulin (different preparations and dosages used); TBI, total body irradiation of 10 to 14 Gy.

*Bu + Cy + TBI (n = 2); Cy + ATG (n = 1); vincristine + prednisone + daunorubicin + teniposide + low-dose ARA-C (n = 1).

Allograft Selection and Manipulation

Regarding the sibling donors, both HLA class I and II antigens were determined serologically, and the HLA identity was further confirmed by mixed lymphocyte culture.

Potential URDs were located through a network of available national and international bone marrow donor registries. Less than one half of the URDs came from the national registries (Denmark, n = 2; Finland, n = 4; Norway, n = 1; Sweden, n = 4), and the other half was located through international search (registries in the United Kingdom, Germany, the Netherlands, Switzerland, the United States).

Patients and donors were typed for HLA-A and B using conventional serologic techniques. All recipient-donor pairs were typed for DR locus by high-resolution DNA techniques, which were often also extended to the HLA-A and HLA-B loci. Donor selection was primarily based on matching for HLA-A, B, and DR/DRB1. Mixed lymphocyte cultures were performed with 25% of the URDs.

Of the 28 URDs, 23 were full 6/6 matches regarding the A, B, and DR loci. Five were 5/6 matches (mismatch at A, n = 3; mismatch at B, n = 1; mismatch at DR, n = 1). There were no 4/6 or poorer matches. Ten recipient-donor pairs had mismatch at other loci, most often at the DP locus (DPBI, n = 10; DQA1, n = 1; DQB1, n = 2; C, n = 3).

T-cell depletion was performed in three URD allografts with one-locus mismatch. The other allografts were given to the patients unmanipulated, except for RBC depletion because of major ABO blood group mismatch in nine URD and eight sibling allografts and plasma depletion because of minor ABO mismatch and high isoagglutinin titer in two URD allografts.

Graft-Versus-Host Disease Prophylaxis

The standard graft-versus-host disease prophylaxis for the Allosib group consisted of cyclosporine for 3 to 6 months including the taper for all patients, and a short standard course of methotrexate, mostly four doses, for two thirds of the patients. Two patients received corticosteroids.

In the URD group, all patients received a short course of methotrexate consisting of three to seven doses, as well as cyclosporine for 6 to 18 months, including the taper. In the URD group, 64% had ATG in the preparative regimen. Three patients (11%) had T-cell depletion performed. One patient received corticosteroids.

Supportive Care

The routine antifungal prophylaxis included oral nonabsorbable antimycotics, usually nystatin but occasionally amphotericin B, in most of the seven centers. Systemic antifungal prophylaxis with fluconazole

was used in four centers. Trimethoprim-sulfamethoxazole as *Pneumocystis carinii* prophylaxis was given to all patients. For antiviral prophylaxis, three centers routinely used acyclovir, and one center used ganciclovir. Routine intravenous gamma-globulin prophylaxis (500 mg/kg/wk for 3 months) was used in two centers. One center used ursodiol liver protection as part of a randomized study. Myeloid growth factors, primarily granulocyte colony-stimulating factor (G-CSF), were given early posttransplantation to 42% of the patients (50% in the URD group and 35% in the Allosib group).

All patients were nursed in single, two-door isolation rooms. One center had laminar air flow system, and another had rooms with positive pressure air conditioning. Four centers had special BMT units for adult and pediatric patients combined, and three centers had the BMT unit in connection with the pediatric oncology ward, with pediatric patients only.

Statistical Methods

SPSS software (SPSS Inc, Chicago, IL) was used in the statistical analyses.[24] Life-table analyses were constructed using the Kaplan-Meier method, and the different subgroups were compared for significance by using the log-rank test.[24,25] The significance limit for *P* values was set to .05 in all tests. Probability of deaths in complete response and probability of second relapse were calculated according to the one minus survival method.[24] This implies censoring of patients dying in remission when analyzing the probability for relapse. In the same way, patients who experienced relapse were censored when analyzing the probability for deaths in remission. Events in the analysis of EFS in 2CR ($P - 2$, EFS) included toxic deaths after BMT and relapse. The χ^2 test was used in comparing frequencies of, eg, graft-versus-host disease.

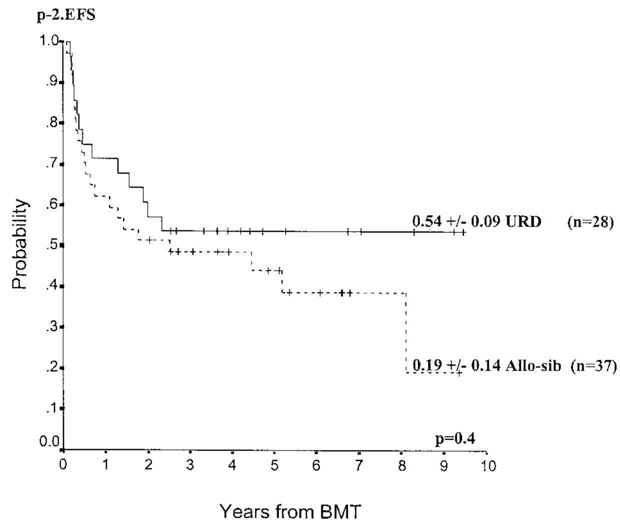

Fig 1. Probability of posttransplantation EFS of the URD and Allosib study groups. The difference is not significant.

RESULTS

Engraftment

Primary engraftment occurred in all transplants in both study groups. One URD group patient engrafted very slowly despite ongoing G-CSF support from day +1 on. He was given pooled leukocyte transfusions to stimulate engraftment[26] on days 26 to 28 and 33 to 35, followed by solid engraftment on day +42. He is alive and well 7 years after BMT.

Later graft failure after primary engraftment was seen in one of 28 patients of the URD group and in two of 37 patients in the Allosib group. The URD group patient achieved an absolute neutrophil count of more than 500×10^6/L on day +23, but the graft faded away. A second graft of $CD34^+$ selected peripheral-blood stem cells from the same donor was given on day +61, but the patient succumbed on day +64 to adenoviral pneumonitis with associated thrombotic microangiopathy (TMA) and acute graft-versus-host disease.

Of the Allosib group patients, the one with late graft failure achieved an absolute neutrophil count of more than 500×10^6/L on day +26 with a low nucleated cell dose of 1.9×10^8/kg. After day +65, the graft function decreased and G-CSF was initiated. The patient died on day +100 of *Aspergillus* infection associated with TMA, while some very weak graft function was still detectable. The other Allosib group patient engrafted on day +12, soon lost her graft, received peripheral-blood stem cells on day +23 from her donor, and achieved durable engraftment on day +28 after peripheral-blood stem-cell transplantation. She is alive and well 3.5 years posttransplantation.

Ultimate Outcome

With a minimum of 2 and median follow-up of 4.5 years, the 5-year EFS was 54% in the URD group and 39% in the Allosib group ($P = .4$) (Fig 1). At 8 years posttransplantation, the EFS of the Allosib group dropped to 19% because of one more late relapse (Fig 1). Total events included 10 relapses and three toxic deaths in the URD group and 15 relapses and seven toxic deaths in the Allosib group. Currently the survivors in 2CR number 15 (54%) in the URD group and 15 (41%) in the Allosib group.

Toxic Mortality

The transplantation-related deaths included three (11%) in the URD group and seven (19%) in the Allosib group (not significant). Nine of these 10 deaths were early, ie, within 100 posttransplantation days. Viral and fungal infections were the most frequent causes of toxic death (Table 5). None died of graft-versus-host disease alone, although it was a contributing factor in several cases. The estimated probability of death in 2CR is illustrated in Fig 2A, with no difference between the study groups.

Table 5. The Causes of Toxic Death

	No. of Patients	
	Allosib (n = 37)	URD (n = 28)
Bacterial infection, *Staphylococcus epidermidis* sepsis	1	
Fungal infection, *Aspergillus*	2	1
Viral infection		
Influenza A		1
Adenovirus	1	1
Respiratory syncytial virus	1	
Viral + fungal combined (pneumonitis, CMV + Candida)	1	
Respiratory failure of unknown origin	1	
Total	7 (19%)	3 (11%)

Graft-Versus-Host Disease

The cumulative incidence of significant (grade 2 to 4) acute graft-versus-host disease was 38% versus 64% ($P < .05$), and the incidence of severe (grade 3 to 4) acute graft-versus-host disease was 14% versus 32% ($P < .10$) in the Allosib and URD groups, respectively. Also, chronic graft-versus-host disease was more frequent in the URD group. The cumulative incidence of chronic graft-versus-host disease in total was 26% versus 57% ($P < .05$), and the incidence of extensive chronic graft-versus-host disease was 13% versus 22% (not significant) in the Allosib and URD groups, respectively. In the URD group patients receiving (n = 18) or not receiving (n = 7) ATG, there was no difference in the incidence or severity of acute graft-versus-host disease.

In the graft-versus-host disease analysis, the three URD group patients with T-cell–depleted grafts were excluded. None of these had significant graft-versus-host disease, and none has stayed in 2CR. Two have died; one of relapse, and one of *Aspergillus* infection. The third one experienced a marrow relapse 2 years posttransplantation.

ALL Posttransplantation Relapses

In the URD group 10 (36%) of 28 children relapsed, compared with 15 (40%) of 37 in the Allosib group (not significant). If the toxic deaths are excluded, the relapse rates were 40% (10 of 25) for the URD group and 50% (15 of 30) for the Allosib group. The estimated probability of relapse after BMT (URD 40% *v* Allosib 76%) was not significantly different (Fig 2B).

Most, but not all, posttransplantation relapses occurred within 2 years of BMT (Fig 2B). Three very late posttransplantation relapses in the Allosib group should be noted. These include a girl who underwent transplantation at 14 years of age who then experienced a posttransplantation relapse in the form of a lymphoblastic tumor of the uterus 8 years posttransplantation, a boy who underwent transplantation at 18 years who then experienced a bone marrow relapse 5 years posttransplantation, and a boy who underwent transplantation at 4 years who experienced an extramedullary relapse in both CNS and testes 4 years posttransplantation.

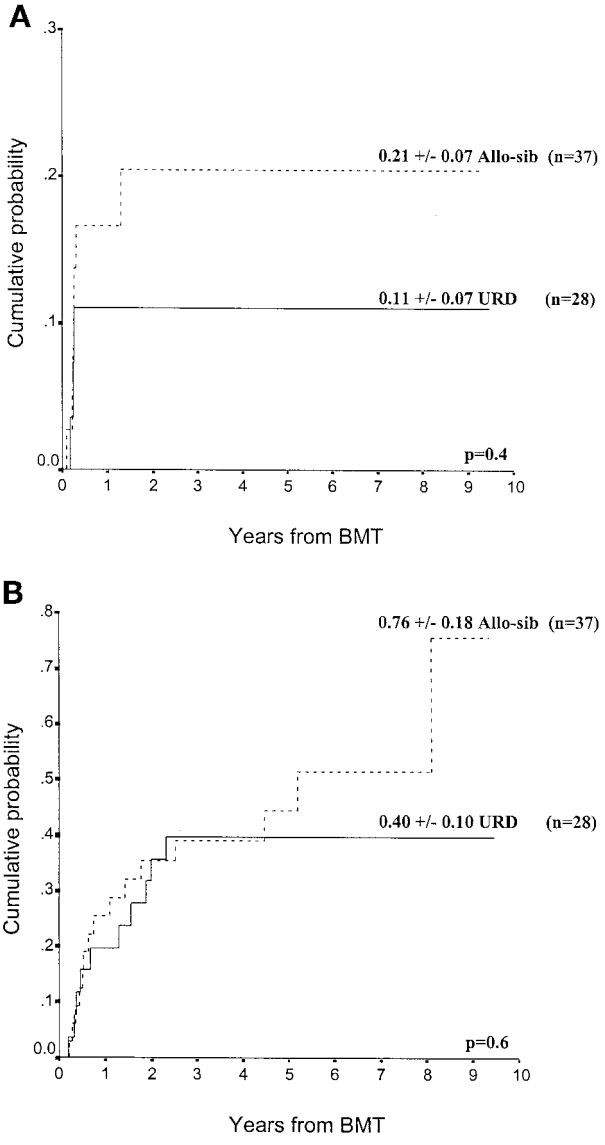

Fig 2. (A) Estimated cumulative probability of death in 2CR, including the posttransplantation toxic deaths of the Allosib group and the URD group; (B) estimated cumulative probability of posttransplantation relapse in the Allosib and URD study groups.

Risk Factors for Posttransplantation Relapse

The duration of the first remission was analyzed by dividing the subjects in three groups: (1) early relapses,

within 0 to 17 months of the initial diagnosis, (2) intermediate relapses, from 18 months after diagnosis until 6 months after discontinuation of therapy, and (3) late relapses, occurring after 6 months from discontinuation of therapy. The group of early relapses differed from the others with a 36% probability of posttransplantation EFS, with all events taking place during the first posttransplantation year. The intermediate and late relapse groups had no difference. This finding was similar regarding the URD and Allosib groups separately and pooled. When using 24 months (first relapse within 24 months of the initial diagnosis) as the cutoff point, the difference faded away; the posttransplantation EFS was 43% for the early ($<$ 24 months) relapses, and 48% for the late ($\geq$ 24 months) relapses (not significant).

The severity/grade of acute graft-versus-host disease was not correlated with survival. When only posttransplantation relapses were concerned, there was a trend to better outcome in those (n = 30) with significant, grade 2 to 4 acute graft-versus-host disease as compared with those with none or grade 1 (n = 35) acute graft-versus-host disease. This difference was seen among the URD recipients only.

Regarding relapses only, those with chronic graft-versus-host disease (limited and extensive combined) seemed to have better EFS during the second and third posttransplantation years; EFS at 2 years posttransplantation was 80% versus 60% for those with versus without chronic graft-versus-host disease, respectively. Four years after BMT, the difference disappeared. This trend was also seen in the Allosib and URD groups separately.

The nucleated cell dose of the graft did not have any significant influence on outcome when analyzed comparing the groups with less than 2.0 versus 2.0 to less than 4.0 versus $\geq$ 4.0 $\times 10^8$ nucleated cells/kg of recipient weight. Those with the highest cell doses (n = 15) had a trend to better outcome.

The initial ALL risk factors including WBC and immunophenotype had no significance as risk factors. The original risk category (SR, IR, HR, infants) correlated with the time of the first relapse; the majority of those with early ($<$ 18 months) relapses were infants or children with HR-ALL.

Quality of Life

The quality of life of the survivors in both study groups was good, as evaluated by the Karnofsky or Lansky score. The patients in the Allosib group tended to have slightly higher scores. Among the surviving patients, the 1-year score of 90 to 100 was given to 75% in the URD group versus 90% in the Allosib group. Regarding the score at the latest follow-up, at 2 to 6 years posttransplantation among the long-term survivors, the score of 90 to 100 was given to 87% in the URD group and 93% in the Allosib group. In the URD group, two patients had a late score of 80, and in the Allosib group, one patient had a decreasing score because of hip problems, scoring 75 at 5 years, after which a late relapse was detected.

DISCUSSION

Our data indicate that in terms of EFS and ultimate outcome, matched unrelated donors bring no disadvantage as compared with HLA-identical sibling donors in children with ALL in 2CR undergoing transplantation. Although the posttransplantation relapse rate was not significantly lower in the URD group, the low toxic mortality rate allowed the URD group to achieve a favorable outcome.

Our joint Nordic study is retrospective, instead of prospective and randomized. The study groups were based on biologic randomization, ie, those who had an HLA-identical sibling donor used that as the first choice. URDs were used as a second choice, and were located for the majority of the candidates. In the early 1990s, randomization between URDs and sibling donors would probably have been considered unethical; in addition, because of the limited number of sibling donors, the number of subjects for a randomized study would never have been sufficient. We are not aware of any randomized study in children with such a design. A case-control study with conventionally treated patients as controls was not feasible either, because suitable controls were too few in number. Furthermore, because the choice between URD transplantation versus conventional chemotherapy was made at the discretion of the doctor in charge, these groups would hardly have been comparable.

There was some heterogeneity in the preparative regimens among the seven centers participating in the study, although it did not constitute major differences between the study groups. What we consider more important is the trend to longer time from relapse to BMT in the URD group patients. This might theoretically have allowed dropping out of bad cases through relapse during ongoing URD search. One more month of waiting within this time frame corresponds in our data to new relapses of 1.3% of all children who had entered 2CR. This potential bias needs to be taken into account while interpreting our results. On the other hand, there were probably in practice more strict indications for URD-BMT as opposed to Allosib BMT, also reflected by the lower proportion of late relapses in the URD group (Table 3), which ended up including more poor-risk patients. The strength of our data lies in the population basis and in the uniformity of the antileukemia therapy given to the patients.

Our toxic mortality rate was 11% in the URD group and 19% in the Allosib group. The toxic mortality of our URD

group seems low as compared with 53% in Minneapolis,[18] 40% in Wisconsin,[19] 28% in Seattle,[17] 25% at St Jude,[21] or 20% in Bristol.[20] Viral infections were frequent causes of death (Table 5), although our grafts were in general not T-cell–depleted. The differences in transplantation-related mortality certainly depend on many different factors, including disease stage and patient selection.

Expectedly, the incidence and severity of both acute and chronic graft-versus-host disease were higher in the URD group than in the Allosib group. Our 64% rate of significant and 32% rate of severe acute graft-versus-host disease in our URD group patients are comparable to those reported from Seattle (90% and 50%, respectively)[17] and from Minneapolis (58% and 29%, respectively),[18] where the data also concern non–T-cell–depleted grafts. On the other hand, centers using T-cell depletion[19-21] report much lower figures: 13% to 33% for grade 2 to 4 (significant), and 6% to 8% for grade 3 to 4 (severe) acute graft-versus-host disease. Reports from unrelated umbilical cord blood transplantations give intermediate figures: a 21% to 50% incidence of significant and 11% to 14% incidence of severe acute graft-versus-host disease.[27-29] Some chronic graft-versus-host disease is generally accepted with the assumed association with a better graft-versus-leukemia effect, unless it is counterbalanced with an increasing toxic mortality rate or poor quality of life. In our series, the toxic mortality rate was quite acceptable and the long-term quality of life was good.

The posttransplantation relapse rates in our study, 36% in the URD group and 40% in the Allosib group, were not significantly different. The study from St Jude comparing URD and sibling transplantation in children with leukemia (ALL, acute myelogenous leukemia, and chronic myelocytic leukemia) also had similar relapse rates, 27% for URD and 23% for sibling transplantation.[21] In contrast, a single-institution study of Danish children with ALL revealed a higher relapse rate for family donor graft recipients (65%) as opposed to URD (11%). The Danish study included children with ALL at different stages, including both first remission, 2CR, and beyond 2CR.[30] Studies reporting URD only give relapse rates of 10% to 20% using nondepleted[17,18] and 23% to 28% using T-cell–depleted grafts.[19-21] Relapse rates in the unrelated cord blood studies are in the same range,[27,29] although the ALL patient numbers are very small. Studies reporting BMT with HLA-matched sibling donors give relapse rates of 19% to 39%,[9-12] which seem higher than with URDs, at least in terms of non–T-cell–depleted grafts. The difference has been attributed to a lower graft-versus-leukemia effect with matched sibling donors as opposed to URDs. In the present study, the three very late relapses at 4, 5, and 8 years posttransplantation, occurring in the Allosib group only, support this view and are contradictory to the common experience that most relapses occur within 2 years posttransplantation.

The ultimate outcome after BMT for children with ALL in 2CR results from a combination of the toxic mortality rate and the posttransplantation relapse rate. Our 5-year EFS of 54% in the URD group compares favorably, although not significantly better, with international data: a 2-year or 3-year EFS of 30% from Minneapolis[18] and 47% from Seattle[17] using non–T-cell–depleted grafts, and 44% from Wisconsin[19] or 53% from Bristol[20] using T-cell depletion. The 5-year EFS of our Allosib group was 41% (Fig 1), which is well within the international range of 37% to 62%.[9-11,31,32] Concerning early marrow relapses, ie, within 24 months of the ALL diagnosis, the lowest reported survival of 3% after BMT using matched sibling donors comes from the United Kingdom,[9] the best one being 48% from the Memorial Sloan-Kettering Cancer Center,[11] compared with 43% in the present data.

In comparing matched sibling donors and unrelated donors, neither our data of childhood ALL in 2CR, nor the data of Hongeng et al[21] from St Jude regarding a combination of different childhood leukemias and risk categories reveal any significant difference in EFS. In studies reporting sibling transplantation only or URD transplantation only, the EFS falls in general within the same range of approximately 40% to 60%, not supporting any major difference in outcome by using these different donor sources. Accordingly, the same indications for BMT could be applied regarding both HLA-identical sibling donors and matched URDs. For children without access to an HLA-identical sibling donor, URDs certainly offer an option superior to autologous BMT, with reported EFS rates of approximately 35%.[9,33]

In the analysis of risk factors for posttransplantation relapse, we found that a shorter than 18 months duration of the first remission was important. This patient group included primarily those with high-risk ALL or infant ALL. The role of other important initial ALL risk factors, WBC and immunophenotype, had lost their prognostic significance at the first relapse. In this material, the nucleated cell dose was not significant. The presence or severity of acute graft-versus-host disease were not significant, but the presence of chronic graft-versus-host disease seemed to be associated with better survival during the first 2 to 3 posttransplantation years, supporting the role of the graft-versus-leukemia effect. This trend faded away with time, however.

Currently, emerging tools in the evaluation of the posttransplantation relapse risk include individual monitoring of

BLOOD, 1 NOVEMBER 2001 • VOLUME 98, NUMBER 12 For personal use only.

minimal residual disease status by techniques such as polymerase chain reaction, fluorescent-activated cell sorter, and fluorescent in situ hybridization. Major implications lie in the induction of the graft-versus-leukemia effect[34] and in the development of therapies using donor cells.[35]

In conclusion, BMT with matched unrelated volunteer donors offers at least equally good outcome for children with ALL in 2CR as BMT using HLA-identical sibling donors. Although both acute and chronic graft-versus-host disease were more frequent with URDs, the toxic mortality rate and the posttransplantation relapse rate were not inferior to those with sibling donors. Indications for using matched URD allografts can be considered the same as for using matched sibling donors in children with ALL.

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