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Allogeneic bone marrow transplantation in second remission of childhood acute lymphoblastic leukemia: a population-based case control study from the Nordic countries

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Summary:

This study compares allogeneic BMT with conventional chemotherapy for childhood ALL in second remission. Seventy-five children were transplanted between July 1981 and December 1995. For each patient two control patients matching the following criteria were selected from the Nordic database of ALL: (1) time of diagnosis, (2) T *vs* non-T ALL, (3) site of relapse, (4) initial risk group, (5) sex and (6) relapse $<$ or $\geqslant$6 months after cessation of therapy. The minimal time of follow-up was 24 months. Mortality rate in CR2, leukemic relapse rate and the proportion in continued second remission were 16/75 (21%), 22/75 (29%) and 37/75 (50%), respectively. *P*2.-EFS for the BMT group was significantly better than that for the control group (0.40 *vs* 0.23, $P = 0.02$). Children transplanted for bone marrow relapses in particular had a higher *P*2.-EFS (0.35 *vs* 0.15 for the control group, $P < 0.01$). Also, children grafted for early BM relapses had a higher *P*2.-EFS (0.32 *vs* 0.11 for the control group $P = 0.01$). The outcome was similar when children were transplanted after early or late relapse. Also, there was no difference in outcome between the BMT and the chemotherapy group for children with late relapses. We conclude that allogeneic BMT with an HLA-identical sibling donor or other family donor should be performed in children relapsing in bone marrow during therapy or within 6 months of discontinuing therapy.

Keywords: allogeneic; BMT; second remission; ALL; childhood

Today, modern multiagent chemotherapy is expected to cure 70–80% of children with acute lymphoblastic leukemia. However about 25–40% of children with ALL will still experience recurrent disease after which the chance of long-term survival and cure is considerably reduced.[1]

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A second remission will be induced in about 80% of patients but a new relapse will occur in 50–90% of children depending on site and time point of the first relapse.[2–7]

There is no general agreement regarding post-relapse therapy although allogeneic bone marrow transplantation (BMT) is commonly recommended.[8,9] This treatment has resulted in long-term disease-free survival of 30–60% of transplanted children in a number of smaller single-institution, non-randomised studies.[10–17] The impact of BMT has, however, not been studied in strictly randomised studies comparing BMT with continuous chemotherapy. Because BMT is generally considered superior to chemotherapy after first relapse of childhood ALL and the chance of finding an HLA-identical sibling donor is small[18] randomised studies will be very difficult to conduct. Therefore, case–control studies with controls carefully matched for the important prognostic variables may form a basis for setting up guidelines for BMT in patients with relapsed ALL.

We have employed the matched case–control method in a previous study of BMT for very high risk ALL in first remission.[19]

The purpose of the present study was to evaluate the outcome of childhood ALL in second remission after BMT with sibling or family donors as compared with conventional chemotherapy in a retrospective case control study utilizing the population-based Nordic ALL database.

Patients and methods

Since July 1981 the five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) have conducted a prospective population-based registration of all cases of acute leukemia in children. All patients are followed up annually and no patient has been lost to follow-up. Patients from the database were eligible for this study if: (1) ALL was diagnosed between 1 July 1981 and 1 January 1992, (2) the first relapse occurred before 1 October 1994 and (3) BMT from a matched family donor was performed before 1 January 1995. The last follow-up was in January 1997.

From July 1981 to December 1991 1668 cases of non-B ALL were diagnosed in children between 1 and 15 years of age. In the study period 562 relapses occurred (441 were

early relapses occurring during or within 6 months of discontinuing maintenance therapy and 121 were late relapses). Seventy-five children were allografted in CR2 with a family donor at a median of 5 months after relapse (60 children after an early and 15 children after a late relapse), 14 children received an unrelated bone marrow transplant, and 44 children were autografted. The remainder of the children (ie 429 patients) were treated with second-line chemotherapy; from this group of patients we selected the control group (150 children) after exclusion of: (1) patients who were treated with any form of bone marrow transplantation and (2) patients with a duration of the second remission of <2 months. For each BMT case, two control children in CR2 treated with chemotherapy were selected who matched with the following criteria: (1) time of diagnosis, (2) T *vs* non-T ALL, (3) site of relapse, (4) initial risk group, (5) sex and (6) relapse $<$ or $\geqslant 6$ months after cessation of therapy. The duration of the second remission had to be at least equal to the time from relapse to BMT, plus 2 additional months.

Treatment

From July 1981 to June 1986: Remission in the standard risk group (SR: defined as age $\geqslant 2$ and <10 years, total white blood cell count $<20 \times 10^9$/l and no high risk criteria) was induced with prednisolone (Pred), vincristine (Vcr). In Finland and Sweden doxorubicin was added to the induction regimen, whereas Denmark, Iceland and Norway gave l-asparaginase for 10 days immediately after induced remission. In July 1984, l-asparaginase was added to the induction treatment in Finland and Sweden. CNS prophylaxis was performed with three 24-h infusions of methotrexate of 0.5 or (after July 1984) 1.0 g/m^2 and eight intrathecal doses of methotrexate (MTX). No cranial irrradiation was given. Maintenance therapy included daily oral 6-mercaptopurine and weekly oral methotrexate for 36 months after diagnosis. No reinduction was given. In a Norwegian pilot study intravenous MTX infusions and Vcr were added to the maintenance therapy during the first year of treatment.

In most of the children belonging to the intermediate risk group (IR: defined as age $\geqslant 1$ and <2 years or $\geqslant 10$ years or total white blood cell count $\geqslant 20$ and $<50 \times 10^9$/l and no high risk criteria. From July 1984 children with WBC $10–20 \times 10^9$/l were 'upgraded' from the SR to the IR group[20]) the induction and consolidation therapy was as in the SR group. However, the maintenance treatment with oral 6-Mp and MTX was intensified with pulses of Pred and Vcr with or without doxorubicin or MTX during the first year. The total duration of therapy was 2 years.

Children with high risk criteria (HR: defined as WBC $\geqslant 50$ or T-ALL, or mediastinal mass or CNS leukemia at diagnosis or t(9;22) or t(4;11)) were treated in many different ways using primarily the intensive regimens of Riehm *et al*[21] and Wollner *et al*[22] for a total of 2 years.

From July 1986 to December 1991: Remission in the SR group was induced and consolidated in the same way as during period I, all children receiving Vcr, Pred and doxorubicin followed by 10 days of l-asparaginase. Maintenance therapy included i.v. infusions of MTX and Vcr.

The IR groups were additionally given early intensification with pulses of cyclophosphamide and cytosine arabinoside and late intensification with 4 weeks reinduction therapy consisting of oral dexamethazone, Vcr, doxorubicin and l-asparaginase. In one group (Denmark, Finland and Sweden) 12–18 Gy cranial irradiation was given before oral maintenance therapy with 6-Mp and MTX, whereas the other group (Iceland and Norway) gave pulses of high-dose MTX (HD-Mtx) and/or high-dose cytosine arabinoside (HD-Ara-C) before oral maintenance therapy with 6-Mp and MTX with repeated pulses of HD-MTX and Vcr and Pred during the first year. The HR-children in period II were treated with intensive national protocols in all five countries. In Denmark, Finland, Iceland and Sweden treatment was more or less adapted to the German HR-protocol implying cranial irradiation. In Norway two different regimens were used with HD-MTX without doxorubicin and HD-MTX, HD-Ara-C with doxorubicin, both regimens without cranial irradiation. In addition, some patients were treated with bone marrow transplantation in first remission.[19]

Reinduction therapy

No uniform relapse protocol was employed in the study period. Reinduction therapy was mostly based on the BFM relapse protocols[23] or other intensive chemotherapy protocols. There was no difference in the initial treatment between children who later underwent BMT and those who received chemotherapy only.

Bone marrow transplant procedure

The 75 patients treated with BMT in CR2 were transplanted 2–25 (median 5) months after relapse. Only five patients were transplanted later than 8 months after relapse. Ninety percent of the BMTs were performed in three centers (Helsinki, Finland; Huddinge, Sweden and Copenhagen, Denmark).

The conditioning regimen consisted of total body irradiation (TBI) of 10–11.5 GY given in four daily fractions plus cyclophosphamide (CY) 60 mg/kg/day on 2 consecutive days (61 patients), busulphan 16 mg/kg in 16 doses and CY 60 mg/kg/day on 2 consecutive days (10 patients) or other TBI containing regimens (four patients). The BMT donor was an HLA-identical sibling in 57 cases, a parent in 12 cases and another relative in six cases. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporin A (CyA) in 39 patients, MTX + CyA in 28 patients, MTX only in six patients and other regimens in two patients.[24–26]

Statistical methods

In the matching procedure each BMT patient was stratified according to the criteria defined above. For each transplanted patient two control patients fulfilling the same stratification criteria were randomly allocated from the group of children with ALL in second remission who had not been transplanted. The procedure was repeated for each patient until 150 control patients had been selected. Statistical analyses were performed with the Statistical Package

for Social Science (SPSS).[27] Life tables were constructed according to the methods of Kaplan and Meier. The distribution of *P*2.-EFS (probability of second event-free survival) for the different subgroups was compared with the log rank test. The limit of significance was $P = 0.05$ in all analyses.

Results

Table 1 shows that it was possible from the Nordic ALL data base to randomly assign a control group of children in second remission which corresponded closely to the BMT group with respect to the important prognostic parameters such as length of first remission, site of first relapse, T-ALL, time period of treatment, and sex.

The treatment-related toxic death rate (acute mortality) within 6 months of the BMT procedure was 14/75 (19%), the main causes being pulmonary infections, sepsis, acute GVHD and bleeding. In addition there were two late deaths from sepsis and chronic GVHD, both in continued second remission, among the BMT patients. There was no difference in toxic death rate between the first and the second part of the study period, but there were only three toxic deaths during the last 4 years of the study period. Five of 18 (28%) patients transplanted with marrow from family donors other than HLA-matched siblings died of BMT-related toxicity, whereas the toxic death rate was 16% when a fully matched sibling was the donor; this difference was not significant.

Table 1 Distribution of selection criteria in the BMT patients and in the matched controls

	Allo BMT in CR2	*Matched controls*
Time of first relapse		
During therapy +6 months	60	120
>6 months after Tx	15	30
Site of first relapse		
Bone marrow (BM±)	63	126
CNS isolated	7	14
Testes isolated	5	10
Treatment period		
7/81–6/86	42	84
7/86–12/91	33	66
Sex		
Girls	27	54
Boys	48	96
Immunophenotype		
Non-T, non-B, biphenotypic and precursor-B ALL	67	137
T ALL	2	4
Unknown	6	9
Age		
2–<6 years	40	80
6–<10 years	21	42
⩾10 years	14	28
Initial risk group		
SR/IR	58	116
High risk	17	34
WBC at diagnosis		
<50	64	123
50–<100	4	10
⩾100	7	17
Mean time of first remission (months)	26.9	27.7

The leukemic relapse rate and the proportion in continued second remission were 22/75 (29%) and 37/75 (50%), respectively. The 22 relapses occurred at a median of 9 months post-transplant, in 19 cases <14 months post-transplant and one isolated CNS relapse 41 months post-transplant. Twenty-one of 22 relapsed children have died of underlying disease apart from one boy with an isolated testicular relapse occurring 12 months after BMT in 1987.

The 75 transplanted patients differed significantly from their controls in probability of remaining in second remission (*P*2.-EFS) (Figure 1) (0.40 *vs* 0.23, $P = 0.02$). The *P*2.-EFS for the BMT group was not different between the first and the second half of the study period, but there was a trend for the control group to do better during the first part of the study.

Children transplanted for bone marrow relapses had a significantly higher probability of staying in second CR compared with the control group (Figure 2) (0.35 *vs* 0.15, $P < 0.01$), whereas there was no difference in children with extramedullary relapses.

Children transplanted for early bone marrow relapse (<6 months after discontinuation of initial therapy) had a higher *P*2.-EFS compared with the chemotherapy group (0.32 *vs* 0.11, $P = 0.01$) (Figure 3a), while there was no difference in outcome between BMT and controls whose first bone marrow relapse occurred later than 6 months after discontinuation of maintenance therapy (0.42 *vs* 0.29, NS, Figure 3b).

In the BMT group ($n = 75$) there was no difference in *P*2.-EFS between early and late relapses in the BMT group (0.41 *vs* 0.40).

For girls the *P*2.-EFS was higher after BMT compared

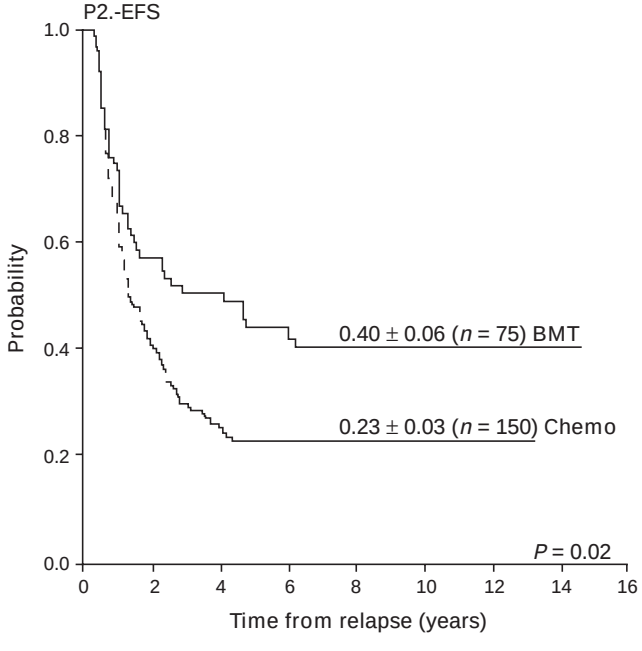

Figure 1 Overall results. Probability of second event-free survival (*P*2.-EFS) for BMT-treated children compared with controls (= children treated with chemotherapy only).

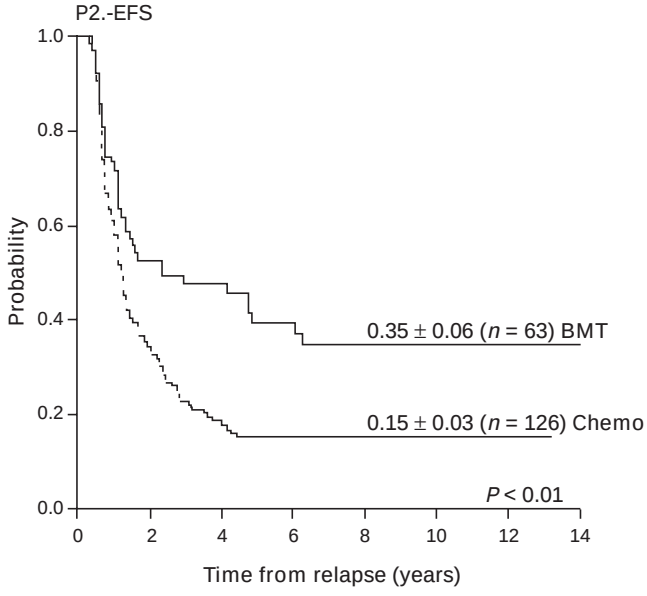

Figure 2 Probability of second event-free survival (*P*2.-EFS) for 63 children with bone marrow relapse compared with 126 controls.

with controls (0.59 *vs* 0.28, $P = 0.02$), and also the outcome for girls was better than for boys after BMT although the difference was not significant (0.59 *vs* 0.30, $P = 0.06$, NS) (data not shown).

The relapse rate was 50% (11/22) in children whose GVHD prophylaxis consisted of both CyA and methotrexate, whereas it was 31% (11/35) in children treated with CyA only. This difference was not statistically significant, however.

The initial white blood cell count, age, initial risk group classification or high-dose therapy before BMT had no influence on outcome after relapse in this study.

Discussion

Randomised studies between BMT and chemotherapy in the treatment of relapsed acute lymphoblastic leukemia are difficult to perform, and have not been published in children. There are many unsolved questions as to the indications for BMT in this group of children.[8,9,15] Suitable HLA-matched sibling donors may only be found in about 20% of possible cases, some of which may never proceed to transplantation.[18] Therefore reports regarding the results of BMT in second remission of ALL originate largely in registry data,[14] data from cooperative groups[4,13] or small single-institution reports, often with no control group[3,10–12] or with a historical control group. There are two recent reports of case–control studies comparing chemotherapy with BMT.[17,28]

This population-based study was able to define a carefully matched control group with respect to all known prognostic factors in relapsed ALL. No uniform protocol was used for relapse therapy. The fact that selection of control patients was also based on the time period of first-line therapy ensured that the pre-transplant chemotherapy was comparable in the two study groups.

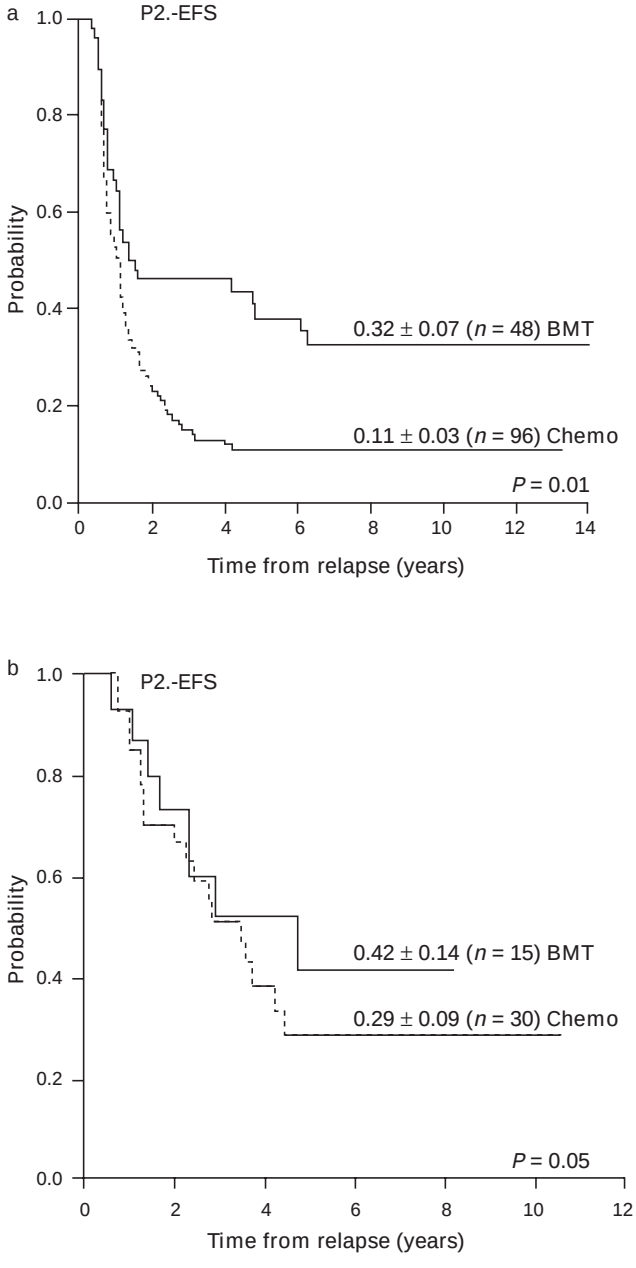

Figure 3 Probability of second event-free survival (*P*2.-EFS) for early (during or within 6 months after discontinuing initial therapy) and late bone marrow relapses (⩾6 months after discontinuation of therapy) compared with controls.

Our results indicate that there is an overall benefit of allogeneic bone marrow transplantation in children with ALL after first relapse when transplanted children were compared with a closely matched control group (Figure 1). Especially in children with early bone marrow relapse, BMT seems to give a significantly better survival compared to the group of children receiving chemotherapy only. Similar results were also reported by the German BFM group[13] comparing transplanted children with all other relapsed patients. However, the duration of first remission, site of first relapse and sex were not taken into account in the non-transplanted patients. Another report from the BFM

group indicated that in children with relapses occurring between 18 months from diagnosis to 6 months after discontinuation of maintenance treatment the outcome was better after BMT as compared with a control group which had been in second remission for the corresponding time after relapse.[17] Our results did not allow any conclusions regarding the benefit of BMT in children with isolated extramedullary relapses or initial T-ALL because of small numbers.

In a selected group of children transplanted in second remission Brochstein *et al*[10] also found a tendency for a better outcome when the first remission was longer than 24 months, in contrast to the report by Kersey *et al*.[11]

Children with early bone marrow relapses have a particularly poor prognosis when treated with chemotherapy alone, with a chance of long-term second remission of 2–20%.[3–5,7] In this group of children allogeneic BMT seems indicated as is also shown in the present study. Since GVHD is presumed to contribute to a better relapse-free survival in these patients,[29–31] BMT using unrelated donors may also be considered in children with early bone marrow relapse.

In children with late relapse the *P*2.-EFS for chemotherapy is 30–50% depending on the site of relapse and first- and second-line therapy.[2,4,6,7] In the present study only 15 children with late relapses were transplanted, and we were not able to show any benefit from BMT for children with late relapse compared with chemotherapy only. However, there was a trend for BMT being slightly better. In our opinion this was not due to selection bias among these patients since the median time from diagnosis to BMT was 46 months and the median time from diagnosis to inclusion as a control patient in the chemotherapy group was 47.5 months. Other reports have also failed to show any better prognosis for late relapses treated with BMT compared with chemotherapy.[3,13,28] Considering the observed early toxic death rate (TDR) of 18% in the group transplanted with fully matched sibling donor marrow and the possible long-term sequelae of the TBI containing conditioning regimen, the indication for BMT in children with late relapses using a matched sibling donor remains relative and related to the TDR, which has declined considerably during the past 3–4 years. When choosing not to perform BMT in second remission of ALL after late relapse one should also consider the lower chance of inducing a third remission, the increased risk of acute morbidity and mortality and of leukemic relapse after BMT if postponed until the third remission.

All the children in this report have been followed up for at least 2 years post-transplant. Since 19/22 relapses post-BMT occurred within 14 months of the procedure (median 9 months) the risk of further relapses in this study is considered small, and further events may largely be caused by complications of chronic GVHD, which was not the focus of the present study. In conclusion, the present study, in accordance with others, indicates that allogeneic BMT with an HLA-identical sibling or other family donor should be performed in children relapsing in the bone marrow during therapy or within 6 months of discontinuing therapy. The poor outlook of these patients when treated with chemotherapy may also justify BMT with an unrelated donor although this procedure is still regarded as experimental.

For relapses occurring later than 6–12 months after elective discontinuation of maintenance therapy, the present study failed to demonstrate any significant impact of allogeneic BMT in overall survival, although post-BMT relapse rates were significantly higher in the chemotherapy group.

Since the overall result after treatment for relapse is highly dependent on the intensity of first-line therapy, the result of BMT as compared with chemotherapy should frequently be re-evaluated.

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