Bone Marrow Transplantation, (1996) 17, 357–363

Allogeneic bone marrow transplantation in first remission for children with very high-risk acute lymphoblastic leukemia: a retrospective case–control study in the Nordic countries

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Summary:

Among children with high-risk (HR) ALL there are subgroups with very-high-risk (VHR) features and poor prognosis despite developments in conventional chemotherapy for childhood ALL. We evaluated the outcome of VHR-ALL in children receiving allogeneic BMT (allo-BMT) in first remission (1CR) in a retrospective case–control study. In the population-based ALL material of the five Nordic countries, 22 children with VHR-ALL have undergone allo-BMT in 1CR between 1981–1991. We compared the outcome in these 22 children with 44 closely matched control patients who received conventional chemotherapy on HR-ALL protocols, as well as with a group of 405 children representing the remaining HR-ALL patients in the Nordic ALL database. The disease-free survival at 10 years was 73% in children receiving allo-BMT in 1CR, 50% in the matched controls ($P = 0.02$), and 59% in the remaining HR-ALL patients. The good prognosis of the allo-BMT group was due to a low relapse rate of 9%, as opposed to 41% in the group of matched controls. The superiority of allo-BMT as therapy in 1CR was mainly apparent in those with a very high WBC of $\geq 100 \times 10^9$/l at diagnosis; in the allo-BMT group 9/10 survived, as opposed to 8/20 of the matched controls ($P = 0.03$). We conclude that allo-BMT in 1CR should be seriously considered for children with a matched sibling donor and a VHR-ALL with WBC of ≥100 and other established VHR criteria.

Keywords: ALL; BMT; 1st remission

Most children with ALL are currently cured with conventional chemotherapy.[1–4] Similar success has been achieved with the Nordic ALL chemotherapy protocols.[5–7] The risk of relapse varies depending on a number of clinical and laboratory features measured at initial diagnosis. Patients are divided into groups or risk categories based on the risk of relapse, and the intensity of the chemotherapy regimen is adjusted according to the risk category.

Despite improvements in conventional chemotherapy, there is a subset of patients with high-risk features at diagnosis who are predisposed to a very high probability of relapse during first remission. This subset of children continues to have a dismal outlook, although some patients who have a first remission of over 18 months may have a prolonged second remission with intensive conventional chemotherapy.[8]

In adult ALL patients, allogeneic bone marrow transplantation (allo-BMT) in first complete remission has been demonstrated as effective therapy.[9–13] In pediatric ALL patients, allo-BMT from matched sibling donors has also been performed in first remission with very-high-risk (VHR) features, although most data are anecdotal, and there are few systematic prospective studies.[14–16] The VHR criteria used have included a very high total white cell count (WBC) at diagnosis (exceeding 100–200 $\times 10^9$/l), specific cytogenetic abnormalities, poor or slow response to remission induction, and age less than 1 year.

To date there are no established criteria for allo-BMT in first complete remission for children with high-risk ALL. In the Nordic countries, allo-BMTs in first remission were performed in the 1980s for different VHR features. The purpose of the present study was to evaluate the outcome of disease in these children, comparing them to matched controls selected retrospectively from the population-based Nordic ALL database.

Patients and methods

The collaborative research group of the Nordic Society for Pediatric Hematology and Oncology (NOPHO) is running a population-based register of children with ALL. Therapy protocols common for the five Nordic countries, ie Denmark, Finland, Iceland, Norway and Sweden are in use. The ALL database of NOPHO, from its beginning in June 1981, was utilized for the present study.

The patients included in the analysis were 471 children from the Nordic countries consecutively diagnosed with high-risk or special group ALL between 1 June 1981 and

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Received 24 March 1995; accepted 24 July 1995

31 December 1991, who were aged 1 to 15 years at diagnosis, and who were minimum 3 months in first remission. The follow-up data are completed up to 31 December 1993.

Criteria of high risk (HR) ALL

High risk criteria included one of the following: (1) WBC of $\geq 50 \times 10^9$/l; (2) CNS-ALL present at diagnosis; (3) T cell ALL; (4) mediastinal mass; (5) specific chromosomal translocation present: t(9;22), or t(4;11).

Criteria of special group (SG) ALL

(1) Infants less than 12 months of age at diagnosis; (2) leukemia with L3 morphology and mature B cell immunophenotype.

The 471 children were divided into three groups for analysis: I Patients treated with allo-BMT in first remission; II matched controls for the allo-BMT patients, two matches for each case; and III the remaining bulk of the HR + SG patients.

I Patients with allo-BMT in first remission

In total 22 children, 17 boys and five girls, underwent allo-BMT before 31 December 1991 at one of three centers (Table 1).

The decision to treat with allo-BMT in first complete remission (1CR) was taken locally at the discretion of the physician responsible, and consequently there was some variation in the indications. Twenty-one children had HR-ALL, and one had SG-ALL (B cell). The HR criteria were as follows: WBC $\geq 50 \times 10^9$/l ($n = 14$); T-ALL ($n = 13$); mediastinal mass ($n = 9$); CNS-ALL at diagnosis ($n = 4$); slow and incomplete response to remission induction ($n = 2$); chromosomal translocation t(4;11) ($n = 1$). Most patients had several HR criteria present: three criteria in six, two criteria in seven, and one criterion in nine patients. In total 10 patients had a WBC of $\geq 100 \times 10^9$/l (WBC >200 in seven). The immunophenotype was T cell in 13, mature B-cell in one, early pre-B in two, non-T, non-B in four, and mixed lineage diagnosed in two patients.

The median time from the ALL diagnosis until the allo-BMT in 1CR was 5.4 months (range 2.9–14.9).

The bone marrow donors were HLA-identical, MLC-negative siblings in 17 cases, siblings mismatched in 1–2 loci in three cases, plus one paternal and one maternal donor, both HLA-mismatches at two loci.

Most of the patients were conditioned with cyclophosphamide of 60 mg/kg/day on 2 consecutive days, plus total body irradiation (TBI) of 10–11 Gy. Two patients received high-dose cytosine arabinoside (HD-ARA-C) at 3 g/m^2 dose q 12 h × 12, in total 36 g/m^2, plus TBI, and one patient received busulfan 4 mg/kg/day × 4 days and cyclophosphamide 50 mg/kg/day × 4 days without TBI.

Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporin A (CsA) ($n = 8$), methotrexate (MTX) ($n = 2$), or CsA plus MTX combined ($n = 10$).[17] T cell depletion was performed on one graft.

II Matched controls

Two control patients were selected for each allo-BMT patient from the Nordic ALL database. Accordingly, there were 44 children, 34 boys and 10 girls. To be eligible for a match, (1) the patient had to achieve complete remission and (2) had to survive event-free for a period equal to or longer than the time of the corresponding 'case patient' from the ALL diagnosis to allo-BMT plus 3 additional months, to ensure as far as possible that the control patient still was in 1CR at the time point corresponding to BMT.

Control patients were fully matched for the following factors at initial ALL diagnosis: (1) WBC of ≤ 100 or $>100 \times 10^9$/l; (2) Age: categories of 1–2, 2–10 and >10 years; (3) Sex: male/female; (4) Time period of the ALL diagnosis: July 1981–June 1984; July 1984–June 1986; and July 1986–December 1991. This was because different ALL protocols were used by NOPHO during these time periods;[5,6] (5) Immunophenotype: T cell, mature B cell, and others (= non-T cell) (Table 2).

Cytogenetic data and response to induction chemotherapy (ie day 14 bone marrow), were not routinely available in all patients during the 1980s, so these parameters could not be taken into account in matching. The distribution of allo-BMT cases and control patients by country was uneven (Table 1), mainly because in Norway allo-BMTs in first remission were not performed during the study period.

III The remaining HR + SG patients

The remaining 405 patients, 235 boys and 170 girls, from the NOPHO database who were neither allo-BMT cases ($n = 22$) nor selected as matched controls ($n = 44$), constituted a somewhat heterogenous group of HR and SG patients, although only children older than 1 year at diagnosis and with 1CR lasting 3 months or longer were included. We felt that using this group for additional comparison would be confirmatory to our results regarding the patients with allo-BMT in 1CR.

Statistical methods

In the matching procedure, each case was stratified according to the criteria defined above (II, matched controls). For each case separately, a list of potential control patients

Table 1 Distribution by country among the three study groups of ALL patients

	I Allo-BMT in 1CR	*II Matched controls*	*III Remaining HR + SG*
Denmark	8	11	88
Finland	6	10	108
Iceland	—	1	3
Norway	—	9	70
Sweden	8	13	136
Total	22	44	405

Table 2 Distribution of risk factors among the three study groups of ALL patients

	I Allo-BMT in 1CR n = 22	*II Matched controls n = 44*	*III Remaining HR + SG n = 405*
WBC, $\times 10^9$/l			
<20	6	11	95
20–100	6	13	192
100–200	3	11	67
>200	7	9	51
Age, years			
1–2	1	2	33
2–10	11	24	276
>10	10	18	96
Sex			
Male	17	34	235
Female	5	10	170
Time period of ALL-dg			
July 1981 to June 1984	10	20	90
July 1984 to June 1986	2	4	82
July 1986 to December 1991	10	20	233
Immunophenotype			
T cell	13	26	96
B cell	1	2	19
Non-T, non-B	4	10	142
Early pre-B	2	5	116
Other	2	1	13
ND	—	—	19
CNS-ALL			
Present	4	7	42
Absent	17	37	354
ND	1	—	9
Mediastinal mass			
Present	9	17	97
Absent	13	26	298
ND	—	1	10
Risk category			
HR	21	42	386
SG	1	2	19

ND = not determined.

fulfilling the same stratification criteria was prepared from the whole cohort of HR + SG patients. From this list, two control patients were randomly allocated for each case. The procedure was repeated for every case until 44 control patients had been selected.

Statistical analyses were performed with SPSS statistical software.[18] Life tables were constructed by using the method of Kaplan and Meier. The distribution of *P*-EFS for the different subgroups at different times from remission were compared with the Wilcoxon–Gehan test.[19] The limit of significance was $P = 0.05$ in all analyses.

Results

Patients treated with allo-BMT in 1CR (group I) clearly had the best survival of the three study groups, with a 73% disease-free survival at 10 years, compared to 50% in the matched controls (group II) ($P = 0.02$), and 59% in the remaining HR + SG patients (group III) ($P = 0.12$) (Figure 1).

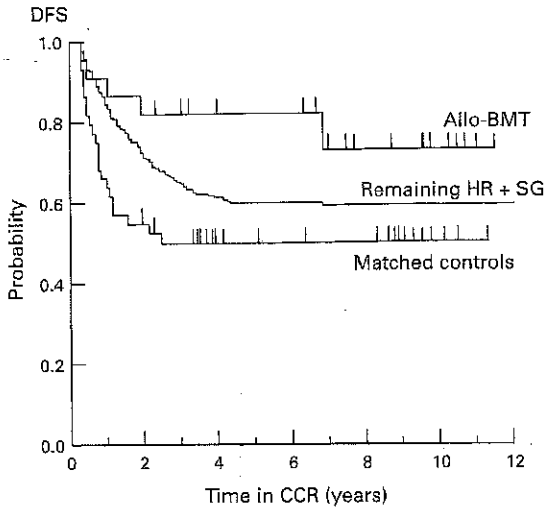

Figure 1 Probability of disease-free survival (DFS) of children with high-risk ALL. Allo-BMT = children who underwent allogeneic bone marrow transplantation from family donors in first remission ($n = 22$). Matched controls = patients matched by multiple factors for the allo-BMT patients ($n = 44$). Remaining HR + SG = the remaining bulk of high-risk ALL patients in the population-based Nordic data ($n = 405$). The difference between allo-BMT and matched controls is significant ($P = 0.02$).

The difference in outcome was due to different relapse rates. Two allo-BMT patients (9%) had ALL relapses in BM and BM + CNS, 20 and 2 months post-transplant, respectively, while 18/44 (41%) of the matched controls relapsed ($P < 0.01$). All of the relapsed patients subsequently died, except for one control patient who received an allo-BMT in second remission. Among the remaining HR + SG patients there were 157/405 (39%) relapses ($P < 0.01$ compared to group I). The patterns of ALL relapse in the three study groups are given in Table 3, and the cumulative incidence of relapse is illustrated in Figure 2.

The toxic death rates in CCR were 3/22 (13%) in the allo-BMT patients (group I), 4/44 (9%) in the matched controls (group II), and 3/405 (1%) in the remaining HR + SG patients (group III). In the allo-BMT group, one patient died 3 weeks post-transplant of septicemia and pneumonitis

Table 3 Patterns of relapse in the three study groups of ALL patients

	I Allo + BMT in 1CR n (%)	*II Matched controls n (%)*	*III Remaining HR + SG n (%)*
Bone marrow	1 (5)	11 (25)	99 (24)
CNS	—	4 (9)	21 (5)
Testis	—	—	12 (3)
BM + CNS	1 (5)	2 (5)	18 (4)
Other	—	1 (2)	7 (2)
No relapse	20 (91)	26 (59)	248 (61)

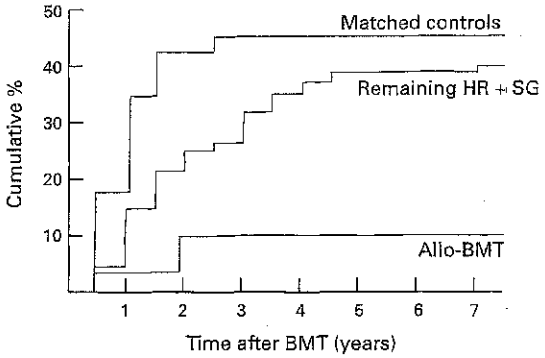

Figure 2 Cumulative incidence of relapse in children with high-risk ALL. The time corresponding to BMT was used as the reference point. Allo-BMT = children who underwent allogeneic BMT from family donors in first remission ($n = 22$). Matched controls = patients matched by multiple factors for the allo-BMT patients ($n = 44$). Remaining HR + SG = the remaining bulk of high-risk ALL patients in the population-based Nordic data ($n = 405$).

caused by *E. coli*; another died of graft rejection 2 months post-transplant; and the third died 6 years post-transplant of severe chronic GVHD and aspergillosis.

In the subgroup with matched sibling donors, 4/17 (23%) of the patients succumbed (two toxic deaths and two relapses). This result is not superior to the subgroup with mismatched/parental donors, in which group one of five (20%) died (early toxic death).

Accordingly, 17/22 (77%) of the allo-BMT patients are current survivors in CCR, compared to 22/44 (50%) of the matched controls, and 245/405 (61%) of the remaining HR + SG patients, with a minimum post-transplant follow-up of 24 months.

The quality of life of 16/17 transplant survivors is very good, despite the common but mostly mild endocrine deficiencies well-known to appear post-TBI. Only one out of the 17 survivors has severe chronic GVHD; this male patient had an allograft from his 2-locus mismatched mother. Two more survivors, with allografts from HLA-identical siblings, have experienced mild chronic GVHD but have recovered.

As patients were treated over a period of 10 years (from July 1981 to December 1991), we evaluated whether the treatment results had improved from the earlier half (July 1981–June 1986) to the later half (July 1986–December 1991) of the study period. Disease-free survival of allo-BMT patients was good early on, the figures for the time periods being 74% and 80%, respectively. The matched controls had improved from 46% to 55%, and the group of remaining HR + SG from 53% to 64%, respectively. These differences did not reach statistical significance.

Among all 471 high-risk ALL patients included in this study, an extremely high WBC of $\geq 100 \times 10^9$/l was associated with poor outcome (Figure 3). We selected out the individuals with WBC $\geq 100 \times 10^9$/l in our study groups I ($n = 10$), II ($n = 20$) and III ($n = 118$) (Table 2). The life table analysis of these extremely high WBC patients is shown in Figure 4, indicating that without allo-BMT in 1CR the survival is poor.

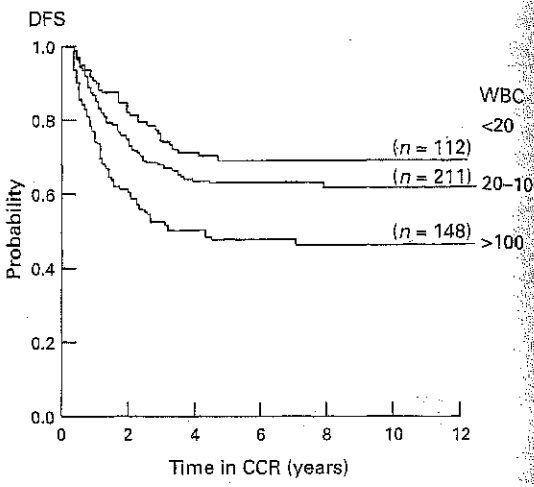

Figure 3 Disease-free survival (DFS) by WBC at diagnosis. Data has been obtained from the Nordic database of HR-ALL patients used in the study ($n = 471$). The prognostic value of WBC is highly significant ($P < 0.001$).

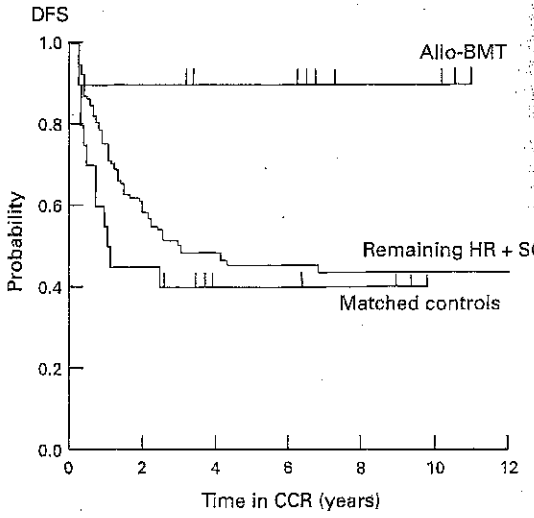

Figure 4 Probability of disease-free survival (DFS) of children with high-risk ALL and extremely high WBC ($>100 \times 10^9$/l) at diagnosis. Allo-BMT = children who underwent allogeneic bone marrow transplantation in first remission ($n = 10$). Matched controls = patients matched by multiple factors for the allo-BMT patients ($n = 20$). Remaining HR + SG = the remaining high-risk ALL patients in the Nordic data ($n = 118$). The difference between allo-BMT and matched controls is significant ($P = 0.03$).

Discussion

Our results indicate that allogeneic BMT performed in first remission is the best therapy for children with VHR-ALL. Children who underwent allo-BMT in 1CR had a 10-year disease-free survival of 73%, compared with 50% ($P < 0.02$) in a group of closely matched control patients with VHR-ALL who received conventional chemotherapy. The remaining group of HR + SG had a 10-year survival of 59% (Figure 1). The good prognosis of the allo-BMT group was due to a low relapse rate of 9%, as opposed

to 41% in the matched controls. The toxic death rate was acceptable (13%).

Other investigators have also found allo-BMT in 1CR beneficial for children with VHR-ALL. Bordigoni and coworkers[14] reported the results of 32 children who received BFM chemotherapy and who were transplanted in 1CR with matched sibling donors. Poor prognostic features included specific cytogenetic abnormalities, slow response to therapy, WBC of $>100 \times 10^9$/l, and infants. The 3-year event-free survival was 84%. The same French group later conducted a prospective study in which allo-BMT with sibling donors, autologous BMT, and augmented conventional chemotherapy were compared. The 18-month DFS rates were 58, 20, and 28%, respectively.[15] As in our study, the probability of relapse was lowest in the allo-BMT group, and the risk of treatment-related deaths was low.[15] Although Chessells and coworkers[16] in their UKALL study did not find statistically significant benefit from allo-BMT in 1CR in children with initial WBCs of $>100 \times 10^9$/l (69% 5-year survival for BMT and 52% for chemotherapy), allo-BMT was associated with a much lower relapse rate. This benefit was diluted by the treatment-related deaths (18%); the BMTs were performed in 10 centers, of which only two had carried out more than five BMTs. The level of center experience has been shown to influence outcome.[20] Analogous results were reported from the large IBMTR multicenter study regarding adult ALL. No benefit in survival was observed in patients undergoing allo-BMT in 1CR compared with those receiving chemotherapy, because the high (59%) relapse rate in the chemotherapy group was offset by the high (39%) toxic death rate in the transplant group.[21]

It is perhaps questionable whether allo-BMT should be carried out in first remission, since not all VHR-ALL patients relapse, and those who do should be rescuable by allo-BMT in second remission. However, it appears that many ALL patients who relapse cannot be rescued. Induction of a second remission is not always successful, and the patient may be ineligible for a transplant. Also, according to the literature, the results of allo-BMT in second remission are not outstanding, the survival figures ranging from 40 to 60% in most studies.[22–26] Swedish data of allo-BMT for ALL in second remission give a long-term survival of 41%,[27] and the entire Nordic data give 44%.[28] These figures are inferior to the survivals reported with allo-BMT in 1CR, the present study included.

Transplanting in first remission is also beneficial for other reasons. In 1CR there is a higher likelihood of the patient being in good general condition with less toxic organ damage caused by previous chemotherapy. This should translate into a lower toxic death rate. Moreover, according to generally accepted principles, high-dose therapy should be offered when there is minimal residual disease and, in particular, before multiple drug resistance of the malignant clone has developed.

There is a small minority of patients at extremely high risk, who either fail to remit or who relapse very early, within the first 2–3 months of diagnosis. Such patients were not included in the present analysis. The Nordic data from the time period concerned shows remission rates of 94% for HR-ALL and 78% for SG-ALL. Most early failures in childhood ALL are induction deaths; individuals with resistant or early recurrent disease are very few.

The preparative regimen most commonly used for ALL patients has been high-dose cyclophosphamide and fractionated TBI.[14,23,24,26] High-dose ARA-C with TBI has proven successful with a relatively low post-transplant relapse rate,[25] and high-dose ARA-C seems to be less cardiotoxic than high-dose cyclophosphamide.[29] It is unclear, however, which component of allo-BMT therapy is the more important long-term: the composition of the preparative regimen itself, or the immunotherapeutic graft-versus-leukemia effect. The potential late effects of TBI and high-dose chemotherapy,[30,31] as opposed to a conventional high-risk ALL regimen, must also be considered.

Conventional chemotherapy for ALL has improved greatly over the past 10–15 years, and the value of allo-BMT has been rechallenged.[31] In our study, the allo-BMTs in 1CR were performed during the 10-year period of 1981–1991. We divided this in an early and late period, and evaluated the data separately. Although the disease-free survival figures of the matched controls receiving conventional chemotherapy improved somewhat (from 46 to 55%) from the earlier to the later period, they remained inferior to the results of the allo-BMT group which showed good survival (74–80%) throughout the study. This further emphasizes the superiority of allo-BMT in first remission; improvements in conventional chemotherapy are not yet sufficient for the VHR-ALL patients. We wish to emphasize that our data are not biased by economic or geographical factors influencing the availability of allo-BMT among patients; in the Nordic countries every child has access to BMT if indicated.

The indications for allo-BMT in 1CR for children with VHR-ALL will most certainly be influenced by the availability of a donor, ie HLA-matched sibling *vs* mismatch family donor *vs* matched unrelated donor *vs* cord blood. Indications used in the literature refer to matched sibling donors, and include several kinds of poor risk features. Infants with ALL have an extremely poor prognosis with a 4-year DFS of only 23%.[32] Recent changes in ALL protocols have not brought any major improvement for this subgroup. Both numerical abnormalities in the chromosomes and translocations have been associated with prognostic importance. Children with ALL and hypodiploid ($\leq$45 chromosomes) features have a 4-year EFS of 40%.[33] The Philadelphia chromosome t(9;22)(q34;q11) is seen in 3–5% of children with ALL; the 5-year DFS is only about 10%.[34] Another important translocation in children with ALL is the t(4;11)(q21;q23) often present in infants, with a reported 4-year EFS of 20%.[35] The 11q23/MLL rearrangement confers a particularly poor prognosis in infants.[36] A slow or poor response to remission induction has also widely been used as a poor prognostic factor.[14,15]

A very high WBC at diagnosis of $\geq$100 or $\geq 200 \times 10^9$/l has recently been used as a VHR criterion and indication for allo-BMT in 1CR.[14–16] According to our Nordic data, children with WBC of $\geq$100 constitute a subgroup with poor prognosis (Figure 3). In our analysis of VHR-ALL children who underwent allo-BMT in 1CR, of those with WBC of $\geq$100 9/10 survive, as opposed to 8/20 survivors

in the matched controls ($P = 0.03$), indicating a clear benefit of allo-BMT in 1CR for this subgroup.

In conclusion, our data indicate that allo-BMT in 1CR is superior therapy for children with VHR-ALL, as opposed to conventional chemotherapy on HR-protocols. Allo-BMT should be seriously considered for children with a matched sibling donor and with a WBC of $\geqslant 100 \times 10^9$/l at diagnosis. The present study did not specifically address other VHR criteria, or the use of matched unrelated or family mismatch donors. However, patients at extremely high risk, such as those with t(9;22), t(4;11), or with the simultaneous presence of several VRH criteria, should be considered for allo-BMT in 1CR even without a matched sibling donor.

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