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Acute lymphoblastic leukemia

Allogeneic bone marrow transplantation *vs* chemotherapy for children with Philadelphia chromosome-positive acute lymphoblastic leukemia

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Summary:

Allogeneic bone marrow transplant (BMT) with an MRD in complete remission (CR)1 is the preferred treatment for children with Philadelphia-positive (Ph^+) ALL. The role of MUD BMT in CR1 is still controversial. We compared the outcomes of two treatment strategies: BMT using an MRD or MUD *vs* chemotherapy in children with Ph^+ ALL in CR1. In total, 21 children were treated from 1985 to 2001. In all, 10 received chemotherapy and 11 received allogeneic BMT: four MRD, seven MUD. In the MRD group, one relapsed 12 months after BMT and died; the remaining three are long-term event-free survivors (median follow-up, 6.1 years). In the MUD group four died; the remaining three are long-term event-free survivors (median follow-up, 7.2 years). The 4-year event-free survival (EFS) for the BMT group was $53 \pm 15\%$. In the chemotherapy group, seven relapsed after a median period of 12.5 months and three remain in continuous CR (median follow-up, 2.4 years). Four chemotherapy patients received CR2 transplants; all died. The 4-year EFS for the chemotherapy and MUD groups was 33 ± 17 and $35.7 \pm 20\%$, respectively. This difference was not statistically significant. We continue to support treating children with Ph^+ ALL with MRD BMT in CR1. The effectiveness of MUD BMT *vs* chemotherapy merits further study.

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The Philadelphia (Ph) chromosome, t(9;22) (q34;q11), is present in about 2–3% of children with newly diagnosed ALL. The presence of the Ph chromosome is an independent adverse prognostic factor characterized by a poor response to chemotherapy, short remission duration and poor likelihood of survival.[1–5] Although conventional chemotherapy can induce remission in 50–70% of patients, chemotherapy fails to maintain durable complete remission (CR) and produces an overall survival of 6–20%.[1,2,5] Similarly, the approach of augmented post-induction chemotherapy, including high-dose chemotherapy with or without autologous stem-cell rescue has failed to improve the outcomes for patients who have this disease.[2–4,6] Myeloablative chemotherapy followed by haematopoietic stem-cell rescue from an allogeneic donor in CR1 has been shown to cure 20–75% of patients.[7–18] Hence, allogeneic bone marrow transplant (BMT) from MRD and MUD has been used as post-induction therapy to improve DFS for patients with Ph^+ ALL.[7–18] Pediatric experience with this disease has suggested that Ph^+ ALL is more heterogeneous with respect to treatment responsiveness than previously suspected.[19–21] Clinical parameters like WBC count at diagnosis,[19,20] good initial steroid response[21] and age of the patient at diagnosis[20] were shown to be predictive of treatment responsiveness and durable remissions. Hence, a small subset of patients may be cured by chemotherapy alone. A recent multi-institutional study by Arico *et al*,[20] and the experience from BFM/AIEOP group[21] could not show that MUD BMT offered a curative advantage over chemotherapy in CR1 for children with Ph^+ ALL. To assess the effectiveness of BMT for children with Ph^+ ALL in CR1 compared with chemotherapy and to clarify the role of MUD BMT, we reviewed our institutional experience.

Patients and methods

Between August 1985 and July 2001, the medical records of all children diagnosed with Ph^+ ALL at The Hospital for Sick Children (HSC), Toronto, Ontario, Canada or referred to HSC for allogeneic BMT were reviewed. Research Ethics Board approval was obtained to review the patient records. The diagnosis of ALL was based on the standard French–American–British (FAB) criteria.[22] The immunophenotype of leukemia cells was used to define early precursor B, precursor B, B-cell and T-cell subtypes.[23] The chromosomal analysis of bone marrow samples was carried out with standard methods[24] at the time of diagnosis and at the time of follow-up, using standard

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G-banding with trypsin–Giemsa or trypsin–Wrights' staining. Karyotypes were interpreted using the International System for Cytogenetic Nomenclature criteria.[24] The use of molecular detection of *bcr/abl* at diagnosis by reverse transcriptase-polymerase chain reaction (RT-PCR) was started in 1995. All the children were treated with a BFM-based chemotherapy protocol for high-risk leukemia. For all these children, a combination of prednisone, vincristine, daunorubicin and L-asparaginase was used to induce remission. Remission status was assessed by morphological criteria at day 28 of induction with remission defined as $<5\%$ blasts on bone marrow aspirate. Consolidation therapy consisted of pulses of vincristine and prednisone, intravenous methotrexate, cyclophosphamide, cytosine arabinoside, oral 6-mercaptopurine and intrathecal methotrexate with either high-dose methotrexate with folinic acid rescue or cranial irradiation. Those children who failed induction therapy were reinduced with VM-26 ($160\,mg/m^2$) and cytosine arabinoside ($300\,mg/m^2$).[25] Upon receipt of cytogenetic and/or molecular results, donor searches were undertaken. HLA typing was performed by serological typing for HLA-A, -B and -DR antigens until 1993. Molecular techniques for HLA-DR antigens were employed from 1993. Those who had a matched donor proceeded to allogeneic BMT while in CR1. If an HLA-identical family donor was not available, donor searches of the unrelated registries were undertaken. In the absence of a matched HLA-identical donor, chemotherapy was continued. Those who relapsed were treated with the BFM-REZ protocol.[26] Salvage BMT was offered to those who achieved second CR (CR2).

Transplant regimen

Pre-transplant remission status was assessed by morphological and cytogenetic criteria. Molecular studies were not carried out prior to 1995. The preparatory regimen consisted of either cyclophosphamide ($50\,mg/kg/day \times 4$ days) or VP-16 ($60\,mg/kg$), followed by fractionated total body irradiation (1200 cGy in six fractions over 3 days) (Table 2). All the children received unmanipulated bone marrow grafts. Standard supportive care was used. Neutrophil engraftment was defined as attainment of an absolute neutrophil count of $>0.5 \times 10^9$ cells/l for 2 consecutive days for those alive beyond 2 weeks.

Clinical grading of GVHD was carried out according to modified Glucksberg *et al's*[27] criteria. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine (CsA) and methotrexate ($10\,mg/m^2$ on days 3, 6, 11 and 18). Acute GVHD (AGVHD) of grade II or more was treated with intravenous methylprednisolone ($2\,mg/kg/day$). Steroid-resistant GVHD was treated with either high-dose methylprednisolone ($10–30\,mg/kg/day$) or antithymocyte globulin (ATG). Chronic GVHD (CGVHD) was treated with CsA and prednisone with additional immunosuppressive agents in refractory cases. Molecular techniques were employed to monitor donor chimerism status after BMT. Post transplant disease remission status was assessed by monitoring of the Ph chromosome and/or *bcr/abl* transcripts. The Lansky performance scale was used to assess the performance status during each follow-up visit.[28]

Statistical analysis

An 'event' was defined as death or disease relapse. Event-free survival (EFS) was calculated from the date of diagnosis to the date of last follow-up or first event. Survival curves were drawn using the Kaplan–Meier method.[29] The log-rank test was used to test the independent influence of the following variables on EFS: age ($<$ or >10 years), sex, WBC count at diagnosis ($<$ or $\geqslant 50 \times 10^9$/l), FAB morphology, immunophenotype, central nervous system (CNS) disease at diagnosis, remission induction with initial chemotherapy and BMT in first CR. Cox's proportional multivariate analysis was carried out to assess the effects of all these factors on outcome of the treatment strategy.

Results

A total of 21 children (14 boys, seven girls) received treatment at The Hospital for Sick Children. Three of these children (*UPN 9*, *10* and *14*) had their disease diagnosed at other hospitals and were referred for BMT to our hospital.

Clinical features

The clinical features of individual patients are provided in Table 1.

Median age at diagnosis was 8.9 years (range, 2.0–16.4 years). The median WBC count at presentation was $32 \times 10^6/mm^3$ (range, $5.2–597.0 \times 10^9$/l). In total, 12 children had FAB L1 morphology and nine children had FAB L2 morphology. Four children had coexpression of myeloid markers. Three children had CNS disease at diagnosis. In all, 10 children had cytogenetic abnormalities in addition to the presence of the Ph chromosome. *UPN 9* did not have any cytogenetic abnormality; however, she had a molecular rearrangement of *bcr/abl* m-RNA expressing the p190 variant by RT-PCR. A total of 16 children achieved CR after 4 weeks of induction chemotherapy. The median interval between diagnosis and remission was 28 days (range, 19–84 days).

BMT group

In all, 11 children underwent allogeneic BMT in CR1. Transplant characteristics are given in Table 2. Four children received grafts from an MRD, whereas seven children received grafts from an MUD. The median interval between remission and BMT was 5.4 months (range, 1.4–16.4 months). The median nucleated cell dose of bone marrow grafts was 4.9×10^8/kg of the recipient's body weight.

Engraftment

Two children failed to engraft (*UPN 8* and *11*), while *UPN 11* died on day $+2$. The median time to engraftment was 21 days (range, 14–33 days). *UPN 8* had primary graft failure and required a stem-cell boost on day $+30$ post-BMT from the same donor after further conditioning with

Table 1 Patient characteristics

UPN	*Age (years)/sex*	*WBC at Dx (109/l)*	*Interval: Dx to remission (days)*	*Additional cytogenetics*	*Treatment received*	*Interval: Dx to event (years)*	*Overall survival (years)*	*Status*
1	8.62/F	17	28	45,XY,−7,der (9) t(?;9) (9;22) (?;p13;q34;q11)	Chemo/CR1 BMT		6.10	DFS
2	8.92/M	67	26	No	Chemo/CR1 BMT		5.42	DFS
3	7.30/M	23	56	44,XY,−2,−6	Chemo/CR1 BMT	1.51	3.25	Died (Re)
4	6.90/M	21	28	No	Chemo/CR1 BMT		12.20	DFS
5	7.03/F	8	33	No	Chemo/CR1 BMT		7.14	DFS
6	4.98/M	19	28	No	Chemo/CR1 BMT		7.33	DFS
7	16.40/M	103	53	46,XY,der (5) t(1;,5)(q21;q15), der(9)t(9,22)(q34;q11)	Chemo/CR1 BMT	0.8	0.82	Died (CGVHD)
8	5.78/F	167	27	44–46,XY,der (9)del (9) (?;p21) t(9;22)(q34;q11),der (22) t(9;22) (q34;q11)	Chemo/CR1 BMT	3.39	3.39	Died (CGVHD)
9	12.93/F	23	28	No**	Chemo/CR1 BMT	0.92	3.34	Died (Re)
10	10.68/M	28	28	No	Chemo/CR1 BMT		2.25	DFS
11	3.79/M	312	28	50–52,XXY,der(2)t(2;?) (q?), +4,t(9;22) (q34;q11), +10, +der (22) t(9;22)	Chemo/CR1BMT	0.57	0.57	Died (Inf)
12	11.61/F	32	38	No	Chemo/CR2 BMT	4.24	4.83	Died (Inf)
13	2.02/F	60	27	48,XY,t(9;22)(q34;q11), +14, +der (22) t(9;22) (q34;q11)	Chemo/CR2 BMT	1.04	4.16	Died (Re)
14	12.44/M	78	28	43–50,XY,9p-,22q-,9q+	Chemo/CR2 BMT	1.41	1.91	Died (Inf)
15	5.26/M	209	28	46 to 47,XY, add(2) (p25), −9,del(15)(q22), −22, der22, +mar1, +mar2	Chemo/CR2 BMT	0.74	1.19	Died (Re)
16	10.84/F	10	30	No	Chemo		12.57	DFS
17	5.64/M	414	31	No	Chemo	0.87	1.39	Died (Re)
18	8.88/M	597	84	No	Chemo	2.52	2.97	Died (Re)
19	13.64/M	5.2	28	46,XY,t(8,22)(q13;q11), t(8,14)(q24;q32),der (9), t(1,9),(q12;p13)	Chemo	0.28	0.52	Died (Re)
20	9.84/M	72	28	53 to 55,XY,+X,+2,+4, +4,+5,+6,+14,+21, +der(22) t(9;22) (q34;q11)	Chemo		2.43	DFS
21	9.23/M	13	28	46 XY, add 3 (q23),der 9(p22), t(9;22)(q34;q11),del (10)(p13), add12(q21),add14(q11), der22 t(9;22) (q34;q11)	Chemo		1.73	DFS[$]

M = male; F = female; Pre-B = precursor B leukemia; der = derivative; add = addition; Chemo = chemotherapy; CR1 = first complete remission; CR2 = second complete remission; BMT = bone marrow transplantation; Dx = diagnosis; DFS = disease-free survival; Re = relapse; Inf = infection; WBC = white blood cell; CGVHD = chronic graft-versus-host disease.
**Molecular evidence of bcr/abl.
[$]Undergoing 5/6 MUD BMT.

Table 2 CR1 BMT characteristics

UPN	*Donor*	*Conditioning*	*AGVHD*	*CGVHD*	*Interval: CR to BMT (years)*	*Interval: BMT to event (years)*	*F/u from BMT (years)*	*Status*
1*	MRD	VP-16/TBI	0	No	0.45	0.0	5.57	DFS
2	MRD	VP-16/TBI	III	No	0.44	0.0	4.90	DFS
3	MRD	VP-16/TBI	0	No	0.5	1.0	2.76	Died (Re)
4*	MRD	Cy/TBI	0	No	0.41	0.0	10.76	DFS
5	MUD	VP-16/TBI	III	Y:Ex	0.55	0.0	6.59	DFS
6	MUD	VP-16/TBI	I	No	0.87	0.0	6.41	DFS
7	MUD	VP-16/TBI	I	Y:Ex	0.11	0.0	0.57	Died (CGVHD)
8	MUD	VP-16/TBI/ATG	0	Y:Ex	0.4	0.0	2.91	Died (CGVHD)
9	MUD	VP-16/TBI	III	No	0.4	0.5	2.93	Died (Re)
10	MUD	Cy/TBI	IV	Y:Ex	0.4	0.0	1.87	DFS
11	MUD	Cy/TBI	0	NA	0.49	0.0	0.01	Died (Inf)

BMT = bone marrow transplantation; R = recipient; D = donor; P = positive; N = negative; AGVHD = acute graft-versus-host disease; CR = complete remission; Y = yes; Ex = extensive; VP-16 = etoposide; TBI = total body irradiation; Cy = cyclophosphamide; NA = not applicable; MRD = matched related donor; MUD = matched unrelated donor; MMURD = mismatched unrelated donor; F/u = follow-up; Dx = diagnosis; Re = relapse; Inf = infection.
*HLA typing by serologic method.

ATG. She had subsequent engraftment on day +27 after the stem-cell boost.

Graft-versus-host disease

Four children had developed AGVHD grade III or IV and required treatment with steroids. Among 10 children who survived more than 100 days after BMT, four developed extensive CGVHD. All four children had received stem-cell grafts from unrelated donors.

Transplant-related mortality

Three (*UPN 7*, *8* and *11*) children died from transplant-related complications. *UPN 7* and *8* had extensive CGVHD and died due to infection. *UPN 11* developed sepsis on day 0 of transplantation and died on the second day after transplantation due to *Streptococcus viridans* bacteremia and multiorgan failure.

Post transplant relapse

Two children (*UPN 3* and *9*) relapsed at 12 and 6 months after BMT and died. *UPN 3* did not have any evidence of GVHD, whereas *UPN 9* had AGVHD grade III. *UPN 3* had documented molecular remission and >90% donor engraftment until 9 months after his transplant when he showed 25% donor chimerism and 33.5% of cells positive for p190 *bcr/abl* transcript by fluorescence *in situ* hybridization. *UPN 3* received two courses of donor leukocyte infusions without any success. *UPN 9*, who had documented minimal residual disease 7 weeks before BMT, showed RT-PCR positivity in 10% of her cells for p190 *bcr/abl* transcripts 3 months after BMT. She was treated with discontinuation of immune suppression and subsequently showed complete molecular remission after 5 months. She had overt hematological relapse 1 year after transplantation and died due to resistant disease.

All the other children remained in continuous molecular remission with >90% donor engraftment documented by PCR. The median follow-up period for this group was 3.4 years (range, 0.6–12.2 years). The Kaplan and Meier 4-year EFS for this group was 53±15% (Figure 1). Lansky performance scale for this group was 100%.

Chemotherapy group

In total, 10 children continued with chemotherapy. Seven of these had hematological relapses at a median of 12.5 months (range, 3.4–51.0 months) after diagnosis. Four of these children received salvage BMT in CR2; all of them died.

Three children remained in CR1 at 21.2, 29.6 and 151.3 months (*UPN 21*, *20* and *16*, respectively). *UPN 21* had evidence of molecular relapse within 3 months of remission. Semiquantitative RT-PCR showed increasing levels (from 4.0×10^5 to 150.0×10^5/l) of *bcr/abl* fusion transcript (p190) within a span of 2 months. The 4-year EFS for this group was 33±17% (Figure 1). The median follow-up period for this group was 2.2 years (range, 0.5–12.6 years). The Lansky performance scale for this group was >90%.

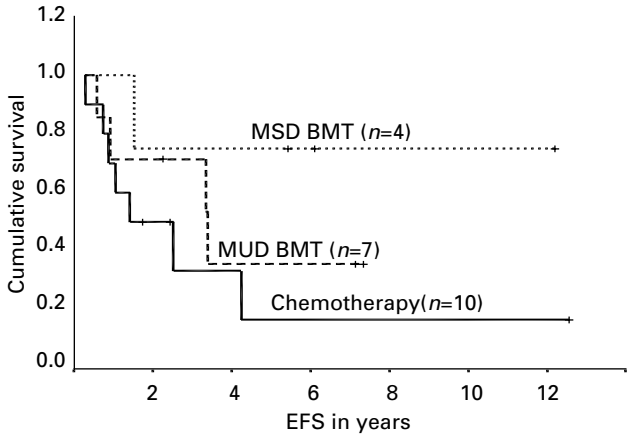

Figure 1 Kaplan–Meier 4-year EFS analysis based on treatment strategy. MSD: matched sibling donor; MUD: matched unrelated donor, BMT: bone marrow transplant.

Analysis of factors influencing treatment outcome

The small sample size limits the ability of statistical analysis to detect differences. On univariate analysis, WBC $>50 \times 10^9$/l, the presence of CNS disease and additional cytogenetic abnormalities were significant in predicting poor outcome ($P<0.05$). In the multivariate analysis, using Cox's regression (forward stepwise conditional model), the following were predictors of poor outcome: the presence of CNS disease (hazard ratio of 0.012, 95% CI 0.001–0.137), the presence of additional cytogenetic abnormalities (hazard ratio of 0.146, 95% CI 0.033–0.640) and failing induction (hazard ratio of 0.205, 95% CI 0.05–0.834). Although there was a survival advantage for BMT over chemotherapy, the influence of treatment strategy on outcome was not statistically significant ($P=0.21$, log-rank test).

Discussion

This report describes our single institutional experience of treating children with Ph+ ALL over a period of 15 years. Ph+ ALL has a poor outcome with aggressive multiagent chemotherapy protocols; hence, many centers including ours use allogeneic BMT as their preferred treatment option for patients in CR1.[8,12,18] The overall experience of allogeneic BMT shows a disease-free survival of 20–75%, with a relapse rate ranging from 11 to 63%.[10–15] These reports include patients in various stages of remission who received autologous stem cells, or allogeneic stem cells from MRD or unrelated donors. Late relapses were seen in all the studies, independent of the type of transplant. No consistent risk factors were identified to predict for relapse or survival, perhaps because the number of patients in each of the studies was small. Although the City of Hope/Stanford study[12] has suggested that disease stage at the time of transplant is a significant predictor of survival, this finding was not confirmed by Dunlop *et al*[11] and Kroger *et al*.[14] Patients who were younger (<30 years) had a better outcome in the study by Kroger *et al*.[14]

The type of allogeneic transplant influences outcome of children with this disease. MRD BMT in CR1 has been shown to offer a DFS ranging from 65 to 86% for young adults and pediatric patients.[8,12,18,20,21] Hence, MRD BMT is the preferred therapeutic option for this subset of ALL in CR1. The fact that three of the four children who had CR1 MRD BMT in our series were long-term survivors (5–11 years) supports the current recommendation of doing MRD BMT in CR1 for these patients.[20,21] However, 70% of patients who may benefit from allogeneic BMT lack an HLA-matched related donor, resulting in the use of alternative donor transplants for some children.[15–17] Unrelated BMT has been shown to offer an EFS of 38–69% in first CR.[9,10,15–17] There are reports suggesting comparable outcomes of MUD BMT and MRD BMT, supporting the use of alternative donors for treating this disease. However, all these reports are confounded by the retrospective nature of the studies, selection bias, lack of control groups and inclusion of patients at varying stages of remission.[11,16] Experience from Seattle has shown that the effectiveness of unrelated donor marrow BMT increase if the transplant is carried out early in the disease.[16] T-cell-depleted mismatched unrelated BMT has been shown to offer a DFS of 69% at 13 months in pediatric patients.[17] Recent data from the National Marrow Donor Program[30] suggest that Ph+ ALL is susceptible to GVL effects, supporting the use of MUD BMT to treat this disease. The advantage of MUD BMT in providing leukemia-free survival is also evident in our series. Seven children in the chemotherapy group had a hematological relapse, and since completion of the analysis *UPN21* has suffered a hematological relapse and died from disease. Only one child in the MUD BMT group has relapsed.

Our experience of treating children with this disease indicated that achieving a durable second remission was extremely difficult and we had no success in salvaging patients beyond first CR. This is in agreement with a report from Tokyo Children's Cancer Study group showing difficulty in salvaging patients after relapse even with intensive therapy, including BMT.[18] Moreover, our own institutional experience has shown no difference in the outcome of children with any ALL treated with MUD BMT and MRD BMT.[31] Hence, it has been our practice to offer allogeneic BMT to all children with this disease in CR1, even with alternative donors.

Our study is limited by small sample size and selection bias towards the BMT group, as children who did not have a donor formed the chemotherapy group. Although the 4-year EFS with CR1 MUD BMT appeared better than chemotherapy group (38.0 ± 20 *vs* $33 + 17\%$), this difference was not statistically significant ($P = 0.21$). Owing to the small number of patients and inevitable selection bias towards the BMT group, it is difficult to conduct any meaningful statistical analysis among the treatment subgroups (MRD BMT *vs* MUD BMT *vs* chemotherapy). However, in order to assess a difference of 33–38% with 80% power and alpha of 0.05 between the chemotherapy group and MUD BMT group, we would need a sample size of 1550 per group with a drop out rate of 15%.[32] Thus, it is not feasible to answer this question prospectively. Arico *et al*[20] have reviewed a multi-institutional experience of 326 children and young adults with Ph+ ALL who were treated over a period of 14 years. This study has shown that because of an excess number of transplantation-related deaths, the group that received MUD BMT ($n = 21$) had a higher risk of treatment failure (RR 1.4; 95% CI 0.8–2.6) than the group that received chemotherapy alone ($n = 147$) (RR 1).[20] Arico's study,[20] despite being multi-institutional had only 21 children who received MUD BMT, and therefore suffers from the same limitation as our single institutional study, that is, small sample size. BFM/AIEOP study[21] had analyzed the outcome of 61 children treated over a period of 14 years in the context of initial steroid responsiveness. Among the 37 children with prednisone good response, 19 received chemotherapy while 18 underwent allogeneic BMT (MRD BMT = 12; mismatched related donor BMT = 2; MUD BMT = 3; mismatched unrelated donor BMT = 1). Although both the groups have nearly 64% overall survival at the end of 4 years, three children in the unrelated donor group died of transplant-related causes, while only one patient in the mismatched related group suffered from GVHD-related complications. Owing to the increased risk of transplant-related deaths, both of these studies have questioned the role of MUD BMT over chemotherapy in CR1. Our study supports this observation, as extensive GVHD was observed only in the MUD BMT group (*UPN 5, 7, 8* and *10*; Table 2). More than 50% (4/7) of children who underwent MUD BMT suffered from GVHD and 50% (2/4) of them died (*UPN 7* and *8*; Table 2). This was not the result of differences in HLA-typing technology as all transplants in our series were performed after 1990, and all donor–recipient pairs were matched by a uniform HLA typing technique (serologic technique for HLA-A and -B and by molecular typing for HLA-DR) except for two children (*UPN 1* and *4*; Table 2), where HLA typing was performed using a serologic technique alone. Similarly, use of T-cell-depleted stem-cell grafts has been shown to decrease the incidence of GVHD in MUD BMT patients,[17,30] but all the patients in our series received T-cell replete bone marrow grafts, thus eliminating the confounding effect of T-cell depletion on transplant outcome. 'MUD BMT' in itself could therefore be an independent risk factor for poor transplant outcome in our series. A recent report from MRC UKALL X, XI has attempted to study the precise role of MUD BMT in CR1 *vs* chemotherapy for children with high risk ALL.[33] A majority (11/25) of the children who received CR1 MUD BMT in this study had Ph+ ALL, although the outcome of this group was not reported separately.[33] This study has failed to show the advantage of MUD BMT over chemotherapy for high-risk leukemia in CR1.[33] Thus, there is mounting evidence in the literature concerning the limited efficacy of MUD BMT over chemotherapy for treating children with Ph+ ALL in CR1.

In conclusion, based on our experience and current literature, we continue to recommend that children who have Ph+ ALL should undergo BMT from an MRD in first CR. Owing to the limitation in studying the precise role of MUD BMT *vs* chemotherapy in CR1 for treating children with Ph+ ALL, strategies including close monitoring of minimal residual disease for early detection of relapse and use of novel therapeutic agents, such as tyrosine

kinase inhibitors in chemotherapeutic regimens need further exploration.

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