

REVIEW

Allogeneic transplantation for childhood ALL

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More than 80% of children with ALL are now cured with chemotherapy without need for transplantation. This remarkable progress is the result of serial large-scale randomized clinical trials incorporating improvements in risk group assignment, administration of risk-adjusted therapy and intensified therapy for children with high-risk disease. Despite these advances, significant numbers of children still die of relapsed or refractory ALL, as ALL is the most frequent malignancy of childhood. This review focuses on the appropriate use of transplantation for children with ALL and optimization of transplant procedures to improve survival and reduce late consequences of therapy.

Bone Marrow Transplantation (2008) **41**, 133–139; doi:10.1038/sj.bmt.1705914; published online 12 November 2007

Keywords: allogeneic transplantation; ALL; children

with unrelated donor stem cell sources, although late morbidity from GVHD may be increased.

The remarkable progress achieved in the use of chemotherapy in treatment of ALL is the result of series of large-scale clinical studies conducted by co-operative clinical trial groups. In contrast, the performance of randomized controlled trials to compare chemotherapy with HCT has proved challenging, due at least in part to a lack of agreement that equipoise exists between the two treatments on the part of physicians and parents. The lack of randomized trials has led to considerable reliance on retrospective registry studies to identify optimum treatment strategies. In this review, we will discuss data available to assist the clinician in deciding which children with ALL should be transplanted, and the best approach for performing the transplant.

Transplant for ALL in first remission

Many case series of HCT for ALL in CR1 have been published over the years (Table 1). Overall, the majority of studies show at least a moderate reduction in relapse rate with transplantation compared with chemotherapy, but with increased treatment-related mortality. Variability in the data from different studies reflects differences in the definitions used for high-risk ALL meriting transplantation in CR1. Many of the criteria used in the past to define high risk (for example, T-cell ALL and mediastinal mass, high white cell count, t(4;11)) are no longer associated with markedly inferior outcomes with modern chemotherapy and would not currently be considered an indication of HCT in CR1. In the US, Ph+ ALL, low hypodiploidy and the small number of cases with primary induction failure are the only sub-types of ALL considered sufficiently high risk to merit consideration of transplantation in CR1 using current Children's Oncology Group chemotherapy, and each of these indications is discussed below.¹ Infants with ALL provide particular challenges, commonly presenting with biologically adverse features, altered drug pharmacokinetics and vulnerability to infection. The role of transplant for infant ALL in CR1 is controversial, and is also discussed below.

Ph-positive ALL

The low frequency (<4% of cases of childhood ALL) of Ph+ ALL has limited the identification of risk factors and

Introduction

Defining the appropriate use of hematopoietic cell transplantation (HCT) for children with ALL is a dynamic process, requiring constant and careful assessment of the likelihood of cure with chemotherapy to identify the subset of children for whom transplant offers a better treatment option. Improved chemotherapy treatments now offer reasonable probability of cure to children previously thought to require transplantation for survival. The role of HCT is also influenced by changes in transplantation, for example, the improved availability of unrelated marrow donors or cord blood units with expansion of national registries means that the majority of children with ALL will have a potential stem cell source if transplant is required. In addition, improved outcomes of unrelated donor transplants with better HLA typing, incorporation of HLA-C into matching algorithms and the use of cord blood units with large cell doses mean that outcomes equivalent to those seen with matched sibling donors can be achieved

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Received 10 September 2007; revised 1 October 2007; accepted 1 October 2007; published online 12 November 2007

Table 1 BMT for children with ALL in first CR

Transplant group/reference	Year of report	(n)	Preparative regimen	Follow-up (years) ^a	DFS (%) as treated/intent to treat	Relapse (%)
France ⁴³	1980–1987	32	TBI/CY	2.5 (0.6–6.8)	84.4/NA	3.5
France ⁴⁴	1982–1992	16	BU + other chemotherapy	3.9 (1.8–6.4)	61.1/NA	38.9
Nordic ⁴⁵	1981–1991	22	TBI/CY	>2	73/NA	9
UK ⁴⁶	1985–1990	34	TBI/CY	3.8 (1.1–5.9)	69/NA	11
USA ¹³	1993–1996	29	TBI/CY	3.1 (0.1–4.6)	58.6/NA	35
Italy ⁴⁷	1995–2000	77	TBI/etoposide, BU/CY/etoposide	5	62.7/56.7	34
Spain ⁴⁸	1993–2002	24	TBI/CY BU/CY	6.5 (1.3–12.4)	45/45	33

Abbreviation: DFS = disease-free survival.

^aMedian and range.

optimal therapy. To try to circumvent this limitation, Aricò *et al.*² analyzed pooled data from 326 children and young adults treated for Ph+ ALL by 10 study groups. The analysis showed that HCT from a matched sibling donor was superior to other types of transplantation (68% surviving at 5 years compared with 39% for unrelated donor transplantation). Results for children treated with chemotherapy and no transplant varied significantly according to age and white cell count at presentation; survival at 5 years was 49% in children with a low white count and age less than 10 years at presentation, but only 20% in those with a white count greater than 100 000/mm³ at presentation.² These data support the common clinical practice of offering HCT in first remission to children with Ph+ ALL and a matched sibling donor. However, for the majority of children without a matched sibling donor, there is less clear consensus on optimum management. Studies reporting outcome of unrelated donor HCT in these patients, so far show mixed results.^{2–4} Some recent reports have shown encouraging results for the use of alternate donor transplant for Ph+ ALL in CR1, and recent registry studies indicate that survival with a well-matched unrelated donor or moderately mismatched cord blood unit can be equivalent to a sibling donor graft.^{5–7} Continued investigation of the role of unrelated donor HCT in first remission for children with Ph-positive ALL is justified, although late morbidity from GVHD should be followed, as comparisons with the outcome of chemotherapy are made. More insight into prognostic factors will also allow better stratification of patients to help improve outcomes. On the basis of current available data,^{2,5} unrelated donor transplant should certainly be considered for children with NCI high-risk characteristics. In contrast, children with NCI good-risk characteristics and no well-matched sibling or unrelated donor may achieve acceptable results with chemotherapy.²

The tyrosine kinase inhibitor imatinib has been shown to have activity in childhood ALL, and current clinical trials are studying whether chemotherapy outcomes can be improved by including imatinib in intensive chemotherapy.⁸ It remains important to follow these studies carefully however, as imatinib, or other newer tyrosine kinase inhibitors may improve survival with chemotherapy sufficiently to allow use of transplantation only in CR2. In addition to incorporation into chemotherapy regimens, investigators have shown that imatinib is well tolerated when given prophylactically post transplantation, although

current follow-up is too short to determine whether outcomes are improved.⁹

Hypodiploid ALL

Children with severe hypodiploidy (<45 chromosomes) have poor outcomes (<40% survival) with chemotherapy.¹⁰ Most recently, Nachman *et al.*¹¹ reported 139 patients with ALL and hypodiploidy (fewer than 45 chromosomes) collected from 10 different national ALL study groups and single institutions. In contrast to previous studies suggesting that near-haploid cases with 24–29 chromosomes have particularly poor outcome, this report found no difference in outcome between patients with 24–29, 33–39 or 40–43 chromosomes, with poor outcomes in all these cases. However, compared to patients with fewer than 44 chromosomes, patients with 44 chromosomes had a significantly better survival (69%) suggesting that this group may not merit HCT in first remission. Twenty-nine children with hypodiploid ALL transplanted in first or second remission with a matched sibling donor between 1990 and 2001 have been reported to the International Bone Marrow Transplant Registry. Three-year survival was 65% (95% confidence interval 45–80%), supporting the use of early HCT in this small subgroup (M Eapen, personal communication, 2002).

Primary induction failure

A small subset (<2%) of children with ALL fail to achieve remission after 28 days of induction chemotherapy, and if they do achieve remission, only 40% will survive, suggesting that early transplantation might be of benefit.¹² Unfortunately, only small case series are available to assess the efficacy of transplant in this setting. Satwani *et al.*¹³ included seven children with ALL and primary induction failure in a co-operative group study of transplantation in CR1, and five of seven survived, supporting this approach. In earlier studies, survival in six of eight children, and in 10 of 18 patients in a study of children and adults was reported.^{14,15} In the absence of larger groups of patients, prognosis must be approached with caution, particularly as the intensity of initial chemotherapy has changed, and children with refractory disease after current regimens may be different from those treated in earlier eras.

Transplantation in CR3

Relatively few children with ALL are transplanted in CR3, as most children with available well-matched donors will be transplanted in CR2. Borgmann *et al.*¹⁶ proposed that children with later relapse might defer transplant in CR2, and only be transplanted if relapse occurred and a third remission was achieved. This proposal was based on review of 33 children transplanted in CR3 who had event-free survival of 48% at 6 years, compared with 49% in those transplanted in CR2. The authors estimated that 60% of children with late relapse treated with chemotherapy would have a further relapse, and of these 60% would achieve CR3 (reasonable estimates). Assuming that about half of those transplanted would survive, the overall survival for this approach would be 58% (40% who never relapse plus 18% ($0.6 \times 0.6 \times 0.5$) who relapse, achieve CR3 and are then cured by transplant). While these estimates are reasonable for children with late relapse, most centers are reluctant to defer transplant for those with early relapse and/or a well-matched donor due to the challenge of achieving CR3.

Prognostic factors predicting outcome of unrelated donor transplant for children with ALL in CR3 were analyzed in a series of 35 consecutive mostly T-depleted transplants performed in Bristol, UK.¹⁷ Event-free survival was 35%, with high rates of relapse and treatment-related mortality. Lengths of CR1 and CR2 predicted outcome, with shorter survival in children with short remissions, and event-free survival was reduced in children whose first relapse was an isolated extramedullary relapse.

Minimal residual disease

Newer technologies are being developed to better assess response to therapy in childhood ALL, as early response is a powerful prognostic indicator. The detection of minimal residual disease (MRD) using immunophenotyping or molecular detection of residual cells is increasingly being applied to clinical trials of chemotherapy for ALL.^{1,18} Future improvements in outcome and applicability of HCT for childhood ALL may result from development of methodologies to identify in the earliest possible time children who are destined to relapse, allowing HCT in first remission when outcomes are superior. The detection of MRD in children receiving chemotherapy, either as a harbinger of relapse or as a measure of inadequate early response to therapy will allow early referral for HCT as intensification therapy.^{19–23} It is important to know that the significance of MRD varies in different genetic subtypes of leukemia. For example, MRD is cleared more promptly in children with ALL and TEL-AML1 compared to children with favorable trisomies, both groups with an excellent long-term prognosis.¹⁸ Recent studies have also shown association between gene-expression profiling of ALL blasts at diagnosis and distinct immunophenotypic/genetic subtypes of ALL, treatment outcomes and risk of relapse.^{24–27} Further validation of these and similar findings in future could allow immediate referral of children with ALL destined to relapse for HCT in first remission.

Similarly, in recent years, there is growing interest in the role of MRD as a predictive marker for relapse following allogeneic transplantation. Most studies have shown that MRD detection in pre- and/or post-HCT samples predict increased risk of relapse following HCT.^{28–30} Different approaches have been suggested to help improve transplant outcomes using MRD detection to modify either pre or post transplant therapy, for example, additional cytoreductive therapy pre-transplant to reduce the malignant clone and render the patients MRD-negative, designing transplant protocols favoring development of GVHD to increase GVL effect, use of donor lymphocyte infusion (DLI), and so on. Some of these interventions are limited by the practicality of these approaches. For example, heavily pretreated patients have limited options for further chemotherapy prior to transplant, rapid withdrawal of immunosuppression and DLI are associated with the risk of life-threatening GVHD and have very limited efficacy, and treatment of GVHD further increases risk of life-threatening infections. Thus, although it is possible to identify patients at risk of relapse with MRD detection, strategies to respond to that information are limited. Moreover, many questions remain unanswered; for example, should we use MRD-negative status to assign patients to non-transplant treatment options to prevent transplant-related mortality and long-term toxicity? Efforts to assess the clinical significance of pre-transplant MRD in children with ALL are hampered by the lack of prospective studies in large cohorts of homogeneously treated patients.

Infant ALL

Molecular rearrangements that involve the MLL gene occur in a high proportion of leukemias arising in infants less than 1 year of age, most frequently a t(4;11)(q21;q23) translocation. Prognosis in MLL-rearranged ALL in infants is very poor with current chemotherapy, with generally less than 20% 5-year event-free survival.^{31–33} Because of the poor response to chemotherapy, infants with MLL-rearranged ALL are often considered as candidates for early transplantation. The Seattle group analyzed results of 40 infants who received an HCT between 1982 and 2003.³⁴ Three-year disease-free survival was 73% in 14 patients transplanted in CR1, suggesting early (in CR1) HCT might benefit these children, as reported by others. In contrast, Interfant-99 enrolled 482 infants with ALL from 22 countries between 1999 and 2005,³⁵ and reported that MLL gene rearrangement, very high white cell count ($>300 \times 10^9/l$), age <6 months and a poor response to the prednisone prophase were independently associated with inferior outcomes. However, the 4-year disease-free survival did not differ significantly between high-risk patients treated with chemotherapy alone (37.4%) versus chemotherapy plus HCT (50.2%) when adjusted for time to transplantation ($P=0.19$). There is a clear need for further prospective studies to define the role of HCT in infants at high risk for treatment failure. Such studies will need to be multi-institutional and possibly multi-national, as infant leukemia is rare. Studies should include evaluation of the late consequences of therapy in survivors, as morbidity can be significant in young children.

Transplant for ALL in second remission

The majority of children with ALL are considered as candidates for transplantation only if they relapse despite receiving chemotherapy. The appropriate use of HCT or chemotherapy alone for children with relapsed ALL remains a controversial topic. A number of co-operative groups, including Children's Oncology Group have attempted to compare outcomes of transplant and chemotherapy in randomized studies and have been unsuccessful, largely due to lack of acceptance of randomization by either or both of physicians and parents. In the absence of randomized data, the best available comparison comes from registry analyses and case series, summarized in Table 2. Eapen *et al.*³⁶ compared 188 patients enrolled in Pediatric Oncology Group chemotherapy trials and 186 children who received HLA-matched sibling transplants between 1991 and 1997. For children with early first relapse (<36 months from diagnosis), risk of a second relapse was significantly lower after transplant with a TBI regimen (relative risk, 0.49; 95% confidence interval, 0.33–0.71, $P < 0.001$) than chemotherapy treatment, and leukemia-free survival was improved. In contrast, transplant in CR2 did not offer an advantage over chemotherapy for children with a late relapse (≥ 36 months) ($P = 0.78$).

The Italian Bone Marrow Transplant group reported on 57 children who received allogeneic transplant for ALL in CR2 and compared them to 230 patients who received chemotherapy following their relapse.³⁷ In agreement with the findings of the Center for International Blood and Marrow Transplant Research study, these authors demonstrated that patients who had an early first relapse (<30 months) had significantly longer disease-free survival following transplant than treatment with chemotherapy, but this advantage was lost in patients with a later relapse (>30 months following diagnosis).

The German pediatric cooperative groups (BFM and COALL) reported 51 children with ALL in CR2, receiving matched sibling donor transplant.³⁸ Comparison of HCT results with outcomes in children treated with chemotherapy for a BM relapse showed that patients with an initial remission longer than 18 months had comparable survival, whether treated with chemotherapy or BMT. Patients with an early relapse (CR1 <18 months) or a relapse of T-ALL had a minimal chance of surviving following chemotherapy, and survival rates were significantly improved by allogeneic HCT.

These data indicate that HCT from a matched family donor is usually the best option for a child with early relapse of ALL. Data are currently insufficient to determine definitively whether similar benefit can be achieved with alternative donor HCT, although in many centers, results comparable to those seen with sibling donors can be achieved with an eight allele-matched unrelated donor, supporting such an approach. Similarly, good outcomes are reported with one or two antigen-mismatched cord blood grafts, and this approach is being widely used. Future analyses of outcomes of unrelated donor stem cell sources should include consideration of late morbidities, including GVHD that may be increased with use of unrelated donor stem cells, in addition to consideration of survival. The majority of studies indicate that children with later relapse (generally a CR1 of ≥ 36 months) can achieve similar survival with chemotherapy or with transplant from a sibling donor, so treatment options for these children should be discussed carefully with the family.

Selecting the optimal conditioning regimen

Early transplant studies used a conditioning regimen of CY/TBI, commonly regarded as a standard approach to

Table 2 BMT for children with ALL in second CR

Transplant group/reference	Years of HCT	(n)	Preparative regimen	Follow-up (years) ^a	DFS (%)
<i>Matched sibling donor transplant—single institution studies</i>					
Seattle ⁴⁹	1973–1985	57	CY/TBI	NS (1.4–10.4)	40
Memorial Sloan Kettering ⁵⁰	1979–1985	31	TBI/CY	5.1 (2.7–6.9)	64
Minnesota ⁵¹	1978–1980	15	CY/TBI	4	43
Minnesota ⁵²	1979–1991	68	CY/TBI TBI/ARAC TBI/CY	7.8 (1–12.7)	29
Boston ⁵³	1986–1992	14	CY/ARAC/TBI	4.6 (3–7.3)	53
Australia ⁵⁴	1988–1993	22	BU/CY/MEL	4.8 (2.5–6.2)	27
Memorial Sloan-Kettering ⁵⁵	1979–1992	37	TBI/CY	NS	62
Australia ⁵⁶	1990–1997	17	TBI/CY	6.3 (4.5–8.5)	55
<i>Matched sibling donor transplant—multi-institutional studies</i>					
German ³⁸	NS	51	CY/TBI etoposide/TBI	2.5 (0.1–5.6)	52
Multiple in US ⁵⁷	1981–1989	119	ARAC + TBI	NS	38
<i>Matched unrelated donor transplant—single institution series</i>					
Bristol, UK ⁵⁸	1988–1997	88	CAMPATH1-G, CY, TBI	3.2 (0.5–8.6)	45
Seattle, USA ⁵⁹	1983–1999	34	CY/TBI	NS	47
<i>Matched unrelated donor transplant—multi-institutional series</i>					
National Marrow Donor Program, USA ⁶⁰	1988–2000	363	Multiple; 90% include TBI	2.4 (0–10.4)	36
German ⁶¹	1983–2001	81	TBI/etoposide \pm CY (86%)	4.1 (1.1–13.1)	42

Abbreviations: Ara-C = cytosine arabinoside; DFS = disease-free survival; HCT = hematopoietic cell transplantation; MEL = melphalan; NS = not stated.

^aMedian and range.

ALL. Data indicate that radiation is an important component of the conditioning regimen, and that higher doses of radiation may be superior to lower doses. An alternative to increasing the dose of radiation is the use of VP-16 instead of CY.

The use of a radiation-free conditioning regimen is an attractive option for young children if equivalent survival can be demonstrated, as fewer late adverse effects on growth, endocrine and cognitive function might be expected. An International Bone Marrow Transplant Registry analysis of children with ALL receiving HLA-identical sibling donor HCT compared outcomes with conditioning regimes of CY and TBI ($n=451$) or BU and CY ($n=176$).³⁹ The 3-year probability of leukemia-free survival was significantly higher in the group receiving CY/TBI compared to the group receiving BU and CY. The risk of relapse was similar in the two groups, but treatment-related mortality was higher in children receiving BU and CY. Bunin *et al.*⁴⁰ reported similar inferior outcomes of a BU and CY conditioning compared with CY/TBI, in a small but prospective trial conducted by the Pediatric Blood and Marrow Transplant Consortium.

A recent large Center for International Blood and Marrow Transplant Research study compared 298 patients with ALL in CR1 or CR2 receiving HLA-matched sibling allografts after CY/TBI with 204 patients receiving VP-16/TBI.⁴¹ Four groups were compared: CY/TBI <13 Gy, CY/TBI \geq 13 Gy, VP-16/TBI <13 Gy and VP-16/TBI \geq 13 Gy. In CR2, important differences in outcome among conditioning groups were identified. Relapse, treatment failure and mortality were reduced in recipients of VP-16 (regardless of TBI dose) or with TBI doses of \geq 13 Gy in patients receiving CY. A striking reduction in relapse risk was observed in patients receiving \geq 13 Gy TBI with CY when compared to CY/TBI using <13 Gy of radiation ($P=0.0016$). These data are further evidence for the importance of the conditioning regimen in disease control in transplantation for ALL.

Umbilical cord blood transplant for ALL

The establishment of banks of cryopreserved umbilical cord blood (UCB) for use in transplantation has been an important development in the treatment of children with ALL. Potential advantages of UCB include immediate availability of stored units (particularly valuable for patients in whom remissions are likely to be short) and reduced GVHD, a major reason for treatment failure in recipients of unrelated donor marrow. In a report from Minnesota, the median time needed to identify a suitably matched UCB graft was 13.5 days compared to 49 days for a compatible unrelated marrow donor.⁴²

Eapen *et al.*⁷ compared outcome of 503 children with acute leukemia transplanted using UCB with 282 marrow recipients between 1995 and 2003. Four hundred and ninety-five patients with ALL were included, 186 in the marrow group and 309 in the UCB group. In comparison with allele-matched bone-marrow transplants, 5-year leukemia-free survival was similar after transplantation of UCB mismatched for either one or two antigens and

possibly higher after transplants of HLA-matched UCB. Treatment-related mortality rates were higher after transplantation of two-antigen HLA-mismatched UCB (relative risk 2.31, $P=0.0003$) and possibly after one-antigen HLA-mismatched low-cell-dose ($\leq 0.3 \times 10^8/\text{kg}$) UCB transplants (relative risk 1.88, $P=0.0455$). Relapse rates were lower after two-antigen HLA-mismatched UCB transplants (54%, $P=0.0045$). These data support the use of HLA-matched and one- or two-antigen HLA-mismatched UCB with units of adequate size in children with acute leukemia who need transplantation.

Conclusion

It is essential to understand outcomes of chemotherapy for ALL to appropriately use HCT in children with ALL. Continuing review and re-evaluation of chemotherapy outcomes, stem cell sources and transplant outcomes is necessary as all these variables are constantly changing, requiring vigilance on the part of transplant physicians. Relapse remains the major reason for treatment failure, and current data illustrate the importance of radiation in the conditioning regimen for disease control. The use of MRD to predict outcome has the potential to identify patients who do or do not need transplant. Novel GVHD prophylaxis agents such as sirolimus, currently under investigation in a randomized study in the US in the Children's Oncology Group, might improve disease control.

References

- Schultz KR, Pullen DJ, Sather HN, Shuster JJ, Devidas M, Borowitz MJ *et al.* Risk-and response-based classification of childhood B-precursor acute lymphoblastic leukemia: a combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). *Blood* 2007; **109**: 926–935.
- Aricò M, Valsecchi MG, Camitta B, Schrappe M, Chessell J, Baruchel A *et al.* Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. *N Engl J Med* 2000; **342**: 998–1006.
- Marks DI, Bird JM, Cornish JM, Goulden NJ, Jones CG, Knechtli CJ *et al.* Unrelated donor bone marrow transplantation for children and adolescents with Philadelphia-positive acute lymphoblastic leukemia. *J Clin Oncol* 1998; **16**: 931–936.
- Sierra J, Radich J, Hansen JA, Martin PJ, Petersdorf EW, Bjerke J *et al.* Marrow transplants from unrelated donors for treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* 1997; **90**: 1410–1414.
- Roy A, Bradburn M, Moorman AV, Burrett J, Love S, Kinsey SE *et al.* Early response to induction is predictive of survival in childhood Philadelphia chromosome positive acute lymphoblastic leukaemia: results of the Medical Research Council ALL 97 trial. *Br J Haematol* 2005; **129**: 35–44.
- Talano JM, Casper JT, Camitta BM, Keever-Taylor CA, Murray KJ, Eapen M *et al.* Alternative donor bone marrow transplant for children with Philadelphia chromosome ALL. *Bone Marrow Transplant* 2006; **37**: 135–141.
- Eapen M, Rubinstein P, Zhang MJ, Stevens C, Kurtzberg J, Scaradavo A *et al.* Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. *Lancet* 2007; **369**: 1947–1954.

- 8 Wassmann B, Pfeifer H, Goekbuget N, Beelen DW, Beck J, Stelljes M *et al.* Alternating versus concurrent schedules of imatinib and chemotherapy as front-line therapy for Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). *Blood* 2006; **108**: 1469–1477.
- 9 Carpenter PA, Snyder DS, Flowers ME, Sanders JE, Gooley TA, Martin PJ *et al.* Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. *Blood* 2007; **109**: 2791–2793.
- 10 Heerema NA, Nachman JB, Sather HN, Sensel MG, Lee MK, Hutchinson R *et al.* Hypodiploidy with less than 45 chromosomes confers adverse risk in childhood acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood* 1999; **94**: 4036–4046.
- 11 Nachman JB, Heerema NA, Sather H, Camitta B, Forestier E, Harrison CJ *et al.* Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia. *Blood* 2007; **110**: 1112–1115.
- 12 Conter V, Aricò M, Valsecchi MG, Basso G, Biondi A, Madon E *et al.* Long-term results of the Italian Association of Pediatric Hematology and Oncology (AIEOP) Acute Lymphoblastic Leukemia Studies, 1982–1995. *Leukemia* 2000; **14**: 2196–2204.
- 13 Satwani P, Sather H, Ozkaynak F, Heerema NA, Schultz KR, Sanders J *et al.* Allogeneic bone marrow transplantation in first remission for children with ultra-high-risk features of acute lymphoblastic leukemia: a children's oncology group study report. *Biol Blood Marrow Transplant* 2007; **13**: 218–227.
- 14 Bordigoni P, Vernant JP, Souillet G, Gluckman E, Marininchi D, Milpied N *et al.* Allogeneic bone marrow transplantation for children with acute lymphoblastic leukemia in first remission: a cooperative study of the Groupe d'Etude de la greffe de Moelle Osseuse. *J Clin Oncol* 1989; **7**: 747–753.
- 15 Chao NJ, Forman SJ, Schmidt GM, Snyder DS, Amylon MD, Konrad PN *et al.* Allogeneic bone marrow transplantation for high-risk acute lymphoblastic leukemia during first complete remission. *Blood* 1991; **78**: 1923–1927.
- 16 Borgmann A, Baumgarten E, Schmid H, Dopfer R, Ebell W, Gobel U *et al.* Allogeneic bone marrow transplantation for a subset of children with acute lymphoblastic leukemia in third remission: a conceivable alternative? *Bone Marrow Transplant* 1997; **20**: 939–944.
- 17 Afify Z, Hunt L, Green A, Guttridge M, Cornish J, Oakhill A *et al.* Factors affecting the outcome of stem cell transplantation from unrelated donors for childhood acute lymphoblastic leukemia in third remission. *Bone Marrow Transplant* 2005; **35**: 1041–1047.
- 18 Borowitz MJ, Pullen DJ, Shuster JJ, Viswanatha D, Montgomery K, William CL *et al.* Minimal residual disease detection in childhood precursor-B-cell acute lymphoblastic leukemia: relation to other risk factors. A Children's Oncology Group study. *Leukemia* 2003; **17**: 1566–1572.
- 19 Nyvold C, Madsen HO, Ryder LP, Seyfarth J, Svejgaard A, Clausen N *et al.* Precise quantification of minimal residual disease at day 29 allows identification of children with acute lymphoblastic leukemia and excellent outcome. *Blood* 2002; **99**: 1253–1258.
- 20 Dworzak MN, Froschi G, Printz D, Mann G, Potschger U, Muhlegger N *et al.* Prognostic significance and modalities of flow cytometric minimal residual detection in childhood acute lymphoblastic leukemia. *Blood* 2002; **15**: 1952–1958.
- 21 Tarusawa M, Yashima A, Endo M, Maesawa C. Quantitative assessment of minimal residual disease in childhood lymphoid malignancies using an allele-specific oligonucleotide real-time quantitative polymerase chain reaction. *Int J Hematol* 2002; **75**: 166–173.
- 22 Willemse MJ, Seriu T, Hetteringer K, d'Aniello E, Hop WC, Panzer-Grumayer ER *et al.* Detection of minimal residual disease identifies differences in treatment response between T-ALL and precursor B-ALL. *Blood* 2002; **15**: 4386–4393.
- 23 Coustan-Smith E, Sancho J, Behm FG, Hancock ML, Razzouk BI, Ribeiro RC *et al.* Prognostic importance of measuring early clearance of leukemia cell by flow cytometry in childhood acute lymphoblastic leukemia. *Blood* 2002; **100**: 52–58.
- 24 Ross ME, Zhou X, Song G, Shurleff SA, Girtman K, Williams WK *et al.* Classification of pediatric acute lymphoblastic leukemia by gene expression profiling. *Blood* 2003; **102**: 2951–2959.
- 25 Haferlach T, Kohlmann A, Schnittger S, Dugas M, Hidemann W, Kern W *et al.* Global approach to the diagnosis of leukemia using gene expression profiling. *Blood* 2005; **106**: 1189–1198.
- 26 Hollerman A, Cheok MH, den Boer ML, Yang W, Veerman AJ, Kazemier KM *et al.* Gene-expression patterns in drug-resistant acute lymphoblastic leukemia cells and response to treatment. *N Engl J Med* 2004; **351**: 601–603.
- 27 Flotho C, Coustan-Smith E, Pei D, Cheng C, Song G, Pui CH *et al.* A set of genes that regulate cell proliferation predicts treatment outcome in childhood acute lymphoblastic leukemia. *Blood* 2007; **110**: 1271–1277.
- 28 Uzunel M, Jaksch M, Mattsson J, Ringden O. Minimal residual disease detection after allogeneic stem cell transplantation is correlated to relapse in patients with acute lymphoblastic leukemia. *Br J Haematol* 2003; **122**: 788–794.
- 29 Schilham MW, Balduzzi A, Bader P. PD-WP of the EBMT. *Bone Marrow Transplant* 2005; **1**: 49–52.
- 30 Sramkova L, Muzikova K, Fronkova E, Krejci O, Sedlacek P, Formankova R *et al.* Detectable minimal residual disease before allogeneic hematopoietic stem cell transplantation predicts extremely poor prognosis in children with acute lymphoblastic leukemia. *Pediatric Blood Cancer* 2007; **48**: 93–100.
- 31 Chen CS, Sorensen HB, Domer PH, Reaman GH, Korsmeyer SJ, Heerema NA *et al.* Molecular rearrangements on chromosome 11q23 predominate in infant acute lymphoblastic leukemia and are associated with specific biologic variable and poor outcome. *Blood* 1993; **81**: 2386–2393.
- 32 Pui CH, Behm FG, Downing JR, Hancock ML, Shurleff SA, Ribeiro RC *et al.* 11q23/MLL rearrangement confers a poor prognosis in infants with acute lymphoblastic leukemia. *J Clin Oncol* 1994; **12**: 909–915.
- 33 Pui C-H, Gaynon PS, Boyett JM, Chessells JM, Baruchel A, Kamps W *et al.* Outcome of treatment in childhood acute lymphoblastic leukaemia with rearrangements of the 11q23 chromosomal region. *Lancet* 2002; **359**: 1909–1915.
- 34 Sanders JE, IM HJ, Hoffmeister PA, Gooley TA, Woolfrey AE, Carpenter PA *et al.* Allogeneic hematopoietic cell transplantation for infants with acute lymphoblastic leukemia. *Blood* 2005; **105**: 3749–3756.
- 35 Pieters R, Schrappe M, De Lorenzo P, Hann I, De rossi G, Felice M *et al.* A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. *Lancet* 2007; **370**: 240–250.
- 36 Eapen M, Raetz E, Zhang M, Muehlenbein C, Devidas M, Abshire T *et al.* Outcomes after HLA-matched sibling transplantation or chemotherapy in children with B-precursor acute lymphoblastic leukemia in a second remission: a collaborative study of the Children's Oncology Group and the Center for International Blood and Marrow Transplant Research. *Blood* 2006; **107**: 4961–4967.
- 37 Uderzo C, Valsecchi MG, Bacigalupo A, Meloni G, Messina C, Polchi P *et al.* Treatment of childhood acute lymphoblastic

- leukemia in second remission with bone marrow transplantation and chemotherapy: ten year experience of the Italian Bone Marrow Transplantation Group and the Italian Pediatric Hematology Oncology Association. *J Clin Oncol* 1995; **134**: 352–358.
- 38 Dopfer R, Henze G, Bender-Gotze C, Ebell W, Ethniger G, Friedrich W *et al*. Allogeneic bone marrow transplantation for childhood acute lymphoblastic leukemia in second remission after intensive primary and relapse therapy according to the BFM- and CoALL-protocols: results of the German Cooperative Study. *Blood* 1991; **78**: 2780–2784.
 - 39 Davies SM, Ramsay NK, Klein JP, Weisdorf DJ, Bolwell B, Cahn JY *et al*. Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia. *J Clin Oncol* 2000; **18**: 340–347.
 - 40 Bunin N, Aplenc R, Kamani N, Shaw K, Cnaan A, Simms S *et al*. Randomized trial of busulfan vs total body irradiation containing conditioning regimens for children with acute lymphoblastic leukemia: a Pediatric Blood and Marrow Transplant Consortium study. *Bone Marrow Transplant* 2003; **32**: 543–548.
 - 41 Marks DI, Forman SJ, Blume KG, Perez WS, Weisdorf DJ, Keating A *et al*. A comparison of cyclophosphamide and total body irradiation with etoposide and total body irradiation as conditioning regimens for patients undergoing sibling allografting for acute lymphoblastic leukemia in first or second complete remission. *Biol Blood Marrow Transplant* 2006; **438**–453.
 - 42 Barker JN, Krepski TP, DeFor TLE, Davies SM, Wagner JE, Weisdorf DJ *et al*. Searching for unrelated donor hematopoietic stem cells: availability and speed of umbilical cord blood versus bone marrow. *Biol Blood Marrow Transplant* 2002; **8**: 257–260.
 - 43 Bordigoni P, Vernant JP, Souillet G, Gluckman E, Marinichi D, Milpied N *et al*. Allogeneic bone marrow transplantation for children with acute lymphoblastic leukemia in first remission: a cooperative study of the Groupe D'Etude de la Greffe de Moelle Osseuse. *J Clin Oncol* 1989; **7**: 747–753.
 - 44 Von Bueltzingslowen A, Esperou-Bourdea H, Souillet G, Demeocq F, Mechinaud-Lacroix F, Michel G *et al*. Allogeneic bone marrow transplantation following a busulfan based conditioning regimen in young children with acute lymphoblastic leukemia: a Cooperative Study of the Societe Francaise de Greffe de Moelle. *Bone Marrow Transplant* 1995; **16**: 521–527.
 - 45 Saarinen UM, Mellander L, Nysom K, Ringden O, Schroeder H, Glomstein A *et al*. 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. Nordic society for Pediatric Hematology and Oncology (NOPHO). *Bone Marrow Transplant* 1996; **17**: 357–363.
 - 46 Chessells JM, Baily C, Wheeler K, Richards SM. Bone marrow transplantation for high-risk childhood lymphoblastic leukaemia in first remission: experience in MRC UKALL X. *Lancet* 1992; **340**: 565–568.
 - 47 Balduzzi A, Valsecchi M, Uderzo C, De Lorenzo P, Klingebiel T, Peters C *et al*. Chemotherapy versus allogeneic transplantation for very high-risk childhood acute lymphoblastic leukaemia in first complete remission: comparison by genetic randomisation in an international prospective study. *Lancet* 2005; **366**: 635–642.
 - 48 Ribera J, Ortega J, Oriol A, Bastida P, Calvo C, Pérez-Hurtado J *et al*. Comparison of intensive chemotherapy, allogeneic, or autologous stem-cell transplantation as post remission treatment for children with very high risk acute lymphoblastic leukemia: PETHEMA ALL-93 Trial. *J Clin Oncol* 2007; **25**: 16–24.
 - 49 Sanders JE, Thomas ED, Buckner CD, Doney K. Marrow transplantation for children with acute lymphoblastic leukemia in second remission. *Blood* 1987; **70**: 324–326.
 - 50 Brochstein JA, Kernan NA, Groshen S, Cirrincione C, Shank B, Emanuel D *et al*. Allogeneic bone marrow transplantation after hyperfractionated total-body irradiation and cyclophosphamide in children with acute leukemia. *N Engl J Med* 1987; **317**: 618–624.
 - 51 Woods WG, Nesbit ME, Ramsay NK, Krivit W, Kim TH, Goldman A *et al*. Intensive therapy followed by bone marrow transplantation for patients with acute lymphocytic leukemia in second or subsequent remission: determination of prognostic factor (a report from the University of Minnesota Bone Marrow Transplantation Team). *Blood* 1983; **6**: 1182–1189.
 - 52 Weisdorf DJ, Woods WG, Nesbit ME JR, Uckun F, Dusenbery K, Haake R *et al*. Allogeneic bone marrow transplantation for acute lymphoblastic leukemia: risk factors and clinical outcomes. *Br J Haematol* 1994; **86**: 62–69.
 - 53 Parson SK, Casellino SM, Lehmann LE, Eickhoff CE, Tarbell NJ, Sallan SE *et al*. Relapsed acute lymphoblastic leukemia: similar outcomes for autologous and allogeneic marrow transplantation in selected children. *Bone Marrow Transplant* 1996; **17**: 763–768.
 - 54 Carpenter PA, Marshall GM, Giri N, Vowels MR, Russell SJ. Allogeneic bone marrow transplantation for children with acute lymphoblastic leukemia condition with busulfan, cyclophosphamide and melphalan. *Bone Marrow Transplant* 1996; **18**: 489–494.
 - 55 Boulad F, Steinherz P, Reyes B, Heller G, Gillio P, Small TN *et al*. Allogeneic bone marrow transplantation versus chemotherapy for the treatment of childhood acute lymphoblastic leukemia in second remission: a single-institution study. *J Clin Oncol* 1999; **17**: 197–207.
 - 56 Bleakley M, Shaw PJ, Nielsen JM. Allogeneic bone marrow transplantation for childhood relapsed acute lymphoblastic leukemia: comparison of outcome in patients with and without a matched family donor. *Bone Marrow Transplant* 2002; **30**: 1–7.
 - 57 Weyman C, Graham-Pole J, Emerson S, August C, Champlin R, Coccia P *et al*. Use of cytosine arabinoside and total body irradiation as conditioning for allogeneic marrow transplantation in patients with acute lymphoblastic leukemia. *Bone Marrow Transplant* 1993; **11**: 43–50.
 - 58 Green A, Clarke E, Hunt L, Canterbury A, Lankester A, Hale G *et al*. Children with acute lymphoblastic leukemia who receive T-cell-depleted HLA mismatched marrow allografts from unrelated donors have an increased incidence of primary graft failure but a similar overall transplant outcome. *Blood* 1999; **94**: 2236–2246.
 - 59 Woolfrey AE, Anasetti C, Storer B, Doney K, Milner LA, Sievers EL *et al*. Factors associated with outcome after unrelated marrow transplantation for treatment of acute lymphoblastic leukemia in children. *Blood* 2002; **99**: 2002–2008.
 - 60 Bunin N, Carston M, Wall D, Adams R, Casper J, Kamani N *et al*. Unrelated marrow transplantation for children with acute lymphoblastic leukemia in second remission. *Blood* 2002; **99**: 3151–3157.
 - 61 Borgmann A, von Stackelberg A, Hartmann R, Ebell W, Klingebiel T, Peters C *et al*. Unrelated donor stem cell transplantation compared with chemotherapy for children with acute lymphoblastic leukemia in a second remission: a matched-pair analysis. *Blood* 2003; **101**: 3835–3839.