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THE ROLE OF BONE MARROW TRANSPLANTATION IN FIRST REMISSION OF PAEDIATRIC ALL

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1. ABSTRACT

Although intensive chemotherapy has improved event-free survival for most children with lymphoblastic leukaemia there remain up to 10% who have not benefited from this approach. These include infants, children with Ph^1 positive leukaemia, with near-haploidy, and slow remitters in most of whom event free survival remains below 40%. Evaluation of the benefits of Bone Marrow Transplantation in high risk ALL is fraught with difficulties and to date has not produced clear evidence of benefit. The way forward lies in prospective evaluation of BMT in tightly defined subsets of highest risk children, a task which will require international collaboration.

2. INTRODUCTION

Now that overall event-free survival rates for paediatric acute lymphoblastic leukaemia (ALL) are approaching 75-80%, there would seem to be little justification for high dose chemo-radiotherapy and stem cell rescue (BMT) for children in first remission. Yet these excellent overall figures mask significant discrepancies in clinical outcome.

2.1. Identification of Highest Risk Patients with ALL

An early attempt to identify prognostic features in ALL based on age and Leukocyte count (1) has been more recently refined (2). Despite a lack of international consensus on risk assessment in ALL (3) these clinical features, in combination with therapy response and biological characteristics, can be used to stratify patients into risk groups (Table 1).

Two-thirds of all children, stratified as standard risk on the basis of age and Leukocyte count have an excellent chance of cure after treatment with induction, intensification, CNS-directed treatment and continuing (maintenance) therapy. A small minority of these may be reassigned as highest risk on the basis of poor treatment response or adverse cytogenetics (see below).

Children in the higher risk group, often selected on the basis of age and Leukocyte count respond well to intensified chemotherapy (3,4) and even those with a poor initial response to *treatment*, judged by bone marrow examination after seven days of therapy, may achieve prolonged remission after intensified induction and re-consolidation therapy (5). Remaining questions about therapy in the higher risk group include: refinement of chemotherapy, identifying the likely treatment failures, possibly by measurement of minimal residual disease and clarification around the need for cranial irradiation (3). The 1-2% of children with surface membrane immunoglobulin positive B-ALL are now highly curable with short term intensive chemotherapy (6) and form a “special” rather than highest risk group.

There remains 8-9% of children, in whom the expected event-free survival is under 40%. Some of these (Table 2) may be identified on the basis of clinical features and/or biology, although there is no consensus about the prognostic significance of all these features. Failure to achieve remission after four weeks of induction therapy (7,8), is always associated with a poor prognosis. Infants under one year form a heterogeneous group, including some with CD10 positive pre-B ALL, but the majority, with high Leukocyte counts, organomegaly and translocations involving the MLL gene, are at high risk of relapse even after intensive therapy (9). The event free survival in two consecutive series of infants treated by the Children’s Cancer Group was 33% and 39 % at four years (10).

A recent international study of Philadelphia-chromosome (Ph^1) positive leukaemia showed that overall long term EFS was poor - 25% at seven years. Some patients with favourable clinical prognostic features responded to intensive chemotherapy but overall, in this retrospective survey, BMT from histocompatible sibling was superior to other types of treatment (11).

Table 1. Prognostic Factors in Acute Lymphoblastic Leukaemia

Risk Group	Proportion of Patients	Clinical and Laboratory Features
Standard risk	65%	Aged 1-9 years inclusive Leukocyte count $< 50 \times 10^9$/L No adverse cytogenetics
Higher risk	25%	Aged >10 years Leukocyte count $>50 \times 10^9$/L
Highest risk	8-9%	Infants under one year Hypodiploid, Ph' chromosome Induction failure
Special	1-2%	B-ALL

Table 2. Highest Risk Lymphoblastic Leukaemia

Category	Proportion of Patients	Reported EFS
Failed induction	1-2%	15%
Infants under 1	2-3%	30-40%
Ph^1 positive ALL	3-4%	28%
Near Haploid ALL	1-2%	15-20%
Hypodiploid ALL	6%	40%

There is little debate about the poor prognosis of the rare near-haploid ALL but the report that ALL in association with less than 45 chromosomes is associated with a poor prognosis (12) has not been confirmed by other groups.

2.1.1 Chemotherapy in Highest Risk Patients

Some published results of chemotherapy in highest risk patients are illustrated in Table 3. These patients have not all been selected on biological criteria and are a heterogeneous group, including some children who are older, have T-ALL and / or a high Leukocyte count, in addition to those with cytogenetic abnormalities, such as Ph^1. Overall the reported event-free survival with chemotherapy is of the order of 30-40%.

2.1.2. Evaluation of BMT in first remission

There has always been reluctance in ALL, in contrast to AML, to recommend or to evaluate high dose therapy and BMT in first remission. This is partly because the overall results in ALL have historically been superior, but also because of a "wait and see" attitude with the concept that BMT can be used as second line treatment for children who fail therapy in first remission. The main problem of this approach for highest risk children, who tend to relapse early, is that second remissions in this population tend to be very unstable, and that BMT like other forms of treatment, is associated with a high risk of subsequent relapse. For example, in an unselected population of all children relapsing after the MRC UKALL X trial (1985-90), only 3% of 106 children with a bone marrow or combined relapse within two years of diagnosis remained alive in second remission, despite further intensive chemotherapy or BMT (17).

The evaluation of BMT in first remission of ALL, as in other diseases, is fraught with logistic and statistical problems. Many small reports come from transplant centres and have no comparable group of patients receiving chemotherapy. The inherent delays in time to transplant may introduce bias. The selection criteria for BMT are inconstant, and often include a mixture of biological and clinical variables. It is impossible to perform randomised trials of BMT and this leads to selection bias, which may be partly overcome by comparing outcome by donor availability rather than actual treatment.

2.1.3. Comparative Studies of BMT and chemotherapy

Most of these studies have been relatively small and retrospective. A Scandinavian case- control study compared 22 patients receiving sibling BMT with 44 closely matched controls (18) and an Italian study compared 30 children receiving BMT with 130 matched controls with similar clinical features (19). Both reports concluded that BMT reduced the risk of relapse.

A recent large American study has compared the outcome for 201 patients who received BMT in first remission ALL and reported to the IBMTR with 683 case matched controls treated by the paediatric oncology group. The definition of very high risk ALL was based on age, Leukocyte count and immunophenotype and patients with Ph^1 positive ALL and t (4;11) were excluded. At ten years of follow up the group of patients with non T-ALL who received BMT had a significant difference in leukaemia–free survival (39% cf 58%), but no difference in overall survival (55% vs 61%). The group with T-ALL showed no significant difference in LFS between chemotherapy (53%) and BMT (63%) and no difference in survival (20).

In the UK we have tried to compare BMT and chemotherapy prospectively in MRC UKALL X (21), and the successor trial UKALL XI, a similar protocol. The results, recently updated (22), compared the outcome of BMT and chemotherapy in a group of highest risk children aged 1-15 treated on the two trials. The highest risk group comprised 13% of the total population. The initial plan was to confine BMT to children with a histocompatible sibling donor, but while only 76 of the 99 children with a donor proceeded to BMT an additional 25 received BMT from a matched unrelated donor. The median time to transplant was five months.

The results comparing children who received either family or unrelated donor transplants are shown in Table 4. Results are shown both unadjusted and after allowing for time to transplant, Leukocyte count, Ph^1 chromosome and ploidy. It can be seen that there was a highly significant increase in treatment related deaths in the transplant group and a significant decrease in relapses in the transplant group. The net result was that there was no benefit overall for BMT.

In order to avoid bias the results were also analysed according to the availability of a histocompatible sibling donor and these are shown in Table 5. Again,

Table 3. Reported Results of Chemotherapy in Highest Risk Patients

Study Group	Criteria	Proportion of Patients	EFS (SE)
AEIOP 91 (13)	Steroid Response	10%	40% (3)
BFM 90 (14)	Poor steroid Response	10.3%	35% (3)
Nordic studies (15)	WBC, age, chromosomes	10%	30-60%
UKALL X (16)	Age, WBC, gender	11%	40%

Table 4. Comparison of BMT and Chemotherapy (CT) in MRC UKALL X and XI

Events	No.	Unadjusted	Unadjusted*	Adjusted
	BMT	CT	Odds ratio (95% CI) p	Odds ration (95% CI) p
Total	101	350		
Relapse	31	188	0.62 (0.45-0.86) p<0.01	0.65 (0.45-0.93) p<0.05
CR death	18	11	10.34 (4.29-28.89) p<0.001	20.42 (7.30-57.11) p< 0.001
Any event	49	199	0.86 (0.64-1.16)	0.94 (0.67-1.33)

Table 5. Comparison of results by donor availability

Events	Donor Match		Unadjusted	Adjusted
	Yes	No	Odds ratio (95% CI) p	Odds ratio (95% CI) p
Total	99	187		
Relapse	36	96	0.73 (0.51-1.05)	0.92 (0.61-1.40)
CR death	16	5	6.08 (2.48-14.91) p<0.001	13.67 (4.73-39.50) p<0.001
Any event	52	101	0.98 (0.70-1.37)	1.32 (0.90-1.95) **

** if censored at UD transplant odds ratio = 1.26 (0.86-1.87)

sibling donor availability was associated with an increased risk of remission death, but and no overall benefit. The results were not influenced by censoring the children who received unrelated donor transplants.

Thus in this relatively large series of patients any possible decrease in relapse rate was outweighed by the increased transplant related mortality.

In conclusion, there is no evidence at present that BMT is superior to conventional treatment in the broad group of children with highest risk ALL. There may, however be a case, for prospective evaluation of BMT in clearly defined subsets of patients.

2.1.4. BMT for Selected Highest Risk Groups

Patients who do not achieve haematological remission at 28 days are a heterogeneous group, including some with classic high risk features or adverse cytogenetics. Their prognosis is poor but they may achieve leukaemia free survival with BMT (23) and delayed remission should be considered as an indication.

The most distinct group of highest risk children are those with Ph^1 postive leukaemia. The recent large multinational retrospective study (11) showed that only BMT from a family matched donor was superior to chemotherapy. In view of the poor prognosis of Ph^1 ALL and recent more encouraging reports of successful UDBMT (24,25) this option should be considered for children with Ph^1 positive ALL in first remission.

There is uniform agreement about the poor prognosis of many infants with ALL especially those with MLL gene rearrangement (26), or a poor response to steroids before induction (27). There are few reports of BMT in remission for infants and continuing uncertainty about the best preparative regimen. A small series from Chicago involved seven infants who received etoposide, and cyclophosphamide and also TBI (28), with four survivors. Many investigators would be reluctant to use TBI in this age group. More recently 41 infants with ALL have received unrelated donor cord blood transplants, 21 in first remission with an EFS of 65% at 2 years (29).

At present in the new international infant protocol it is proposed that BMT be evaluated for children with a poor steroid response. The significance of MLL gene rearrangement in older children remains controversial but there is some evidence that children aged 2-9 and t (4;11) may not have the poor prognosis of older and younger children (30).

3. CONCLUSIONS

The results of chemotherapy in higher risk children with ALL have improved, but there remains a rump of about 10% of children with an expected EFS of 40% or less. There is little evidence that the outlook for these children has, to date, been improved by BMT in first remission. However there is a place for investigation of BMT in clearly defined subsets of high-risk children. National and international collaboration will be needed to achieve this aim.

4. REFERENCES

1. Mastrangelo R; Poplack D; Bleyer A; Riccardi R; Sather H; D'Angio G: Report and Recommendations of the Rome Workshop Concerning Poor-Prognosis Acute Lymphoblastic Leukemia in Children: Biologic Bases for Staging, Stratification, and Treatment. *Med Pediatr Oncol* 14, 191-4 (1986)

2. Smith M; Arthur D; Camitta B; Carroll AJ; Crist W; Gaynon P; Gelber R; Heerema N; Korn EL; Link M; Murphy S; Pui CH; Pullen J; Reamon G; Sallan SE; Sather H; Shuster J; Simon R; Trigg M; Tubergen D; Uckun F; Ungerleider R: Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J Clin Oncol* 14, 18-24 (1996)

3. Chessells JM. The management of high-risk lymphoblastic leukemia in children. *Br J Haematol* 108, 204-16 (2000)

4. Gaynon PS; Steinherz PG; Bleyer WA; Ablin AR; Albo VC; Finklestein JZ; Grossman NJ; Novak LJ; Pyesmany AF; Reaman GH, *et al*.: Improved therapy for children with acute lymphoblastic leukemia and unfavourable presenting features: A follow-up report on the Children's Cancer Group Study CCG-106. *J Clin Oncol* 11, 2234-42 (1993)

5. Nachman JB; Sather HN; Sensel MG; Trigg ME; Cherlow JM; Lukens JN; Wolff L; Uckun FM; Gaynon PS: Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. *N Engl J Med* 338, 1663-71 (1998)

6. Patte C, Michon J, Frappaz D, Leverger G Rubie H, Soussain C, Pico JL . Therapy of Burkitt and other B-cell acute lymphoblastic leukaemia and lymphoma: Experience with the LMB protocols of the SFOP (French Paediatric Oncology Society) in children and adults. *Ballieres Clin Haematology* 7, 339-48 (1994)

7. Silverman LB; Gelber RD; Young ML; Dalton VK; Barr RD; Sallan SE: Induction failure in acute lymphoblastic leukemia of childhood. *Cancer* 85, 1395-404 (1999)

8. Janka-Schaub GE; Harms D; Goebel U; Graubner U; Gutjahr P; Haas RJ; Juergens H; Spaar HJ; Winkler K: Randomized comparison of rotational chemotherapy in high-risk acute lymphoblastic leukaemia of childhood--follow up after 9 years. Coall Study Group. *Eur J Pediatr* 155, 640-8 (1996)

9. Pui CH, Kane JR, Crist WM. Biology and treatment of infant leukemias. *Leukemia* 9, 762-9 (1995)

10. Reaman GH; Sposto R; Sensel MG; Lange BJ; Feusner JH; Heerema NA; Leonard M; Holmes EJ; Sather HN; Pendergrass TW; Johnstone HS; O'Brien RT; Steinherz PG; Zeltzer PM; Gaynon PS; Trigg ME; Uckun FM: Treatment outcome and prognostic factors for infants with acute lymphoblastic leukemia treated on two consecutive trials of the Children's Cancer Group [see comments]. *J Clin Oncol* 17, 445-55 (1999)

11. Arico M; Valsecchi MG; Camitta B; Schrappe M; Chessells J; Baruchel A; Gaynon P; Silverman L; Janka-Schaub G; Kamps W; Pui CH; Masera G: Outcome of treatment in children with philadelphia chromosome-positive acute lymphoblastic leukemia. *N Engl J Med* 342, 998-1006 (2000)

12. Heerema NA; Nachman JB; Sather HN; Sensel MG; Lee MK; Hutchinson R; Lange BJ; Steinherz PG; Bostrom B; Gaynon PS; Uckun F: Hypodiploidy with less than 45 chromosomes confers adverse risk in childhood acute lymphoblastic leukemia: A report from the children's cancer group. *Blood* 94, 4036-46 (1999)

13. Conter V; Arico M; Valsecchi MG; Rizzari C; Testi A; Miniero R; Di Tullio MT; Lo Nigro L; Pession A; Rondelli R; Messina C; Santoro N; Mori PG; De Rossi G; Tamaro P; Silvestri D; Biondi A; Basso G; Masera G: Intensive BFM chemotherapy for childhood ALL: interim analysis of the AIEOP-ALL 91 study. Associazione Italiana Ematologia Oncologia Pediatrica. *Haematologica* 83, 791-9 (1998)

14. Schrappe M; Reiter A; Ludwig WD; Harbott J; Zimmermann M; Hiddemann W; Niemeyer C; Henze G; Feldges A; Zintl F; Kornhuber B; Ritter J; Welte K; Gadner H; Riehm H: Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. *Blood* 95, 3310-22 (2000)

15. Gustafsson G, Kreuger A, Clausen N *et al*. Gustafsson G; Kreuger A; Clausen N; Garwicz S; Kristinsson J; Lie SO; Moe PJ; Perkkio M; Yssing M; Saarinen-Pihkala UM: Nordic Society of Paediatric Haematology and Oncology (NOPHO). *Acta Paediatr* 87, 1151-61 (1998)

16. Chessells JM, Bailey C, Richards SM. Intensification of treatment and survival in all children with lymphoblastic leukaemia: results of UK Medical Research Council trial UKALL X. *Lancet* 345, 143-8 (1995)

17. Wheeler K, Richards S, Bailey C, Chessells JM. Comparison of bone marrow transplant and chemotherapy for relapsed childhood acute lymphoblastic leukaemia - the MRC UKALL X experience. *Br J Haematol* 101, 94-103 (1998)

18. Saarinen UM; Mellander L; Nysom K; Ringden O; Schroeder H; Glomstein A; Gustafsson G: 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 Transpl* 17, 357-63 (1996)

19. Uderzo C, Valsecchi MG, Balduzzi A, Dini G, Miniero R, Locatelli F, Rondelli R, Pession A, Arcese W, Bacigalupo A, Polci P, Andolina M, Messina C, Conter V, Arico M, Galimberti S, Masera G. Allogeneic bone marrow transplantation versus chemotherapy in high-risk childhood acute lymphoblastic leukaemia in first remission. Associazione Italiana di Ematologia ed Oncologia Pediatrica (AIEOP) and the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). *Br J Haematol* 96, 387-94 (1997)

20. Warwick AB, Zhang M-J, Camitta BM, Shuster JJ, Horowitz MM. Chemotherapy versus HLA-identical sibling bone marrow transplantation for childhood acute lymphoblastic leukemia (ALL) in first remission. [Abstract] *Blood* 99 A.D.;94:(Supplement 1)350a (1999)

21. Chessells JM, Bailey C, Wheeler K, Richards SM. Bone marrow transplantation for high-risk childhood lymphoblastic leukaemia in first remission: experience in MRC UKALL X. *Lancet* 340 (ii), 565-8 (1992)

22. Wheeler K, Richards S, Bailey C, Gibson B, Hann IM, Hill FG, Chessells JM. Comparison of bone marrow transplantation with chemotherapy for high risk childhood acute lymphoblastic leukaemia in first remission. *Blood* 96, 2412-8 (2000)

23. Biggs JC; Horowitz MM; Gale RP; Ash RC; Atkinson K; Helbig W; Jacobsen N; Phillips GL; Rimm AA; Ringden O.: Bone marrow transplants may cure patients with acute leukemia never achieving remission with chemotherapy. *Blood* 80, 1090-3 (1992)

24. Sierra J; Radich J; Hansen JA; Martin PJ; Petersdorf EW; Bjerke J; Bryant E; Nash RA; Sanders JE; Storb R; Sullivan KM; Appelbaum FR; Anasetti C: Marrow transplants from unrelated donors for treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* 90, 1410-4 (1997)

25. Marks DI; Bird JM; Cornish JM; Goulden NJ; Jones CG; Knechtli CJ; Pamphilon DH; Steward CG; Oakhill A: Unrelated donor bone marrow transplantation for children and adolescents with Philadelphia-positive acute lymphoblastic leukemia. *J Clin Oncol* 16, 931-6 (1998)

26. Behm FG; Raimondi SC; Frestedt JL; Liu Q; Crist WM; Downing JR; Rivera GK; Kersey JH; Pui CH: Rearrangement of the MLL gene confers a poor prognosis in childhood acute lymphoblastic leukemia, regardless of presenting age. *Blood* 87, 2870-7 (1996)

27. Dordelmann M; Reiter A; Borkhardt A; Ludwig WD; Gotz N; Viehmann S; Gadner H; Riehm H; Schrappe M: Prednisolone response is the strongest predictor of treatment outcome in infant acute lymphoblastic leukemia. *Blood* 94, 1209-17 (1999)

28. Pirich L; Haut P; Morgan E; Marymount M; Kletzel M: Total body irradiation, cyclophosphamide, and etoposide with stem cell transplant as treatment for infants with acute lymphocytic leukemia. *Med Pediatr Oncol* 32, 1-6 (1999)

29. Scaradavou S, Castellino SM, Stevens CE, Brochstien J, Wagner J, Kletzel M, Yu L, Rubinsrein J, Kurtzberg J.. Acute lymphoblastic leukemia in infancy: improved outcome with unrelated placental cord blood (PCB) transplants. [Abstract] *Blood* 94, (Suppl 1)712a (1999)

30. Johansson B; Moorman AV; Haas OA; Watmore AE; Cheung KL; Swanton S; Secker-Walker LM: Hematologic malignancies with t(4;11)(q21;q23) - a cytogenetic, morphologic, immunophenotypic and clinical study of 183 cases. European 11q23 Workshop participants. *Leukemia* 12, 779-8 (1998)

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