

* CHAPTER 36

HSCT for acute lymphoblastic leukaemia in children

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1. Introduction

ALL in childhood is a disease which is currently curable by first line treatment in about 80% of cases. The BFM Study Group has reported an EFS at 8 years of 75.9% for patients in the ALL BFM 90 study (1). The same is true for other large study groups, for example the St. Jude Group (2). Even after relapse, e.g. late bone marrow and isolated extramedullary relapse, long term EFS of 35% and 44% can be achieved with conventional chemotherapy alone (3). Therefore, indications for stem cell transplantation in childhood ALL must be defined in close collaboration with study groups conducting chemotherapy trials. An excellent overview on the role of allo- and auto-HSCT is given in the systematic review of Theresa Hahn (4).

2. The role of allo-HSCT in ALL in first remission (CR1)

The role of allo-HSCT particularly in first remission of childhood ALL has been a matter of intense debate. There is an ongoing cooperative trial of the BFM, I-BFM and EBMT Paediatric Diseases Working Party study groups to define exactly the role of HSCT in CR1. The trial is based on four digit high-resolution HLA typing for all non-sibling donors, standardised GvHD prophylaxis and a uniform conditioning regimen. This is a prospective trial comparing HSCT and chemotherapy.

There is a broad agreement that at present a benefit for HSCT in first remission has been demonstrated only for high-risk ALL patients. Data on 326 children and young adults from study groups in several countries have been analysed (5). 267 patients achieved a complete remission after induction chemotherapy and were stratified into three subgroups; for these 267 patients the estimates of disease-free survival at 5 years were $49 \pm 5\%$ for the subgroup with the best prognosis, $30 \pm 5\%$ for patients with an intermediate prognosis and $20 \pm 5\%$ for the subgroup with the worst prognosis. An analysis of the role of post-remission therapy demonstrated that transplantation of bone marrow from HLA identical related donors ($n=38$) offered significantly greater benefit than intensive chemotherapy alone in terms of protecting patients from relapse or other adverse events (relative risk 0.3) whereas other types of transplantation (matched unrelated donors, mismatched related donors and autologous transplantation) had no benefit compared to chemotherapy alone. This finding was consistent in all three risk groups. In a more recent study in very high-risk ALL (defined as failure to achieve complete remission after the first four-drug induction phase; $t(9;22)$ or $t(4;11)$ clonal abnormalities; poor response to prednisone in combination with T-immunophenotype and/or white blood cell count $>100 \times 10^9/L$) a comparison was made between children treated with chemotherapy alone or HSCT from an HLA matched sibling donor (6). 357 children entered the study of whom 280 were treated by chemotherapy and 77 by sibling donor transplantation.

5-year-DFS was 40.6% in children treated with chemotherapy alone and 56.7% in children receiving stem cell transplantation.

3. The role of allo-HSCT in second and subsequent remission (\geq CR2)

There is evidence for the superiority of allo-HSCT from HLA-identical siblings in patients with bone marrow and combined relapses. However the benefit of unrelated allo-HSCT is restricted to certain subgroups.

Barrett (7) analysed data of 376 HLA identical sibling transplants in comparison to 540 children treated with chemotherapy alone by the American Pediatric Oncology Group in second remission after a bone marrow relapse. The mean probability of a relapse at 5 years was significantly lower among transplant recipients ($45 \pm 4\%$) compared to the chemotherapy recipients ($80 \pm 3\%$, $p < 0,001$); correspondingly the 5 year probability of leukaemia-free survival was higher after transplantation ($40 \pm 3\%$) than after chemotherapy ($17 \pm 3\%$, $p < 0,001$). Uderzo (8) compared the results of allo-HSCT with those obtained with chemotherapy in second complete remission for the Italian Bone Marrow Transplantation Group and the Italian Paediatric Haematology Oncology Association. Of 287 eligible patients 230 were treated with chemotherapy and 57 underwent allo-HSCT. After transplant the DFS was significantly longer than after chemotherapy (relative risk 0.54); in this analysis, in contrast to the Barrett analysis, no benefit was found for patients with a late relapse. Harrison (9) presented the results of the MRC UKALL R1 trial analysed by HLA matched donor availability. In this analysis patients with a first remission less than 2 years having a donor had a significant advantage over patients having no donor ($p = 0.05$). For the BFM relapse (ALL-REZ BFM) study group Borgmann (10) performed a matched-pair analysis comparing unrelated donor transplantation with continuation of chemotherapy after a first relapse. 81 pairs were identified that could be matched for site of relapse and immunophenotype and as closely as possible for duration of first remission, age, date of diagnosis and peripheral blast cell count at relapse. For patients with intermediate prognosis no benefit for unrelated donor transplantation was found, whereas for patients with a poor prognosis benefit was evident (probability of EFS at 4 years 0.44 ± 0.7 for patients after unrelated HSCT vs. 0.00 for patients with chemotherapy alone). Taken together, for patients with a high risk of relapse related or unrelated allo-HSCT is clearly of benefit.

4. Haploidentical transplantation (haplo-HSCT)

For patients lacking an HLA identical sibling donor in the family and where an HLA identical unrelated donor cannot be identified in time, stem cell transplantation from

a mismatched family member (haploidentical stem cell transplantation) is an alternative.

It has been shown in children with ALL transplanted with large numbers of purified CD34+ stem cells and low numbers of CD3+ cells (below $2.5 \times 10^3/\text{kg}$) that an engraftment rate of more than 95% can be achieved and a long term leukaemia free survival of $44 \pm 11\%$ is possible. There was no statistical difference in survival for patients with 1, 2 or 3 antigen-mismatched donors or for patients in first, second or third remission. However as well as the relapses (10 patients of 27) there were 7 cases of transplant related mortality (11). With a new technique for CD3/CD19 depletion a more reliable engraftment and a more rapid T-cell reconstitution can be seen. It is expected that using this approach the rates of TRM can be reduced (12).

5. The role of outcome of cord blood transplantation

Since the first report on the use of cord blood for stem cell transplantation many children with ALL have been treated in first and second CR. In a large registry analysis (13) 503 children with ALL transplanted with umbilical cord blood were compared with 282 bone marrow recipients. All patients had been treated in the USA. Cord blood was either fully matched ($n = 35$), mismatched for one HLA-antigen ($n = 201$) or for 2 antigens ($n = 267$); donor marrow was matched at the allele level for HLA A, B, C and DRB ($n = 116$) or mismatched ($n = 166$). The five year probabilities of leukaemia free survival were 38% after HLA-matched bone marrow transplants, 37% after mismatched bone marrow transplants, 60% after HLA-matched cord blood transplants, 36% after one antigen mismatched cord-blood transplant with low cell dose, 45% after one antigen mismatched cord-blood with high cell dose and 33% after two antigen-mismatched cord blood. Therefore, it seems that umbilical cord blood in experienced centres plays a role for the treatment of patients with ALL.

6. Related versus unrelated allo-HSCT

In spite of a large number of studies, the outcome of related vs. unrelated donor allogeneic stem cell transplantation has not yet been adequately studied. There are no reported studies that compare outcome of HLA identical sibling donors with unrelated donors matched on allele level. Here the results of the BFM/IBFM/EMBT studies are pending. However there is an analysis from Eapen (14) in which the results of unrelated donor transplantation with bone marrow ($n = 85$) or cord blood ($n = 81$) were compared with those of HLA matched sibling transplants ($n = 101$) for acute leukaemia (ALL and AML) in children. Treatment related mortality was 6% for matched sibling transplantation, 15% for unrelated donor and 31% for cord blood

HSCT respectively. The reason for the higher mortality rates is presumed to be secondary to slower myeloid recovery and higher rates of death from infections. Risks of relapse, overall and leukaemia free survival rate were closely associated with disease state at transplantation. However, leukaemia recurrence was lowest after unrelated donor HSCT in first clinical remission. After adjustment for disease status overall survival and leukaemia-free survival were similar after matched sibling and unrelated donor bone marrow or cord blood transplantation. It can be expected that using the same eligibility criteria results for related and unrelated stem cell transplantation for adequately matched donors will be identical.

7. Comparison of conditioning regimen

It is accepted that TBI containing regimens in ALL have better outcomes than non-TBI containing regimen (15).

8. The role of additional cellular leukaemia therapy post transplant

There has been a long-term debate as to whether ALL is a subject for immunotherapy. If additional immunotherapy is offered to patients who have already relapsed after transplantation only a very few patients will respond. It seems to be important to offer such treatment pre-emptively to avoid frank relapse. It was shown in a prospective study in 163 children with ALL in different remission states transplanted from sibling, unrelated and haploidentical donors that pre-emptive immunotherapy has an important effect on chimerism and thereby prevents relapse (16). There were 101 patients with complete chimerism, whereas increasing mixed chimerism was found in 46 and decreasing in 16 patients. Relapse was significantly more frequent in patients with increasing mixed-chimerism (26/46), whereas in patients with complete or low level chimerism only 8/101 relapsed and there were no relapses in patients with decreasing mixed-chimerism. The probability of three year EFS was 54% for all patients, 66% for patients with complete or low level mixed-chimerism, 66% for patients with decreasing mixed-chimerism and 23% for patients with increasing mixed chimerism. Of the 46 patients with increasing mixed chimerism 31 received immunotherapy and this group had a significant higher three year EFS (37%) than the 15 patients who did not receive any immunotherapy (EFS 0%). It can therefore be concluded that immunotherapy either by withdrawal of cyclosporin A or additional donor lymphocyte infusion alters the fate of patients with increasing mixed-chimerism.

9. Role of minimal residual disease monitoring after stem cell transplantation

It is well known that relapse is the most frequent complication after allo-HSCT in

childhood leukaemia. It is now possible to measure minimal residual disease (MRD) by real time quantitative PCR frequently and nearly in real time after HSCT. However, results of large prospective trials within IBFM and EBMT Paediatric Working Party are pending.

10. Conclusions

The benefit of allo-HSCT in ALL patients in CR1 for high-risk subgroups has been established. In CR2 related HLA identical transplantation has proven as the gold standard of care. There is a clear indication for unrelated donor transplantation in all high-risk subgroups, whereas its role for low-risk groups needs to be defined within current clinical trials.

Cord blood and haploidentical donors widen the spectrum of allo-HSCT in children. In experienced centres the same results can be achieved as in unrelated donor transplants.

Pre-emptive immunotherapy post HSCT may be effective. The role of MRD analysis post transplant is still under investigation.

References

1. Schrappe M, Reiter A, Zimmermann M. Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995. Berlin-Frankfurt-Munster. *Leukemia* 2000; 14: 2205-2222.
2. Pui CH, Sandlund JT, Pei D. Improved outcome for children with acute lymphoblastic leukemia: Results of Total Therapy Study XIIIIB at St. Jude Children's Research Hospital. *Blood* 2004; 104: 2690-2696.
3. Einsiedel HG, von Stackelberg A, Hartmann R. Long-term outcome in children with relapsed ALL by risk-stratified salvage therapy: Results of trial acute lymphoblastic leukemia-relapse study of the Berlin-Frankfurt-Munster Group 87. *J Clin Oncol* 2005; 23: 7942-7950.
4. Hahn T, Wall D, Camitta B. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in children: An evidence-based review. *Biol Blood Marrow Transplant* 2005; 11: 823-861.
5. Arico M, Valsecchi MG, Camitta B. Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. *N Engl J Med* 2000; 342: 998-1006.
6. Balduzzi A, Valsecchi MG, Uderzo C. 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.
7. Barrett AJ, Horowitz MM, Pollock BH. Bone marrow transplants from HLA-identical siblings as compared with chemotherapy for children with acute lymphoblastic leukemia in a second remission. *N Engl J Med* 1994; 331: 1253-1258.
8. Uderzo C, Valsecchi MG, Bacigalupo A. Treatment of childhood acute lymphoblastic

- leukemia in second remission with allogeneic 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; 13: 352-358.
9. Harrison G, Richards S, Lawson S. Comparison of allogeneic transplant versus chemotherapy for relapsed childhood acute lymphoblastic leukaemia in the MRC UKALL R1 trial. MRC Childhood Leukaemia Working Party. *Ann Oncol* 2000; 11: 999-1006.
 10. Borgmann A, von Stackelberg A, Hartmann R. 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.
 11. Klingebiel T, Handgretinger R, Lang P. Haploidentical transplantation for acute lymphoblastic leukemia in childhood. *Blood Rev* 2004; 18: 181-192.
 12. Bader P, Willasch A, Niethammer D. Haploidentical stem cell transplantation in childhood. *Current Cancer Therapy Reviews* 2007; 3: 37-44.
 13. Eapen M, Rubinstein P, Zhang MJ. 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.
 14. Eapen M, Rubinstein P, Zhang MJ. Comparable long-term survival after unrelated and HLA-matched sibling donor hematopoietic stem cell transplantations for acute leukemia in children younger than 18 months. *J Clin Oncol* 2006; 24: 145-151.
 15. Eapen M, Raetz E, Zhang MJ. 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.
 16. Bader P, Kreyenberg H, Hoelle W. Increasing mixed chimerism is an important prognostic factor for unfavorable outcome in children with acute lymphoblastic leukemia after allogeneic stem-cell transplantation: Possible role for pre-emptive immunotherapy? *J Clin Oncol* 2004; 22: 1696-1705.

Mutiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/ebmt-handbook2008answers.htm>

1. Which one of the following statements about transplantation in ALL is correct?

- a) A benefit for allogeneic stem cell transplantation in ALL-patients has been demonstrated for all patients in first remission.....
- b) It has been proven that transplantation from all donors protects children with high-risk and very high-risk leukaemia from relapse.....
- c) It has been proven that transplantation from identical related donors protects patients with high risk ALL from relapse.....

- d) It has been proven that autologous stem cell transplantation protects patients with high risk ALL in first remission from relapse

2. Which one of the following statements about transplantation in ALL is correct?

- a) There is evidence that unrelated stem cell transplantation protects children with CR2 in all risk groups from relapse
- b) There is evidence that patients with high risk ALL in CR2 (short first remission, T-cell-phenotype etc.) benefit from unrelated transplantation
- c) There is evidence that chemotherapy is of advantage in CR2 in early relapse
- d) There is no controversy about the role of allo-stem cell transplantation from patients with late relapse

3. Which one of the following statements about haploidentical transplantation in ALL is correct?

- a) The number of CD34⁺-cells does not affect outcome
- b) The number of CD3⁺-cells should be below one million per kg
- c) Patients receiving haploidentical transplantation for ALL in remission can have a long term leukaemia free survival of more than 40%
- d) TRM is not higher in haploidentical transplantation than in other forms of transplantation

4. Which one of the following statements about transplantation in ALL is correct?

- a) Umbilical cord blood does not play any role for treatment of patients ALL
- b) Even with one or two antigens mismatched cord blood results are comparable with allele matched bone marrow
- c) Treatment related mortality is not higher for cord blood transplantation
- d) The risk of relapse is not associated with disease state at transplantation

5. Which one of the following statements about transplantation in ALL is correct?

- a) There is no evidence that TBI is better than other conditioning regimen in ALL.....
- b) There is evidence that DLI after stem cell transplantation can convert chimerism and prevent relapse.....
- c) Immunotherapy (e.g. reduction of CSA) is useless in ALL.....
- d) There is clear proven data from large trials that MRD post transplantation has an influence on outcome.....

NOTES