Treatment of Pediatric ALL

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The prognosis of Acute Lymphoblastic Leukaemia (ALL) in children has significantly improved with the use of modern therapeutic protocols. Currently, about 80% of children with ALL are cured with chemotherapy alone[1].

Stem Cell Transplantation (SCT) plays an important role in patients with very high-risk (VHR) ALL in first remission or second complete remission (CR). Unfortunately, 70% of patients who might benefit from this therapy lack an HLA-matched sibling donor, and HLA polymorphism is still a major obstacle in finding a fully matched unrelated donor (UD) for 40% of the patients for whom the search for an UD is activated.[2] That is why several Institutions have recently explored alternative sources for SCT, such as unrelated Umbilical Cord Blood (UCB) or mismatched relatives (i.e. Haploidentical Transplantation: HT). [3-4]

Stem Cell Transplantation (SCT) in First Complete Remission (CR1) ALL

Children with VHR CR1 ALL, as defined in Table 1,[5] benefit more from related donor SCT than from chemotherapy. The gap between the two strategies increases as the risk profile of the patient worsens[6].

This is related to a higher relapse rate in children lacking a matched sibling donor (MSD), as compared to children with a MSD.

Stem Cell Transplantation (SCT) in Second Complete Remission (CR2) ALL

The I-BFM Study Group has defined Indications for allogeneic SCT in CR2 ALL, on the basis of the site and timing of the relapse (Table 2)[5]. DFS of patients given a MSD SCT following early relapse is significantly higher, as compared to chemotherapy. For those experiencing late relapse, the difference does not reach statistical significance.[7, 8]

Unrelated Donor Stem Cell Transplantation (UD-SCT)

Over the last 25 years, more than 18,000 UD-SCTs have been performed world-wide and facilitated by a network that includes more than 11 million volunteer UDs enrolled in 89 registries. Currently, a suitable donor is located for 85% of the patients for whom a search is activated, and 70% of the donor phenotypes are found more than 4 times. The outcome of UD-SCT correlates with HLA matching: a single Class I or a single Class II mismatch is not relevant; multiple Class II mismatches are better than multiple Class I mismatches, which are better than Class I plus Class II mismatches[2] .Presently, the outcome of children with CR2 ALL given an UD SCT is comparable to that of SCT from MSDs. This improvement is mainly due to refinements in HLA typing, GvHD prophylaxis and supportive care.[9, 10]

Unrelated Umbilical Cord Blood Transplantation

Throughout the last 7 years, 373 Transplant Centres in 43 countries have performed more than 3,000 UCBTs by means of a network that includes more than 130,000 cord blood units in 37 banks. In children, the results of UD bone marrow or UCBT are similar; however, types of complications differ, with more GvHD being observed in the UD

Table 1. Indications for CR 1

Very high risk	MSD	UD	Haplo
PPR & t (9:22)	+	+	+
NR day 33	+	+	+
MRD day 77: > 102	+	+	+
Pro-B-ALL	+	+	-
M3 day 15 (except T)	+	+	-
WBC > 100,000/μl (except T)	+	+	-
T-ALL: siblings only	+	+	-
Hopefully benefit	+	-	-
PGR & t(4;11)	+	-	-

MSD, matched sibling donor; ; UD, unrelated donor; Haplo, haploidentical; BM, bone marrow; PPR, prednisone poor responders; MRD, minimal residual disease; NR, non responders; WBC, white blood cell count; PGR prednisone good responders

Table 2. Indications for CR2, > CR2

Very High Risk			MSD	UD	Haplo
all T-phenotypes			+	+	+
Non T:	Very early	BM Or combined	+	+	+
	Or early		+	+	+
(> CR 2)			+	+	+
High risk			+	+	-
non T:	Early combined	MRD n.r. MRD > 103	+	+	-
	Late BM		+	+	-
all	T (9;22)		+	+	-
"Standard risk"			+	-	-
non T:	Late BM		+	-	-
	Late combined	MRD < 103	+	-	-

MSD, matched sibling donor; ; UD, unrelated donor; Haplo, haploidentical; BM, bone marrow; MRD, minimal residual disease

SCT group and more early deaths in the UCBT group. UCBT is a reasonable option when there is no HLA identical donor available.[4]

Haploidentical Transplantation

Few reports are available regarding the use of haploidentical transplantation for childhood ALL. This approach offers a promising treatment option for children with ALL requiring an urgent transplantation but lacking a suitable donor.[3, 11]

Autologous Stem Cell Transplantation

ABMT is an effective treatment modality after early, isolated**,** extramedullary relapse, however only a few patients survive after late bone marrow relapse.[12]

Conclusions

A summary of the results that have been achieved by various strategies are reported in Table 3. We suggest that when a patient is found to have an indication for SCT, HLA typing of the patient, of the parents and siblings must be performed, including the study of ABC loci with median resolution and of DR and DQ loci with high resolution techniques. The AB0 group must be studied as well. If a MSD or a phenotypically matched or 1-antigen mismatched relative is available, the patient should proceed to transplantation as soon as possible. Otherwise, the patient should be HLA-typed by high-resolution testing and a simultaneous search for an UD and an UCB should be started. A crucial point is the impact of the marrow UD search duration on the outcome of children with CR2: relapse during the search is the main limiting factor for the success of UD SCT in children with CR2 ALL.[13] On the basis of whether an UD or an UCB is available within 3 months from search activation, one of the 2 options must be offered or, as an alternative, haploidentical SCT should be performed.

A further improvement in results of transplants from alternative donors should be achieved by an extensive and accurate HLA typing (allele level: A, B, C, DR, DQ, DP) to select the best match among the alternative sources of SC donors, by reducing the the relapse incidence (monitoring minimal residual disease and chimerism, modulation of GvHD prophylaxis and treatment) and by reducing toxicity and infections through homogeneous supportive care and monitoring of viral and fungal infections.

Future goals include: improving results of transplants from alternative donors through precise HLA typing and homogeneous donor selection reducing relapse incidence, shortening GvHD-prophylaxis, and monitoring minimal residual disease and chimerism; reducing toxicity and infections through homogeneous supportive care and monitoring of viral and fungal infections.

Table 3. Results of various strategies

Allo SCT from MSD	superior to CT in high risk patients
Allo SCT from UD	Comparable to Allo SCT from MSD
T-cell depletion	Promising treatment option
UCB transplantation	Comparable to UD SCT

Allo SCT, allogeneic stem cell transplant; MSD, matched sibling donor ; CT, chemotherapy; UD, unrelated donor; UCB,unrelated cord blood transplant

References

1. Schrappe M, Reiter A, Zimmermann M, Harbott J, Ludwig WD, Henze G, Gadner H, Odenwald E, Riehm H. 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. Petersdorf EW, Anasetti C, Martin PJ, Gooley T, Radich J, Malkki M, Woolfrey A, Smith A, Mickelson E, Hansen JA. Limits of HLA mismatching in unrelated hematopoietic cell transplantation. Blood. 2004 Nov 1;104(9):2976-80.
3. Handgretinger, T Klingebiel, P Lang, M Schumm, S Neu, A Geiselhart, P Bader, PG Schlegel, J Greil, D Stachel, RJ Herzog and D Niethammer Megadose transplantation of purified peripheral blood CD341 progenitor cells from HLA-mismatched parental donors in children. Bone Marrow Transplantation (2001) 27, 777–783
4. Rocha V, Cornish J, Sievers EL, Filipovich A, Locatelli F, Peters C, Remberger M, Michel G, Arcese W, Dallorso S, Tiedemann K, Busca A, Chan KW, Kato S, Ortega J, Vowels M, Zander A, Souillet G, Oakill A, Woolfrey A, Pay AL, Green A, Garnier F, Ionescu I, Wernet P, Sirchia G, Rubinstein P, Chevret S, Gluckman E. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. Blood 2001; 97: 2962-2971.
5. Peters C, Schrauder A, Schrappe M, von Stackelberg A, Stary J, Yaniv I, Gadner H, Klingebiel T; BFM Study Group, the IBFM-Study Group and the Paediatric Disease Working Party of the EBMT. Allogeneic haematopoietic stem cell transplantation in children with acute lymphoblastic leukaemia: the BFM/IBFM/EBMT concepts. Bone Marrow Transplant. 2005 Mar;35 Suppl 1:S9-11.
6. Balduzzi A, Valsecchi MG, Uderzo C, De Lorenzo P, Klingebiel T, Peters C, Stary J, Felice MS, Magyarosy E, Conter V, Reiter A, Messina C, Gadner H, Schrappe M. 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 Aug 20-26;366(9486):635-42.
7. Uderzo C, Valsecchi MG, Bacigalupo A, Meloni G, Messina C, Polchi P, Di Girolamo G, Dini G, Miniero R, Locatelli F, et al. 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 Feb;13(2):352-8.
8. Matsuzaki A, Nagatoshi Y, Inada H, Nakayama H, Yanai F, Ayukawa H, Kawakami K, Moritake H, Suminoe A, Okamura J. Prognostic factors for relapsed childhood acute lymphoblastic leukemia: impact of allogeneic stem cell transplantation--a report from the Kyushu-Yamaguchi Children's Cancer Study Group. Pediatr Blood Cancer. 2005 Aug;45(2):111-20.
9. Locatelli F, Zecca M, Messina C, Rondelli R, Lanino E, Sacchi N, Uderzo C, Fagioli F, Conter V, Bonetti F, Favre C, Porta F, Giorgiani G, Pession A. Improvement over time in outcome for children with acute lymphoblastic leukemia in second remission given hematopoietic stem cell transplantation from unrelated donors. Leukemia. 2002 Nov;16(11):2228-37.
10. Eapen M, Rubinstein P, Zhang MJ, Camitta BM, Stevens C, Cairo MS, Davies SM, Doyle JJ, Kurtzberg J, Pulsipher MA, Ortega JJ, Scaradavou A, Horowitz MM, Wagner JE. 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 Jan 1;24(1):145-51.
11. Klingebiel T, Handgretinger R, Lang P, Bader P, Niethammer D. Haploidentical transplantation for acute lymphoblastic leukemia in childhood. Blood Rev. 2004 Sep;18(3):181-92.
12. Messina C, Cesaro S, Rondelli R, Rossetti F, Locatelli F, Pession A, Miniero R, Dini G, Uderzo C, Dallorso S, Meloni G, Vignetti M, Andolina M, Porta F, Amici A, Favre C, Basso G, Sotti G, Varotto S, Destro R, Gazzola MV, Pillon M, Petris MG, Rabusin M, Scarzello G, et al. Autologous bone marrow transplantation for childhood acute lymphoblastic leukaemia in Italy. AIEOP/FONOP-TMO Group. Italian Association of Paediatric Haemato-Oncology. Bone Marrow Transplant. 1998 May;21(10):1015-21
13. Dini G, Valsecchi MG, Micalizzi C, Busca A, Balduzzi A, Arcese W, Cesaro S, Prete A, Rabusin M, Mazzolari E, Di Bartolomeo P, Sacchi N, Pession A, Georgiani G, Lanino E, Lamparelli T, Favre C, Bosi A, Manzitti C, Galimberti S, Locatelli F. Impact of marrow unrelated donor search duration on outcome of children with acute lymphoblastic leukemia in second remission. Bone Marrow Transplant 2003; 32: 325-31.