Eligibility for allogeneic transplantation in very high risk childhood acute lymphoblastic leukemia: the impact of the *waiting time*

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ABSTRACT

The advantage of allogeneic transplant from compatible related donors versus chemotherapy in children with very-high-risk acute lymphoblastic leukemia in first complete remission was previously demonstrated in an international prospective trial. This study quantified the impact of time elapsed in first remission in the same cohort. Of 357 pediatric patients with very-high-risk acute lymphoblastic leukemia, 259 received chemotherapy, 55 transplantation from compatible related and 43 from unrelated donors. The 5-year disease-free survival was 44.2% overall and 42.5% for chemotherapy only patients. The chemotherapy conditional 5-year disease-free survival increased to 44.4%, 47.6%, 51.7%, and 60.4% in patients who maintained their first remission for at least 3, 6, 9, and 12 months respectively. The overall outcome was superior to that obtained with chemotherapy-only at any time-point. The relative advantage of transplant from compatible related donors in very-high-risk childhood acute lymphoblastic leukemia was consistent for any time elapsed in first remission.

Key words: acute lymphoblastic leukemia, childhood, very high risk, waiting time to transplant, allogeneic transplantation.

Citation: Balduzzi A, De Lorenzo P, Schrauder A, Conter V, Uderzo C, Peters C, Klingebiel T, Stary J, Felice MS, Magyarosy E, Schrappe M, Dini G, Gadner H, and Valsecchi MG. Eligibility for allogeneic transplantation in very high risk childhood acute lymphoblastic leukemia: the impact of the waiting time. *Haematologica 2008; 93:925-929. doi: 10.3324/haematol.12291*

Introduction

In a previously reported international prospective study based on treatment allocation by genetic chance, we provided evidence that, among children with acute lymphoblastic leukemia, the 8% carrying very high risk characteristics and achieving first complete remission benefit from hematopoietic cell transplant from a compatible related donor (Table 1).[1] Results achieved by allogeneic transplant from related donors may nowadays be extrapolated to those from unrelated donors whose outcome is becoming increasingly similar due to improvements in HLA typing and supportive care.[2-6] Nevertheless, since the search for a donor requires time, subsequent transplant from unrelated donors is likely to occurr late.[7] Therefore, apart from eligibility *per se*, whenever transplant is delayed (most frequently due to no donor availability and search duration) its possible benefit must be re-evaluated. For example, we must ask ourselves whether transplant still offers advantages over chemotherapy to patients who, after experiencing induction failure, have already spent nine months in first remission. In this study, for the first time to our knowledge, the impact on prognosis of the time elapsed in CR1, therefore the potential influence of the *waiting time to transplant*, is quantified in the previously reported cohort of children with very high-risk acute lymphoblastic leukemia.

Acknowledgments: the authors wish to thank the "Comitato Maria Letizia Verga per lo studio e la cura della leucemia del bambino" for its continuous support and Andreina di Palma for her secretarial assistance.
Funding: this work was partially supported by grants from the Associazione Italiana Ricerca sul Cancro (AIRC) (to MGV).
Manuscript received September 26, 2007. Revised version arrived on January 9, 2008. Manuscript accepted January 11, 2008.
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Design and Methods

Patients

For the purpose of this study, all the 357 children enrolled were analyzed according to treatment received: 259 patients received chemotherapy (22 of them despite having a related donor available), 55 received hematopoietic cell transplant from a compatible related donor and 43 underwent transplant from an unrelated donor, thus deviating from the protocol design.

Statistical analysis

The primary endpoint of this study was time of disease-free survival (DFS), calculated as the time from achieving first remission to last follow-up or to the first event (relapse, death in complete remission or second malignant neoplasm). DFS curves were estimated according to Kaplan-Meier and standard errors (SE) according to the Greenwood formula. The DFS of transplanted patients was calculated from the date of transplant.

The *conditional 5-year disease-free survival* is the 5-year DFS of patients who are still in first remission at a given time (the conditioning time-point). It is defined as the ratio between the overall disease-free survival at 5 years (unconditonal) and at each conditioning time point. We started conditioning at year 0 (i.e. achievement of first remission), which results in the conventional 5-year DFS, up to conditioning at year 5, which results in the upper limit of 100% by definition. The conditional 5-year DFS was estimated for all patients and for those treated with chemotherapy only. This latter estimate was calculated by excluding patients who were transplanted before the conditioning time-point and censoring at the time of transplantation occurring thereafter. Estimates of the conditional 5-year DFS at the conditioning time-points of 3, 6, 9 and 12 months correspond to the 5-year DFS estimates calculated on the subgroups of patients who remained in first remission for at least the conditioning time.

Results and Discussion

All but 3 out of 55 transplants from compatible related donors were performed within six months after achieving first remission (13 in the first trimester and 39 in the second trimester), while only approximately half of 43 unrelated donor transplants were performed within six months after achieving first remission with 8, 15, 13, and 6 in each subsequent trimester, the latest being performed just after 13 months. Disease-free-survival at 5 years after transplant are shown in Table 1.

The innovative *conditional 5-year disease-free survival* is shown in Figure 1. At the origin (time zero) the 5-year DFS corresponds to the standard (unconditional) 5-year DFS of the entire cohort upon achieving first remission. This was 44.2% (SE 2.7) when calculated for all patients regardless of treatment received, i.e. without censoring at transplant (*any treatment*) and 42.5% (SE 3.2) for those treated with chemotherapy, i.e. with censoring at transplant (*chemotherapy only*). The conditional 5-year DFS (Figure 1) for the first year is relevant to the decision whether to transplant or not. For instance, the conditional 5-year DFS obtained by *chemotherapy only* was 44.4% (SE 3.3), 47.6% (SE 3.5), 51.7% (SE 3.6), and 60.4% (SE 3.9) at the conditioning time-points of 3, 6, 9, and 12 months (Figure 2).

For indirect comparison, the outcome of compatible related donor transplant (Table 1) is higher than the best conditional 5-year DFS obtained with chemotherapy only. The conditional 5-year DFS increases for patients who spent a progressively longer time in first remission. This was 76% (SE 3.9) for patients whose first remission elapsed at at least two years (the approximate time of elective discontinuation of chemotherapy) and 91.1% (SE 3.9) for those whose first remission elapsed at at least three years (approximately one year after off-therapy). When a conditioning time of five years was considered, the 5-year DFS was 100% by definition. Some very high risk patients actually maintained their first remission for up to five years with chemotherapy only, nevertheless the *any treatment* curve was consistently higher than the *chemotherapy only* curve for any first remission duration, suggesting the benefit of transplant.

Table 1. Outcome of the prospective international trial, performed in seven countries, between 1995 and 2000, enrolling 357 very high risk (VHR) acute lymphoblastic leukemia (ALL) children in first complete remission (CR1), with a median observation time of 5 years.[1]

		By ITT[a]		*By treatment received*[b]		
		N. donor	*Donor*	*Chemotherapy only*	*Compatible related donor*	*Unrelated donor*[c]
Overall	N	280	77	259	55	43
	5-year DFS	40.6 (3.1)	56.7 (5.7)	42.5 (3.2)	63.1 (6.6)	41.6 (7.6)
	p value		0.02		0.0169	
Induction failure	N	58	25	83	16	19
	5-year DFS	26.5 (5.9)	56.0 (9.9)	30.7 (7.3)	50.0 (12.5)	– (11 events)
	p value		0.03			
PPR+ only[c]	N	130	38	168	28	13
	5-year DFS	54.3 (4.5)	62.4 (8.0)	53.5 (4.5)	74.3 (8.4)	– (5 events)
	p value		0.32			

VHR features were defined by the presence of at least one of the following: (i) failure to achieve CR after the first four-drug induction phase (induction failure); (ii) t(9;22) or t(4;11) clonal abnormalities; (iii) prednisone poor response (PPR) after the first seven-day prednisone pre-phase associated with T immuno-phenotype and/or white blood cells (WBC) ≥100×10⁹/L at the onset. [a]ITT: intention to treat analysis, i.e. outcome is reported as per treatment allocation, according to availability of a compatible related donor [b]DFS time from date of transplantation, if performed [c]unrelated donor transplantations were not therapeutic options but deviations from the study design [c]PPR patients associated with T immuno-phenotype and/or WBC ≥100×10⁹/L, without induction failure or t(9;22) or t(4;11) translocation.

The two largest subgroups of our cohort included patients at very high risk due to the worst prognostic feature and to the least unfavourable feature. The former subset includes patients who failed to achieve first remission after the first four-drug induction phase (*induction failure*) and the latter subset includes patients with prednisone-poor-response after the first seven-day prednisone pre-phase, associated with T immunophenotype and/or WBC ≥100×10^9/L, who did not experience induction failure and did not present with t(9;22) or t(4;11) translocation (*PPR+ only)*. In both subgroups, nine months elapsed in first remission increased the 5-year DFS from 30.7 (SE 7.3) to 38.3 (SE 8.3) and from 53.5 (SE 4.5) to 64.6 (SE 4.9) for the two subgroups respectively (Figure 2). For indirect comparison, the outcome of compatible related donor transplant in each subgroup (Table 1) is higher than the best conditional 5-year DFS obtained with *chemotherapy only*. Among those with longer first remission duration, the proportion of the least unfavourable very high-risk feature *PPR+ only* progressively increased from 47% in the enrolled population to 48% and 58% in the 178 and 105 patients who maintained their first remission for at least one and three years, respectively. This study quantified for the first time how the outcome of children with very high risk acute lymphoblastic leukemia improves with time elapsed in first remission and proposes an indirect approach to account for the *waiting time* to transplant. Outcomes from chemotherapy after fixed first remission durations provide useful figures to compare with the expected outcome after transplant. The clinical issue is relevant when transplant is delayed due to organizational, financial or biological issues.[6] As soon as very high risk features and patient eligibility are recognized and a compatible related donor is not available, an unrelated donor search should be promptly initiated through worldwide international registries.

Nevertheless the time elapsed before transplant, defined as the *waiting time to transplant*, may be extended, especially when patients carry rare HLA haplo-

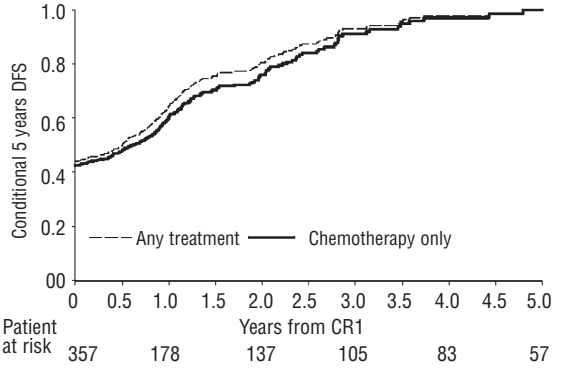
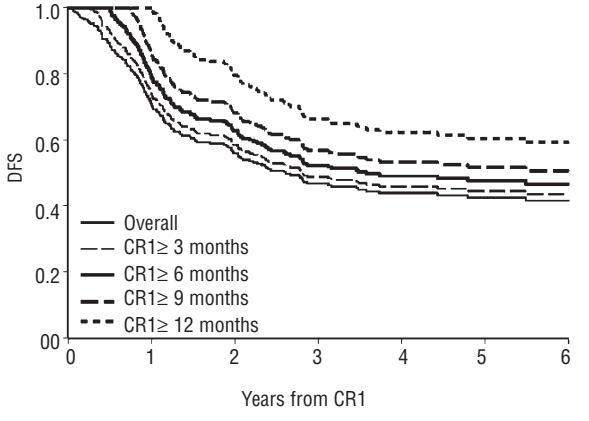


Figure 1. Conditional 5-year disease-free survival (DFS) of all patients, regardless of treatment received (dotted curve *any treatment*), and of patients treated with chemotherapy (continuous curve *chemotherapy only*). The effect of the time elapsed in CR1, depicted in the X-axis, on the conditional estimates of the 5-year DFS, depicted in the Y-axis. Each value of the two curves represents the standard 5-year-DFS calculated for patients still in CR at the time expressed in the X-axis. Values of the curves at the origin (time zero) are 44.2% (SE 2.7) for the entire cohort and 42.5% (SE 3.2) for chemotherapy patients, and correspond to the respective standard (unconditional) 5-year DFS. As progressively higher CR1 duration are considered, the curves steadily increase and show the projected 5-year DFS of patients who have been in CR1 for at least that time. The *any treatment* curve was consistently higher than the *chemotherapy only* curve, for any conditioning time, suggesting the benefit of transplant for any time elapsed in CR1.



	ALL PATIENTS			BY MAIN SUBGROUPS					
				INDUCTION FAILURE*			"PPR+ ONLY"		
Minimum time in CR1 (months)	N. pts.	N. events (relapses)	5-year DFS (SE)	N. pts.	N. events (relapses)	5-year DFS (SE)	N. pts.	N. events (relapses)	5-year DFS (SE)
0	357	150 (134)	42.5 (3.2)	83	34 (30)	30.7 (7.3)	168	61 (53)	53.5 (4.5)
3	320	135 (124)	44.4 (3.3)	64	30 (27)	32.4 (7.5)	154	52 (47)	56.5 (4.7)
6	247	116 (107)	47.6 (3.5)	42	24 (22)	36.5 (8.1)	119	44 (40)	60.0 (4.8)
9	212	97 (94)	51.7 (3.6)	37	22 (20)	38.3 (8.3)	102	36 (35)	64.6 (4.9)
12	178	67 (66)	60.4 (3.9)	31	17 (16)	44.5 (9.1)	86	21 (21)	75.8 (4.9)

Figure 2. Estimates of disease-free survival (DFS) of all patients at achievement of CR1 and after maintaining their remission for at least 3, 6, 9, and 12 months. Curves (upper panel) included all patients and are censored if and when they underwent transplant. Given the patients' selection, these Kaplan-Meier curves were characterized by an initial plateau and a subsequent decline, which reflected the events occurring after the minimum CR1 duration considered. The 5-year DFS of all patients and of the subsets of patients enrolled for *induction failure* and *prednisone poor response*. are reported in the table (lower panel). *Induction failure* (failure to achieve CR after the first four-drug induction phase) is the worst prognostic feature, and the so-called *PPR+ only* (i.e. prednisone poor response, associated with T immuno-phenotype and/or WBC ≥100×10^9/L, but not with induction failure or t(9;22) or t(4;11) translocation) is the least unfavourable feature. In both subgroups the 5-year DFS increased with time elapsed in CR1.

types. In our cohort, almost all transplants from compatible related donors were performed within six months after achieving first remission but only half of the unrelated donor transplants. Statistical methods are usually applied to adjust for the *waiting time* whenever chemotherapy and transplant outcomes are compared. Nevertheless, when these pediatric patients are going to be transplanted late in first remission it should be considered that outcome with *chemotherapy only* at that time-point is expected to be better than that assessed at presentation, as time elapsed in first remission *selects* patients with the best prognosis.

The conditional probabilities proposed here allow the clinician to quantify and account for the waiting time and could be applied in different settings.

The conditional 5-year DFS shown in this study (Figure 1) is always higher for patients considered overall than for patients treated with chemotherapy only, which indirectly suggests that transplant is consistently beneficial, regardless of first remission duration. The first year of the conditional analysis is important for the decision of whether to transplant or not. The 5-year DFS, conditional on having maintained CR1 for at least 3, 6, 9, or 12 months, becomes progressively higher with a final gain of more than 15 percentage points. Estimates can be extrapolated at any time-point for comparison with the expected outcome of transplant from any donor. First remission prolongation could improve the outcome of chemotherapy to a larger extent than transplant outcome. In fact, failures after chemotherapy are mostly due to relapses which are likely to decrease as first remission duration increases, while failures after transplant are also due to transplant-related mortality.[3,4,8] This might only be influenced by first remission duration to a limited extent and possibly with the opposite effect, since the longer the waiting time to transplant the higher the cumulative toxicity due to previous chemotherapy. Furthermore, at later time-points after diagnosis the advantage of transplant could decrease, since patients potentially curable (or already cured) by chemotherapy only would be progressively selected.

In our series, the impact of first remission prolongation on outcome is similar for both patients overall and patients treated with chemotherapy only. The same impact for transplanted patients in this cohort could only be assessed indirectly, due to the limited transplant cohort and since all patients grafted from a related compatible donor were transplanted early, at a median of four months after achieving first remission as per protocol.[1] However, the relative advantage of transplant over chemotherapy in children with very high-risk acute lymphoblastic leukemia was consistent for any first remission duration, since estimates of DFS after transplant were invariably 10-20% higher than conditional DFS estimates of patients treated with chemotherapy who had maintained their first remission for at least nine months.

The curve in Figure 1 has been plotted for completeness up to five years, as an alternative way to show that outcomes are heterogeneous even for very high risk patients. Our analysis beyond the first year is important for counselling parents about the prognosis of their children experiencing a long period of time in first remission, even if originally classified as *very high risk*, since events may still occur late after achieving first remission. Conditional probabilities estimate the long-term prognosis at each observation time-point. For example, a 5-year DFS of 76% can be provided for children with very-high-risk acute lymphoblastic leukemia who achieve off-therapy, and of 91% for children who may come to the long-term follow-up clinic one-year after off-therapy. These conclusions are drawn on a genetically randomized prospective trial conducted to compare allogeneic transplant from related compatible donors to chemotherapy. Nevertheless, our analysis of the effect of first remission prolongation is intended to support the decision-making process mostly for transplant from unrelated donors, since the time needed to find a volunteer compatible donor is the major cause of transplant delay.[6] In this cohort, transplants from unrelated donors had a dismal outcome, regardless of time elapsed in first remission. In fact, unrelated donor transplants were not treatment options but sporadic deviations from the study design, and were, therefore, subject to selection bias. At present, results achieved by allogeneic transplant from related donors may be extrapolated to those from unrelated donors since outcome of these two donor categories are becoming increasingly similar. This is due to improvements in HLA typing and matching criteria and in supportive care.[2-6]

Since, as expected, the gap between transplant and chemotherapy increases as the risk profile of the patient worsens, the prolongation of first remission affected to a larger extent the best rather than the poorest candidates. Patients experiencing *induction failure* unquestionably benefited from transplant, even when performed late after diagnosis. The benefit of transplant decreased as time elapsed in first remission increased for patients with least unfavourable features, such as *PPR+ only*, and should be counterbalanced by treatment-related late effects.

Nevertheless, very few patients treated with chemotherapy could be rescued after relapse. Eligibility criteria for transplant are now mostly based on minimal residual disease which should provide a *better* method to select those patients who can really benefit from transplant, regardless of time elapsed in first remission.[9,10]

In conclusion, the proposed approach allows the impact of time elapsed in first remission on prognosis to be quantified. This will allow clinicians to base their decision as to whether to transplant or not on donor identification.

Authorship and Disclosures

AB participated in the study planning and wrote the paper; PDL was in charge of data pooling, study reporting, data checking and analyses and contributed to writing the paper; AS was the co-ordinator of transplantation in ALL in CR1 within the BFM Group and

reviewed the paper; VC was the Italian chemotherapy co-ordinator, contributed to the study planning and contributed to writing the paper; CU was the clinical co-ordinator of the study and reviewed the paper; CP was the transplant co-ordinator within the I-BFM-SG Group and reviewed the paper; TK was the transplant co-ordinator for pediatric patients in Germany and reviewed the paper; JS co-ordinated the study in the Czech Republic and reviewed the paper; MSF co-ordinated the study in Argentina and reviewed the paper; EM co-ordinated the study in Hungary and reviewed the paper; MS was the ALL Committee chairman within the I-BFM-SG Group, contributed to the study planning, co-ordinated the study in Germany and reviewed the paper; GD was the EBMT Pediatric Working Party Co-ordinator and reviewed the paper; HG contributed to the study planning and reviewed the paper; MGV was the statistician responsible for the study design and analyses, co-ordinated the trial data center and wrote the paper. The authors reported no potential conflicts of interest.

References

1. Balduzzi A, Valsecchi MG, Uderzo C, De Lorenzo P, Klingebiel T, Peters C, et al. Chemotherapy versus allogeneic transplantation in childhood very high risk acute lymphoblastic leukaemia in first complete remission: a comparison by genetic randomization in an international prospective study. Lancet 2005;366: 635-42.
2. Saarinen-Pihkala UM, Gustafsson G, Ringden O, Heilmann C, Glomstein A, Lonnerholm G, et al. No disadvantages in outcome of using matched unrelated donors as compared with matched sibling donors for bone marrow transplantation in children with acute lymphoblastic leukaemia in second remission. J Clin Oncol 2001;19:3406-14.
3. Locatelli F, Zecca M, Messina C, Rondelli R, Lanino E, Uderzo C, et al. Improvement over time in outcome for children with acute lymphoblastic leukemia in second remission given hematopoietic stem cell transplantation from unrelated donors. Leukemia 2002;16:2228-37.
4. 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;99:2002-8.
5. Al-Kasim FA, Thornley I, Rolland M, Lau W, Tsang R, Freedman MH, et al. Single-centre experience with allogeneic bone marrow transplantation for acute lymphoblastic leukemia in childhood: similar survival after matched-related and matched-unrelated donor transplant. Br J Haematol 2002;116:483-90.
6. Eapen M, Rubinstein P, Zhang MJ, Camitta BM, Stevens C, Cairo MS, et al. Improvement over time in outcome for children with acute lymphoblastic leukemia in second remission given hematopoietic stem cell transplantation from unrelated donors. Leukemia 2002;16:2228-37.
7. Dini G, Valsecchi MG, Micalizzi C, Busca A, Balduzzi A, Arcese W, et al. 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.
8. 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 leukaemia: a Children's Oncology Group Study Report. Biol Blood Marrow Transplant 2007;13:218-27.
9. Flohr T, Schrauder A, Cazzaniga G, Panzer-Grümayer R, van der Velden V, Fischer S, et al. Minimal residual disease-directed risk stratification using real-time quantitative PCR analysis of immunoglobulin and T-cell receptor gene rearrangements in the international multicenter trial AIEOP-BFM ALL 2000 for childhood acute lymphoblastic leukemia. Leukemia 2008;31[Epub ahead of print].
10. Schrauder A, Reiter A, Gadner H, Niethammer D, Klingebiel T, Kremens B, et al. Superiority of allogeneic hematopoietic stem-cell transplantation compared with chemotherapy alone in high-risk childhood T-cell acute lymphoblastic leukemia: results from ALL_BFM 90 and 95. J Clin Oncol 2006;24:5742-9.