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REVIEW

Searching for alternative hematopoietic stem cell donors for pediatric patients

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The use of alternative hematopoietic stem cell (HSC) donors has been witnessing important progress, mainly due to: (i) better HLA matching at the allelic level between donor and recipient in unrelated HSC transplantation (HSCT) translating into better patient outcome; (ii) better donor choice and patient selection in unrelated, often HLA-mismatched, cord blood transplantation and (iii) new strategies of adoptive cell therapy aimed at improving the results of T-cell-depleted haploidentical HSCT from a relative. Currently, it is possible to find an HSC donor for virtually almost all children with an indication to receive allogeneic HSCT and lacking an HLA-identical sibling. Each of the three options of HSCT from alternative donors has advantages and limitations. Therefore, any physician has to carefully evaluate, for each single pediatric patient in need of an allograft, all the possible alternatives to choose the best HSC donor, taking into account type of disease to be treated, urgency of transplantation, donor characteristics and center's experience. This review will analyze in detail the advantages and limitations of each of the three options of alternative donor HSCT and the main criteria to be used for choosing the most suitable donor for pediatric patients lacking an HLA-identical sibling.
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Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is largely employed for treating children affected by many hereditary and/or hematological conditions, of both malignant and non-malignant origin.[1] Nearly 40 years have elapsed since the first successful HSCT, then performed using BM cells,[2,3] and through this procedure thousands of children have been cured of their original disease.

Many significant changes and improvements have occurred over time in the use of HSCT. In particular, while for many years an HLA-matched sibling was the only type of donor routinely employed, more recently, matched unrelated volunteers, unrelated umbilical cord blood (UCB) units and full-haplotype-mismatched family members are largely utilized to transplant patients lacking an HLA-identical relative.[1] Indeed, only 25% of patients who need an allograft of HSCs have an HLA-identical sibling. For transplant candidates without an available HLA-compatible sibling, the preferred strategy has long been that of searching for an unrelated HLA-matched BM donor. However, recently, retrospective studies have shown that both unrelated UCB transplantation (UCBT) and full-haplotype (Haplo)-mismatched family donors can represent suitable alternatives to HLA-matched unrelated donor BM transplantation (UBMT).[1,4] Therefore, nowadays, for virtually all patients an alternative HSC donor can be found, the decision whether to employ either an unrelated volunteer, an HLA-mismatched UCB unit or a full-haplotype-mismatched relative depends on many patient-, disease-, transplant- and center-related factors.

This review will address the advantages and limitations of each of the three options and the main criteria to be used for choosing an alternative HSC donor for pediatric patients for whom an HLA-identical sibling is not available (Table 1).

Unrelated BM donors

Registries of volunteer BM donors are well established in most developed countries. They now contain more than 11 million HLA-typed prospective volunteer donors and are advantageously integrated with UCB banks; it can be estimated that a significant proportion of patients in need of HSCT and lacking an HLA-identical sibling have the possibility to locate a non-consanguineous donor suitable to be employed for transplantation in a median time of 3–5

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Table 1 Advantages and limitations of unrelated donor BMT, UCBT and haploidentical HSCT from a relative, and main criteria to be considered for choosing an alternative donor for patients without an HLA-identical sibling[a]

	UBMT	*UCBT*	*Haplo-HSCT*
Information on A + B + DRB1 (DNA) typing (%)	16–56	~80	100
Median search time (months)	3–6	<1	Nil
Donors identified but not available (%)	20–30	~1	None
Rare haplotypes represented (%)	2–10	20	Not applicable
Main limiting factor to graft acquisition	HLA identity	Cell dose	Poor mobilization
Ease of rearranging the date of cell infusion	Difficult	Easy	Easy
Potential for immunotherapy	Yes	No	Yes (limited)
Potential for viral transmission to recipient	Yes	No	Yes
Potential for congenital disease transmission to recipient	No	Yes	No
Risk for the donor	Very low	No	Very low
Main problems to be overcome	GvHD	Graft failure, delayed immune recovery	Delayed immune recovery, lack of T-cell-mediated GVL effect

Abbreviations: Haplo-HSCT = haploidentical hematopoietic stem cell transplantation; UBMT = unrelated donor BM transplantation; UCBT = umbilical cord blood transplantation.
[a]Modified from Grewal *et al.*[4]

months.[4] For all donors, serological typing of class I HLA loci is available, and for approximately one-third of these subjects there is information on DRB1 typing. It is widely accepted that the most important HLA loci influencing post-transplant outcome of patients given HSCT from an unrelated volunteer are HLA-A, -B, -C (class I loci) and -DRB1 (class II locus).[5–7] The role played by other class II loci (namely DQB1 and DP1 loci) remains controversial.[7–9] The possibility of finding a donor suitable to be employed for the allograft mainly depends on the ethnic group, ranging from 60 to 70% for Caucasians to less than 10% for patients belonging to ethnic minorities, and the frequency of the HLA phenotype of the patient. This wide range is explained by the enormous polymorphism of HLA molecules, as new DNA-based techniques for HLA typing continuously reveal an impressive number of new alleles within antigens that were previously defined by serology, and it is now clear that low- to intermediate-resolution HLA typing techniques do not provide adequate information for the selection of the most appropriate unrelated donor. Matching by the more recent and sophisticated methods of high-resolution HLA typing certainly reduces the risk of immune complications, namely graft rejection and GvHD and also the chance of finding a suitable donor.[7]

Despite all the limitations reported above, thousands of pediatric patients have received HSCT, using BM cells, or less frequently, peripheral blood progenitors, from an unrelated donor.[1] Mainly because of HLA polymorphism and the limits of conventional techniques for HLA typing, increased difficulties for engraftment and augmented incidence of both acute and chronic GvHD have been initially reported in recipients of unrelated donor HSCT, thus leading to a final outcome inferior to that reported using a compatible sibling as donor.[10,11] At that time, recourse to this type of transplant for patients in whom HSCT does not represent a life-saving procedure (that is, thalassemia or sickle cell disease) did not meet consensus. More recently, however, better selection of unrelated BM donors, with high-resolution molecular typing for both HLA class I and II loci, as well as refinements in both prophylaxis and treatment of GvHD, has allowed a reduction of transplantation-related mortality (TRM) and a relevant improvement over time in the outcome of patients transplanted from an unrelated volunteer, so that when a donor fully matched at the allelic level for the most important HLA loci is selected, results achievable with this type of transplant may be expected to compare well with those of HSCT from an HLA-identical sibling.[7,12] Support for this conclusion is provided by results recently obtained using an unrelated donor in children with ALL in second CR, with juvenile myelomonocytic leukemia or with thalassemia.[9,13,14]

Immune genetic disparity in the donor–recipient pair (that is, one allelic/antigenic disparity or multiple disparities at different HLA loci) is associated with a worse patient outcome, mainly due to the high incidence of transplantation-related complications. Indeed, a recent analysis by the Center for International Blood and Marrow Transplant Research on patients with hematological malignancies, mainly transplanted with BM cells, has documented that, as compared to patients transplanted from a donor matched at the allelic level for the HLA loci A, B, C and DRB1, patients given an allograft from a donor with a single, either antigenic or allelic, disparity had an increased risk of both acute GvHD and TRM, this translating into a lower probability of disease-free survival (DFS).[7] Disparities at two or more loci compounded the risk. Single disparities at the HLA loci B and C appear to be better tolerated than mismatches at the loci A and DRB1, while a single disparity at the HLA loci DQ and DP was not found to be associated with any adverse effect on DFS, although single disparities at the HLA-DP locus correlated with an increased risk of acute GvHD and showed a tendency toward a reduced risk of leukemia recurrence.[7] Less than 20% of unrelated donor–recipient pairs matched for the HLA loci A, B, C, DRB1 and DQB1 are also compatible for HLA-DPB1, due to the very weak linkage disequilibrium existing between the DR/DQ loci and the DP locus. Consequently, over 80% of unrelated transplants are performed across the HLA-DPB1 barrier.[7,8] An algorithm for the determination of non-permissive HLA-DPB1 disparities, which were found to be associated with a significantly increased risk of TRM and grades II–IV acute GvHD, in patients transplanted for malignant hematopoietic disorders, has been recently proposed.[15] This algorithm, based on the identification of an immunogenic T-cell epitope shared by a defined subset of HLA-DBP1 alleles, which, if expressed by self-HLA-DP molecules protects from mounting a response against allogeneic HLA-DP antigens carrying the epitope,[15,16] proved also to predict the occurrence of graft failure in children with thalassemia major transplanted with BM cells from an unrelated volunteer.[17] Thus, at least in some groups of patients transplanted from an unrelated volunteer, the incidence of immune complications (namely GvHD and graft failure) can be reduced by appropriate selection of the donor, taking into account the functional rules of immune genetics.

Besides HLA compatibility, several other patient-, donor-, disease- and transplant-related variables have been reported to influence the outcome of children given an allogeneic HSCT from an unrelated donor.[7,18,19] Among these, the cell dose infused has the advantage of being, in large part, controlled by clinicians, as it results from the number of BM cells harvested with respect to the recipient's body weight. One study, grouping together adults and pediatric patients given the allograft from an unrelated volunteer for acute leukemia, suggested that a greater number of BM cells infused correlated with a better outcome.[18] Another example of a factor easily modifiable that can improve outcome after an unrelated HSCT is the use of fludarabine in the conditioning regimen of Fanconi anemia patients.[19]

The use of younger donors has been initially reported to be associated with a lower incidence of GvHD and with improved survival in unrelated donor HSCT recipients.[20] This observation has supported the concept of considering donor age as a risk factor when selecting among comparable HLA-matched volunteers. However, a more recent analysis does not support the previous observation.[7]

In patients given an unrelated donor allograft, procedures of *ex vivo* T-cell depletion of the graft have been largely employed to decrease the risk of acute GvHD. However, in a randomized trial of unrelated donor HSCT for leukemia patients, this favorable effect of T-cell depletion did not translate into better survival, due to the higher incidence of fatal viral complications, and of recurrence in patients with CML.[21] Thus, the final outcome in patients given a T-cell-depleted HSCT from an unrelated volunteer is substantially comparable to that of patients given an unmanipulated graft and pharmacological GvHD prophylaxis.

The survival rates of unrelated donor HSCT refer only to patients who undergo transplantation and do not take into account those who did not find a donor. Furthermore, the time needed to identify the right donor from a potential panel, to establish eligibility and to harvest the cells may, in patients who urgently need a transplant, favour the occurrence of leukemia relapse/progression, thus precluding the transplant feasibility. Consequently, for patients who do not have a matched donor or who urgently need HSCT, attention has focused on UCBT and Haplo-HSCT, using a three HLA-loci mismatched family member.

UCB transplantation

UCB has extended the possibility to perform HSCT in HLA-mismatched situations, due to peculiar immunological characteristics of placental blood lymphocytes, which display a lower alloreactive potential than BM or peripheral blood lymphocytes. The number of UCBT from unrelated donors has increased dramatically, and it can be estimated that to date, more than 10 000 patients have undergone UCBT for a variety of genetic, hematological, immunological, metabolic and oncologic disorders. Progress in the field of UCBT parallels the interest in establishing and developing UCB banks worldwide and today, more than 300 000 units are available in more than 40 UCB banks. More than 60% of UCBTs are performed in pediatric patients and in comparison to unrelated BM donors, UCB offers substantial logistic and clinical advantages (Table 1). Outcomes of UCBT in children have been extensively reported and series of children with specific diseases, such as AML,[22] Hurler syndrome,[23] Krabbe disease,[24] Fanconi anemia,[25] and lysosomal and peroxisomal storage disorders,[26] have been published. In these retrospective studies, patient-, disease- and transplant-related factors influencing outcome have been identified. Among them, early disease status at transplantation, recipient-negative human cytomegalovirus serology prior to UCBT and use of fludarabine in conditioning regimens have been associated with better outcomes.[22,25] However, in almost all studies, the most important factor influencing patient outcome was the cell dose per kilogram of recipient body weight, expressed either as total nucleated cells (NCs) or number of CD34 + cells, which was found to correlate with engraftment, adverse transplant-related events and survival.[22,27–29] It has also been suggested that cell dose and number of HLA mismatches interact mutually, influencing probability of engraftment and other outcomes.[30] Indeed, a higher cell dose in the graft could partially overcome the negative impact of HLA for each level of HLA disparity; although this hypothesis has not been yet been fully demonstrated. However, based on previously published data from the USA.[28,29] and Eurocord data,[30] it is recommended to select cord blood units with no more than two HLA disparities and with more than 3×10^7 NC/kg before thawing. Other factors, such as the disease treated, may also have an important role in the rate of engraftment. In fact, patients with non-malignant disorders are more prone to experience graft failure.[25,31] Several factors may explain the high incidence of graft failure after UCBT in these patients, including previous sensitization to alloantigens through repeated transfusions (for patients with either acquired or congenital BM failure and hemoglobinopathies), no chemotherapy treatment before transplantation, and in some patients, such as those with thalassemia, expanded erythropoietic marrow together with splenomegaly.[25,31] Recently, in light of the observation that requirements regarding cell dose and HLA matching may differ in malignant and non-malignant diseases, the Eurocord group has analyzed more than 1200 patients with malignant ($n = 925$) and non-malignant diseases ($n = 279$) (Eurocord data; manuscript in preparation). Donor–recipient histocompatibility was determined by serology or antigen typing for HLA-A and -B and by DNA typing for HLA-DRB1. In the malignant disease group, cell dose was the most important factor influencing outcome; a minimum cell dose of 3×10^7 NC/kg at collection, and of 2×10^7 NC/kg at infusion should be employed. In these patients, the number of HLA mismatches was associated with the risk of delayed engraftment and with a higher incidence of TRM and chronic GvHD; however, it also decreased the risk of relapse, thus leading to an overall lack of influence of HLA mismatch on DFS. There are no sound data for predicting which type of HLA disparity could have the most detrimental impact on outcome; however, matching for HLA-DRB1 appeared to be privileged for 'patients receiving a unit with two HLA incompatibilities. As stated earlier, increasing the cell dose abrogated the effect of HLA mismatching, but not for grafts with three or four HLA incompatibilities.

In non-malignant disorders, HLA mismatching played a major role in engraftment, GvHD, TRM and survival, which was partially compensated by increasing the cell dose. A UCB unit containing two or more HLA disparities with a cell dose inferior to 3.5×10^7 NC/kg should be avoided. If a cell dose equal or greater than 3.5×10^7 NC/kg is not achieved with a single unit, a double UCBT should be investigated in prospective protocols.

While more protected than UBMT recipients from GvHD-related mortality, patients given UCBT are exposed to an increased risk of dying for other, early transplant-related complications, especially of infectious origin.[27,28,30] Both the delayed kinetics of neutrophil recovery and the lack of adoptive transfer of donor, antigen-experienced (that is, memory) T cells certainly contribute to this increased risk of early death. Despite this latter disadvantage, however, the reconstitution of T- and B-cell-specific immunity in patients given UCBT does seem to be at least comparable, or even better, than that of patients receiving UBMT.[32–35] This finding is probably due to the low incidence and severity of GvHD, which is a well-known factor impairing the immune recovery.

Overall, available evidence shows that unrelated UCBT can be considered a suitable option for children with both malignant and non-malignant disorders. Better patient selection and attention to factors easily modifiable, such as selection of an UCB unit rich in cells and with no more than two HLA disparities, as well as optimization of the conditioning regimen and GvHD prophylaxis, can further improve patient outcome.

Full-haplotype-mismatched family donors

HSCT from an HLA-haploidentical relative offers an immediate transplant treatment to almost all patients without a matched donor, whether related or unrelated, or a suitable UCB unit. As the infusion of BM cells from an HLA-haploidentical relative has been reported to be associated with a high incidence of graft failure,[1] a 'megadose' of G-CSF-mobilized peripheral blood stem cells is essential for overcoming the barrier of HLA incompatibility in the donor–recipient pair and for eluding residual antidonor CTL-precursor activity.

While the outcome of Haplo-HSCT in adults has been extensively reported by the Perugia Team (which also discovered the importance of donor natural killer cell-mediated alloreactivity toward leukemia blasts),[36,37] only limited data are available in the literature on the outcome of full-haplotype-mismatched family donor HSCT in children.[38,39] The reported probability of survival at 3–4 years after the allograft ranged from 48 to 18%; it was influenced by many factors, the most important being the state of remission at the time of transplantation, which seems to be poorer in children with myeloid leukemias.[38,39] Both TRM, mainly attributable to infectious complications, and in patients with malignancies, leukemia recurrence significantly contributed to treatment failure. Recently, the Acute Leukemia and the Pediatric Disease Working Parties (ALWP and PDWP) of the European Blood and Bone Marrow Transplant (EBMT) have performed a collaborative retrospective study analyzing the risk factors influencing outcome in 118 children with high-risk ALL given HSCT after a myeloablative regimen from 1995 to 2004 in Europe using an HLA-haploidentical relative.[40] Only transplants with two or more HLA disparities out of the six loci considered (namely HLA-A, -B and -DRB1) were included. The median age was 8.5 years and median follow-up was 56 months (range 8–116). At transplant, 21 patients (18%) were in CR1, 72 (61%) in CR2 or CR3 and 25 (21%) in more advanced phase. The 3-year DFS was 32 ± 10, 28 ± 5 and 0%, respectively.[40] The analysis was then restricted to patients transplanted in remission ($n = 93$) in 30 EBMT centers. Thirty-four (37%) patients were treated in centers performing more than 10 Haplo-HSCT in the study period. Twenty-seven children (29%) had t(9;22) or t(4;11). The Clinimacs device was used in 74% of CD34+ cell selections. The median number of CD34+ cells infused was 12.8×10^6/kg. The median time to neutrophil recovery was 15 days (range 8–55) and 90% of patients were engrafted. Grades II–IV acute GvHD were observed in 24% of the patients. In a univariate analysis for DFS, there was a trend toward better results for patients receiving higher CD34+ cell dose ($P = 0.08$) and a significantly better outcome for patients transplanted in centers performing more Haplo-HSCT (49 vs 17%, $P = 0.002$). Relapse incidence and TRM tended to be different between the experienced and less experienced centers. In the less experienced centers, TRM was 41 vs 27% ($P = 0.13$) and relapse incidence 41 vs 24% ($P = 0.10$).[40]

The main disadvantage associated with Haplo-HSCT refers to immune reconstitution. The physical elimination of mature T cells from the graft, necessary for preventing GvHD occurrence in the context of great immune genetic disparity, leads to the consequence that recipients cannot benefit from the adoptive transfer of memory T lymphocytes that, through their peripheral expansion, is the main reason for protection from infections in the first months after transplantation. A state of profound immune deficiency lasts for at least 4–6 months after transplantation in Haplo-HSCT recipients;[41] at the end of this period, the immune recovery of children given a Haplo-HSCT does not substantially differ from that of patients given the allograft from other alternative donors. Sophisticated strategies of adoptive infusions of T-cell lines or clones specific for the most common and life-threatening pathogens (namely EBV, human cytomegalovirus, *Aspergillus* and adenovirus) have been envisaged and successfully tested in a few pilot trials to protect the recipients in the early post-transplant period.[42–44]

Available data suggest that Haplo-HSCT is an alternative option to treat children with very high risk ALL in the absence of an HLA identical donor and it should be reserved to centers with a specific program for this type of allograft. Approaches of adoptive immunotherapy with infusion of pathogen specific T-cell lines/clones for prevention/treatment of infectious complications or co-infusion of mesenchymal stem cells to reduce the risk of graft failure are promising to improve post-transplant outcome.[45,46]

Retrospective comparative studies

UCBT compared to BMT from unrelated donors

Three published reports, namely two single-center studies and a Eurocord registry analysis, have compared the outcome of UCBT and UBMT in children.[47–49] Briefly, in these three studies, recipients of UCBT who were transplanted earlier had a delayed neutrophil and platelet recovery and reduced incidence of acute GvHD as compared to children given an UBMT. Nevertheless, the overall survival probability was not significantly different in UCBT or UBMT pediatric recipients.[47–49] Recently, a meta-analysis combining these comparative studies was published.[50] A total of 161 children undergoing UCBT (mostly one or two antigen-mismatched) and 316 children undergoing UBMT were analyzed; this study confirmed that there was no difference in 2-year overall survival between children given an unrelated UCBT or UBMT (Figure 1). In a more recent analysis, Eapen *et al.*[51] have compared results observed in 503 UCBT recipients with those of 282 UBMT recipients (116 were HLA allele-matched (HLA-A, -B, -C and -DRB1, thus eight out of eight) and 166 mismatched). Of the UCBT recipients, 35 were matched at the HLA-A, -B (antigen level) and -DRB1 (allele level), 201 were mismatched at one locus and 267 were mismatched at two loci. All patients (aged <16 years) had acute leukemia. In comparison with children given an allele-matched UBMT, patients transplanted with one or two HLA-disparate UCB unit had a similar 5-year DFS (45% for patients given a one-antigen disparate UCBT with a cell dose greater than 3×10^7 NC/kg, decreasing to 36% with a lower cell dose and 33% for patients given a two-antigen disparate UCB vs 38% in allelic-matched UBMT), while an even possible better outcome was evident for the 35 children given HLA-matched UCBT, the 5-year DFS being 60% (Figure 2).[51] TRM rates were higher after transplants of two-antigen HLA-mismatched UCB (relative risk 2.31, $P=0.0003$) and possibly after one-antigen HLA-mismatched UCB units containing less than 3×10^7 NC/kg (relative risk 1.88, $P=0.0455$). In contrast, the incidence of relapse was lower after two-antigen HLA-mismatched UCBT (relative risk 0.54, $P=0.0045$). These data support the use of HLA-matched and one- or two-loci HLA-mismatched UCB in children with acute leukemia, provided that a good cell dose is available.

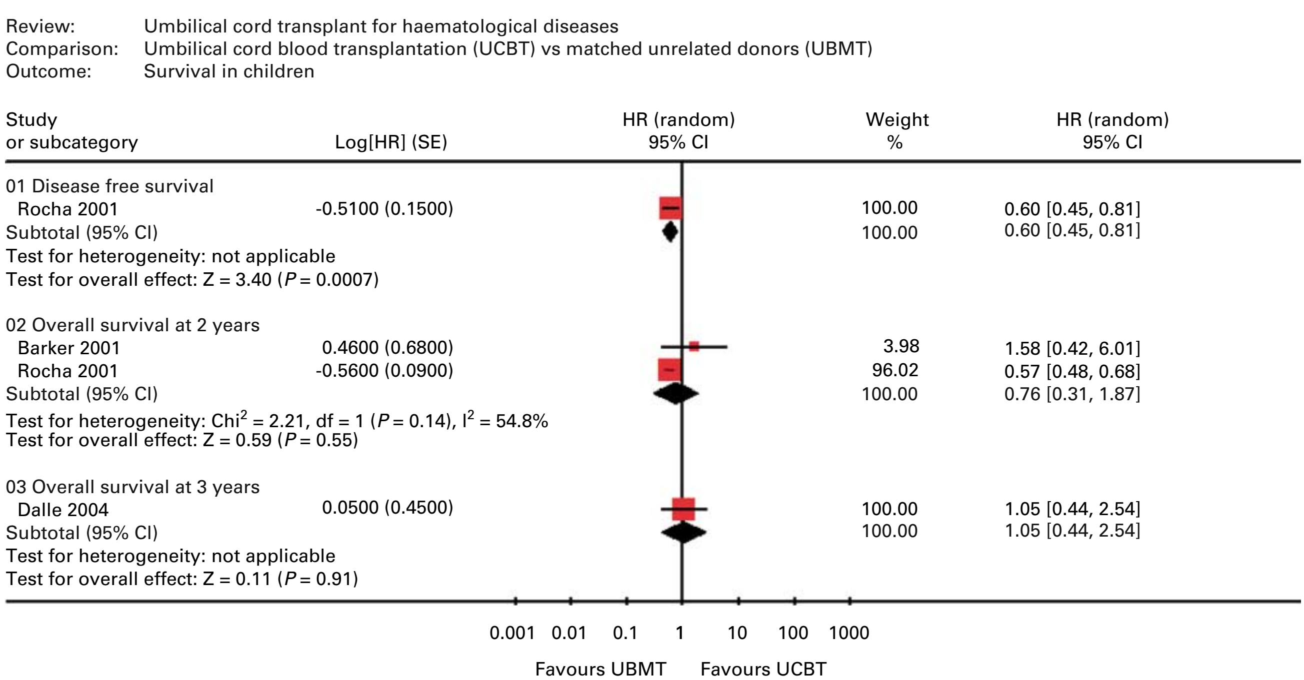

Figure 1 Meta-analysis of studies comparing the outcome of UCBT and UBMT in children with acute leukemia. From Hwang *et al.*[50] with permission.

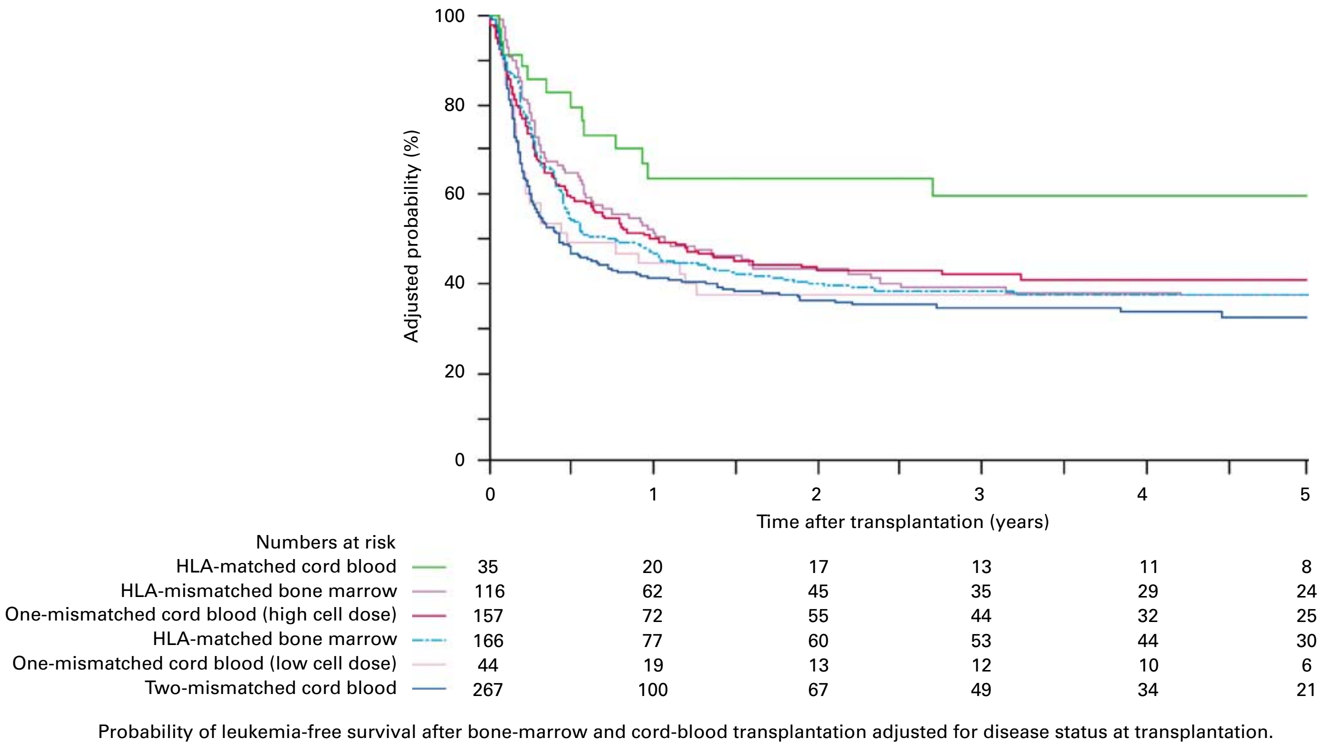

Figure 2 Kaplan–Meier estimates of leukemia-free survival in children with acute leukemia given either UCBT or UBMT according to the HLA disparity in the donor–recipient pair and the number of UCB cells infused. From Eapen *et al.*[51] with permission.

Table 2 Unadjusted outcomes of UCBT and haploidentical transplants with T-cell-depleted HSCT in children with ALL transplanted in Eurocord and EBMT transplant centers[52]

Type of transplant	*% of grades II–IV aGvHD*	*3-year TRM*	*3-year relapse*	*3-year LFS*
Haplo ($n=118$)	21	50 ± 6	56 ± 6	22 ± 4
UCBT ($n=341$)	39	46 ± 3	45 ± 4	29 ± 3
P-value	0.001	0.87	0.04	0.23

Abbreviations: aGvHD = acute graft-versus-host disease; Haplo = haploidentical; HSCT = hematopoietic stem cell transplantation; LFS = leukemia-free survival; TRM = transplant-related mortality; UCBT = unrelated umbilical cord blood transplantation.

Comparison of UCBT with full haplotype disparate donor HSCT in children with ALL

The Eurocord group in collaboration with the ALWP and the PDWP of the EBMT have compared the outcome of patients given either UCBT or Haplo-HSCT, by performing a retrospective comparison of pediatric patients (16 years or younger) with high-risk ALL (Table 2).[52] Children had received either Haplo-HSCT ($N=118$) or UCBT ($N=341$) in EBMT-Eurocord centers between 1998 and 2004. Haplo-HSCT recipients tended to be older, had CMV-positive serology, and t(9;22), more frequently. The median follow-up was 56 and 24 months for Haplo-HSCT and UCBT patients, respectively. Failure of engraftment was significantly higher following UCBT than after Haplo-HSCT (23 vs 11%, $P=0.007$). In a multivariate analysis, adjusted for differences between the groups and prognostic factors, relapse incidence was higher in Haplo-HSCT recipients compared to UCBT (relative risk 1.7, $P=0.01$), but TRM and DFS were not significantly different. In conclusion, in pediatric patients with ALL, UCBT is associated with inferior rate of engraftment, higher incidence of grades II–IV acute GvHD and lower incidence of relapse compared to Haplo-HSCT; however, there was no difference in terms of TRM and DFS. Therefore, in the absence of an HLA-identical donor, both strategies are suitable options to treat a child with high-risk ALL.

Conclusion

For children in need of an allograft and lacking an HLA-identical sibling, HLA-matched UBMT, HLA-matched or -mismatched UCBT and Haplo-HSCT are options that are able to offer the chance of a transplant treatment. Each of these has advantages and limitations, but rather than being considered competing alternatives, they should be regarded as complementary options to be chosen after a careful evaluation of the relative risks and benefits in the patient's best interest. The choice of the donor will depend on various factors related to urgency of transplantation, patient-, disease-, and transplant-related factors and center's experience.

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