A Meta-Analysis of Unrelated Donor Umbilical Cord Blood Transplantation versus Unrelated Donor Bone Marrow Transplantation in Adult and Pediatric Patients

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ABSTRACT
Several studies have compared the results of unrelated donor bone marrow transplantation (UBMT) and unrelated donor cord blood transplantation (UCBT). To objectively analyze these data, we performed a systematic review and meta-analysis of pooled data on comparative studies of UCBT and UBMT in patients requiring hematopoietic stem cell transplantation. Combining the studies, 161 children and 316 adults undergoing UCBT (mostly 1 or 2 antigen-mismatched), along with 316 children and 996 adults undergoing UBMT (almost entirely fully matched with the recipient), were analyzed. T-cell–depleted UBMT was excluded; where data were available, only fully matched UBMT was used in the analysis. Pooled comparisons of studies of UCBT and UBMT in children found that the incidence of chronic graft-versus-host disease (GVHD) was lower with UCBT (relative risk [RR] = 0.26; 95% confidence interval [CI] = 0.12–0.57; P = .16), but the incidence of grade III–IV acute GVHD did not differ (RR = 1.46; 95% CI = 0.42–5.03; P = .55). There was no difference in 2-year OS in children when studies were pooled (RR = 0.76; 95% CI = 0.31–1.87; P = .55). For adults, transplantation-related mortality (pooled estimate, 1.04; 95% CI = 0.52–2.08; P = .91) and disease-free survival (DFS) (pooled estimate, 0.59; 95% CI = 0.18–1.96; P = .39) were not statistically different. Because of the unavailability of randomized controlled trials, pooled analysis of nonrandomized comparative studies was performed. Thus, our meta-analysis confirmed that UCBT in children and adults had consistently equivalent survival outcomes compared with UBMT despite greater donor–recipient HLA disparity with UCBT.

INTRODUCTION
Bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT) from HLA-matched donors have been successfully used to treat many malignant and nonmalignant disorders [1]. Cord blood transplantation (CBT) has gradually emerged as an alternative mode of hematopoietic stem cell transplantation (HSCT) [2]. Since the first sibling CBT in 1989 [3] and the first unrelated donor CBT (UCBT) in 1993 [4], there has been a rapid increase in the use of this treatment modality for patients lacking a suitably matched bone marrow donor. The numbers increased from a few hundred UBCTs in the 1990s to approximately 2000 by the year 2002 [5], followed by an exponential rise to more than 7000 UCBTs performed to date. This increased use of UCBT has been fueled in large part by reports of excellent outcomes with this modality emerging from a number of studies...
directly comparing the outcomes of unrelated donor BMT (UBMT) and UCBT.

In UBMT, a donor fully matched at all 6 HLA-A, -B, and -DRB1 alleles is often required. However, because of the vast polymorphism of HLA alleles, not all patients will be able to find a matched donor, either sibling or unrelated [6,7]; the likelihood of this is even lower for patients of non Caucasian ethnic groups [8,9]. However, the hematopoietic robustness [10,11] and immunologic naivety [12] of cord blood (CB) cells allows us to select CB with up to 1 to 2 antigen mismatches out of the standard 6 alleles. This immunologic permissiveness of CB has dramatically increased the likelihood of finding a suitable donor for HSCT [13].

Despite increased HLA disparity using CB, comparable results have been obtained between UCBT and UBMT in terms of probabilities of engraftment, graft-versus-host disease (GVHD), and survival. This is likely because the excessive mortality secondary to delayed engraftment and graft failure compared with UBMT is balanced by lower mortality from other causes, including GVHD [14]. Immune recovery has also been shown to be prompt and comparable to that in UBMT [15]. Several major comparative studies of UCBT versus UBMT have reported some similarities as well as differences. The main objective of this systematic review was to evaluate whether UCBT is equivalent to UBMT in treating adults and children with malignant and nonmalignant disorders.

METHODS

To aid in making treatment decisions for patients needing allogeneic HSCT, we systematically reviewed all data on comparative studies of UCBT versus UBMT in which survival was the key outcome measure. To obtain reliable evidence on the relative effect of UCBT versus UBMT in the primary treatment of adults and children with malignant and nonmalignant disorders, results from independent and comparable studies were integrated to increase statistical power. The primary outcome of interest for our analysis was survival; secondary outcomes studied included engraftment, GVHD, transplantation-related mortality (TRM), and relapse.

Search Strategy

Following established guidelines, we performed a literature search using OVID. The databases searched were Medline (1966–January 28, 2006), The Cochrane Central Register of Controlled Trials (Cochrane Library, Issue 1, 2006), Cochrane Database of Systematic Reviews, ACP Journal Club, and Database of Abstracts of Reviews of Effect. EMBASE (197–January 28, 2006) was searched using Dialog Datastar.

The search terms used were “cord blood,” “bone marrow,” and the alternate search terms “transplant,” “transplantation,” and “transplants.” Whereas the initial search limited publications to randomized controlled trials, this did not yield any useful search results, and consequently we expanded our search criteria to include all listed clinical trials. To further enhance our search, we included all journal articles and limited the search terms to the title. Abstracts of papers presented at the American Society of Hematology, International Bone Marrow Transplant Registry, American Society of Blood and Marrow Transplantation, and European Society of Bone Marrow Transplant Meeting published before January 2006 were also hand-searched, checking for “cord blood,” “bone marrow,” and “transplant” in the indexes. Full text papers were obtained to extract the data for this analysis. References of retrieved articles were also checked for any relevant trials.

Selection Criteria

All comparative studies of UCBT versus UBMT were selected. Patients were children and adults requiring allogeneic HSCT to treat malignant and nonmalignant disorders (principally leukemia). Data for neutrophil and platelet engraftment, TRM, relapse, GVHD, and overall or event-free survival had to be available either on paper or through personal communication. Each study was critically appraised for validity based on consistency, accuracy, and balance between treatment groups. Three independent reviewers independently extracted data from each study into standardized data extraction forms and reviewed the identified studies from the aforementioned sources for the eligibility criteria specified earlier. Studies without comparable patient demographics between the 2 comparative groups were excluded. Where a study in abstract form was updated (in eg, the form of a full paper), the latest version was used. There were far more review papers than primary studies on cord blood transplantation, and all review papers reiterating previous data were excluded. The results of assessment by independent reviewers were compared, and any apparent disagreement was referred to the responsible statistician so that errors and omissions could be rectified whenever possible.

Statistical Analysis

To estimate the treatment effects, outcomes were calculated as either relative risks (RR) or hazard ratios (HR), with their respective 95% confidence intervals (CIs). HRs were the preferred form of data for calculating overall mortality, disease-free survival (DFS), TRM, and relapse occurring over time. When HRs were not given in a paper, data were extracted from the respective Kaplan-Meier curves to estimate HRs.
The pooled effect estimates were calculated using the Review Manager 4.2.8 statistical package. The I² statistic was used to assess statistical heterogeneity, with I² > 50% considered to indicate significant result heterogeneity. When significant result heterogeneity was found with the fixed-effects model, a random-effects model was used to estimate the overall treatment effect.

RESULTS

Outcome of Search

From the MEDLINE and PubMed database as of August 20, 2006, there were 1124 initial hits using “cord blood,” “bone marrow,” and “transplant,” “transplants,” or “transplantation” as search terms, which included 2 randomized controlled trials and 35 clinical trials. The listed randomized controlled trials were inappropriate for our analysis; 1 was a comparison of conditioning regimens [16], whereas the other was a broad summary of a symposium [17]. Of the 35 studies, only 2 fit our criteria for selection—that they be comparisons of clinical outcomes between BMT and CBT in either children or adults including long-term survival as part of the analysis. To expand our search, we included all journal articles, limiting the search terms to the title, and found 49 studies, 6 of which fit the aforementioned criteria for selection. A Japanese study [18] that analyzed only patients with acute leukemia and that had some overlap with later papers was excluded. Also excluded were a pediatric paper that studied only patients with “bone marrow failure syndromes” [19] and a study from China that was a retrospective analysis of only patients with acute lymphoblastic leukemia [20]. A study that analyzed only hematopoietic reconstitution, but not overall outcomes, was excluded [21], as was an interesting paper that analyzed only patients requiring mechanical ventilation [22]. A paper by Schonberger et al. [23] was excluded because 1/2 of the BMTs and 1/3 of the CBTs were from related donors.

The significant hits that we found in the OVID database (CENTRAL, CDSR, ACP, DARE) had already appeared in our Medline search. We searched abstracts of conference proceedings/meetings of the American Society of Hematology (ASH) and European Bone Marrow Transplant (EBMT) between 1995 and January 2006. We found 6 suitable abstracts, which were overlaps or superseded by subsequent full-text papers. We found no suitable clinical trials in our search of databases of ongoing trials (http://www.controlled-trials.com; http://clinicaltrials.gov/ct/gui; and http://www.trialscentral.org/index). Finally, we chose 6 studies for our analysis, 3 in adults and 3 in children (Figure 1). Table 1 presents a summary of study design, patient characteristics, and treatment of each of these studies.

Characteristics of Included Studies

As shown in Table 1, 3 studies were in pediatric patients (Rocha et al. [24], Dalle et al. [25], Barker et al. [26]) and 3 studies were in adults (Takahashi et al. [27], Laughlin et al. [28], and Rocha et al. [29]). The studies in children involved a total of 161 patients receiving UCBT and 316 patients receiving UBMT. Although fewer adults had CB samples with adequate cell counts, there were more adults with hematologic diseases necessitating HSCT. Consequently, there were more adults, with a combined total of 316 adults undergoing UCBT and 996 undergoing UBMT in the comparative studies. In 2 of the adult studies [28,29] and 2 of the pediatric studies [25,26], comparisons were made between only full-matched UBMT (6/6 match) and 0–2 antigen-mismatched UBCTs. The pediatric study of Rocha et al. [24] included UBMT, which were 6/6 matched (80.5%), 5/6

![Figure 1.](image-url)
<table>
<thead>
<tr>
<th>Author</th>
<th>Center/Study Group</th>
<th>Study Population</th>
<th>Study Arm</th>
<th>Number of Patients</th>
<th>Disease Status</th>
<th>Median Age (Range), Years</th>
<th>Male: Female Ratio</th>
<th>HLA Matching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocha et al.24</td>
<td>Eurocord</td>
<td>Acute leukemia/children</td>
<td>UCBT</td>
<td>99</td>
<td>Poor risk: 32% Good risk: 68%</td>
<td>6 (2.5-10)</td>
<td>1.41</td>
<td>8% 6/6 HLA-matched</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>UBMT</td>
<td>262</td>
<td>Poor risk: 39% Good risk: 61%</td>
<td>8 (5-12)</td>
<td>1.54</td>
<td>43% 1 antigen-mismatched</td>
</tr>
<tr>
<td>Barker et al.24</td>
<td>Minneapolis</td>
<td>Haematologic diseases/children</td>
<td>UCBT</td>
<td>26</td>
<td>High risk: 58% Standard risk: 42%</td>
<td>4.5 (0.2-17.9)</td>
<td>Not available</td>
<td>17.6% 1 antigen-mismatched</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>UBMT</td>
<td>26</td>
<td>High risk: 58% Standard risk: 42%</td>
<td>4.6 (0.6-17.7)</td>
<td>Not available</td>
<td>100% 6/6 HLA-matched</td>
</tr>
<tr>
<td>Dalle et al.25</td>
<td>Hopital Sainte-Justine, Canada</td>
<td>Hematologic diseases/children</td>
<td>UCBT</td>
<td>36</td>
<td>Hematologic malignancies: 83%</td>
<td>7.5 (0.1-19.5)</td>
<td>1.40</td>
<td>6% 6/6 HLA-matched</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>UBMT</td>
<td>28</td>
<td>Hematologic malignancies: 71%</td>
<td>6.8 (0.4-21.2)</td>
<td>2.11</td>
<td>50% 2 antigen-mismatched</td>
</tr>
<tr>
<td>Rocha et al.29</td>
<td>Eurocord</td>
<td>Acute leukemia/adults</td>
<td>UCBT</td>
<td>98</td>
<td>Poor risk: 48% Good risk: 52%</td>
<td>24.5 (15-55)</td>
<td>1.04</td>
<td>6% 6/6 HLA-matched</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>UBMT</td>
<td>584</td>
<td>Poor risk: 33% Good risk: 67%</td>
<td>32 (15-59)</td>
<td>1.17</td>
<td>51% 1 antigen-mismatched</td>
</tr>
<tr>
<td>Takahashi et al.27</td>
<td>Institute of Medical Science, Tokyo</td>
<td>Haematological malignancy/adults</td>
<td>UCBT</td>
<td>68</td>
<td>Poor risk: 60% Good risk: 40%</td>
<td>36 (16-53)</td>
<td>1.63</td>
<td>39% 2 antigen-mismatched</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>UBMT</td>
<td>45</td>
<td>Poor risk: 57% Good risk: 42%</td>
<td>26 (16-50)</td>
<td>2.03</td>
<td>4% 3 antigen-mismatched</td>
</tr>
<tr>
<td>Laughlin et al.28</td>
<td>IBMTR/NYBC</td>
<td>Hematologic malignancy/adults</td>
<td>UCBT</td>
<td>150</td>
<td>CR1, CP1 or RA: 20% CR2, CP2 or AP: 32%</td>
<td>16-30: 52% 31-50: 41%</td>
<td>1.70</td>
<td>13% 1 antigen-mismatched</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>UBMT</td>
<td>367</td>
<td>CR1, CP1, or RA: 40% CR2, CP2, or AP: 31%</td>
<td>16-30: 52% 31-50: 41%</td>
<td>1.25</td>
<td>23% 1 antigen-mismatched</td>
</tr>
</tbody>
</table>

Risk definitions are adapted from different definitions used in the papers. Standard risk = patients with no malignancy or malignancy in first or second complete remission (CR1 or CR2), chronic phase CML, or no high-risk cytogenetics (eg, acute lymphoblastic leukemia with t(4;11) or t(9;22)). High risk = patients in malignancy in third complete remission (CR3), relapse, chronic myeloid leukemia (CML) beyond chronic phase, or who had myelodysplasia or high-risk cytogenetics. Poor risk = patients with malignancy in CR3 or beyond or CML in accelerated or blast phase (AP or BP). Good risk = Patients with malignancy in CR1 or CR2 or CML in chronic phase.
matched (17.6%), and 4/6 matched (0.4%). Because the data for the patients with 6/6 matches were not analyzed separately, the data extracted for meta-analysis included some mismatched UBMTs from that study. The study of Laughlin et al. [28] analyzed the adults with mismatched UBMT separately, and we included only the patients with matched UBMT in our analysis of that study. In all other instances, we used only fully matched UBMT in our analysis. We excluded from our analysis patients receiving T-cell–depleted UBMT in the studies by Rocha et al. [24] and Barker et al. [26].

Validity of Included Studies

Complete randomization was not possible in either the pediatric or adult studies. In view of longstanding data on the use of unrelated BM to treat patients with hematologic malignancies, all patients had at least a search initiated for a fully matched unrelated BM donor either before or concomitant with the search for CB blood. When this was not available, when transplantation was urgent, or when the transplant physician preferred to search for a CB unit directly, a 0–2 antigen-mismatched unrelated CB donor was searched for. In all of the studies, the patients had minor differences in terms of age, sex, and disease type and stage, but the differences between UCBT and UBMT usually were not significant (Table 1). Because the procurement and availability of CB and BM units differ greatly, blinding of the studies was not possible.

Endpoints Measured

The chosen studies all explored the endpoints of overall survival (OS) and recurrence-free survival/DFS. All of the studies also explored white cell and platelet engraftment, GVHD, and TRM.

Children

In the studies on children, white cell count recovery was not very comparable between the studies. Both studies (Barker et al. [26] and Rocha et al. [24]) showed a lower probability of white cell engraftment for UCBT, at 45 days (HR = 0.92; 95% CI = 0.79–1.08) and at 60 days (HR = 0.84; 95% CI = 0.76–0.93), respectively, although the difference was not statistically significant in Barker’s study. Time to platelet independence or engraftment in children was similar in both UCBT and UBMT when the Barker et al. [26] and Rocha et al. [24] studies were pooled (HR = 1.06; 95% CI = 0.97–1.15; P = .19).

As shown in Figure 2, the risk of having early (day 100) TRM in children was evaluated in 2 studies by Rocha et al. [24] and Barker et al. [26], and the pooled estimate favored UBMT (HR = 2.08; 95% CI = 1.37–3.16; P = .0006). Only the Rocha et al. [24] study provided HRs for the risk of relapse and showed a significantly lower relapse rate in patients with UCBT (HR = 1.96; 95% CI = 1.12–3.43). There were no significant differences in OS at 2 years when the Barker et al. [26] and Rocha et al. [24] studies were pooled (HR = 0.76; 95% CI = 0.31–1.87; P = .55). OS at 3 years in the Dalle et al. study [25] also revealed no significant differences (HR = 1.95; 95% CI = 0.44–2.54; P = .91). Only the Rocha et al. [24] study provided HRs for the data on DFS (Figure 3).

Combining the studies by Barker et al. [26], Rocha et al. [24], and Dalle et al. [25], there was no significant difference in the incidence of acute GVHD grade II–IV (HR = 0.96; 95% CI = 0.44–2.09; P = .92) and

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>log[HR] (SE)</th>
<th>HR (fixed) 95% CI</th>
<th>Weight %</th>
<th>HR (fixed) 95% CI</th>
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</thead>
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<tr>
<td>Barker 2001</td>
<td>0.7100 (0.3100)</td>
<td>47.18 2.03 [1.11, 3.73]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocha 2001</td>
<td>0.7560 (0.2930)</td>
<td>52.82 2.13 [1.20, 3.78]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>100.00 2.08 [1.37, 3.16]</td>
<td></td>
<td></td>
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<tr>
<td>Test for heterogeneity: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 3.45 (P = 0.0006)</td>
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</tbody>
</table>

Figure 2. Early TRM in children.
grade III–IV (HR = 1.46; 95% CI = 0.42–5.03; P = .55) between UCBT and UBMT (Figure 4). However, there was considerable result heterogeneity between the studies in this measure (I² = 50%). Pooling the Barker et al. [26] and Rocha et al. [24] studies with regard to chronic GVHD (Figure 4) indicated that the risk of this complication is significantly lower in patients with UCBT (HR = 0.26; 95% CI = 0.12–0.57; P = .0007).

### Adults

The pooled estimate from the trials on adult patients showed that the risks of experiencing a relapse (HR = 0.86; 95% CI = 0.62–1.19; P = .36) and early TRM (HR = 1.04; 95% CI = 0.52–2.08; P = .91) were the same in UCBT and UBMT recipients (Figures 5 and 6). Although measures of OS could not be pooled because of different definitions used, 3 studies...
had adequate data on DFS in adults (Figure 7). The overall treatment effect shows that DFS was similar in both groups (HR = 1.56; 95% CI = 0.76–3.17; \( P = .23 \)). However, Takahashi et al.\[27\] reported a statistically significant difference (HR 4.48, 95% CI 2.44–8.23) in favor of UCBT (Figure 7). We believe that the difference cannot be completely explained by the degree of HLA matching of the UCBT and UBMT recipients. As shown in Table 1, in Laughlin et al.\[28\], most of the CB was 4/6 antigen matched, and our analysis comparison was made only with BM that was 6/6 antigen-matched. For the adult study of Rocha et al.\[29\], almost equal numbers of CB were 4/6 and 5/6 antigen-matched, whereas BM was all at least 6/6 antigen-matched. However, in the Japanese study, most of the CB was 4/6 antigen-matched, with some 5/6 or 3/6 matched; 87% of the BM was 6/6 antigen-matched, and 13% was 5/6 matched. The excellent results of UCBT in the Japanese study cannot be explained by patient weight or nucleated cell counts of the CB unit.

White cell engraftment in adults was consistently superior with UBMT, although the studies could not be pooled, because this was measured at day 42 by Takahashi et al.\[27\] (HR = 0.90; 95% CI = 0.82–0.99; \( P = .03 \)) and day 100 in the Laughlin et al.\[28\] (HR = 0.76; 95% CI = 0.69–0.84; \( P < .00001 \)). Platelet engraftment, somewhat superior with UBMT, was measured on day 120 in Takahashi et al.\[27\] (HR = 0.89; 95% CI = 0.77–1.02; \( P = .10 \)) and at 1 year in Laughlin et al.\[28\] (HR = 0.50; 95% CI = 0.40–0.62; \( P < .00001 \)), so these results also could not be pooled. Acute GVHD was seen less often in UCBT, but the studies by Takahashi et al.\[27\] (HR = 0.45; 95% CI = 0.31–0.66; \( P = .05 \)) and Rocha et al.\[29\] (HR = 0.69; 95% CI = 0.46–1.04; \( P = .01 \)) could not be pooled, because Takahashi et al.\[27\] evaluated this only in patients surviving 21 days or longer after transplantation with evidence of engraftment. Nevertheless, both studies clearly showed that UCBT was significantly associated with less acute GVHD.

**DISCUSSION**

In this meta-analysis of UCBT versus UBMT, UCBT was associated with slower engraftment, less GVHD, a similar relapse rate, and equivalent survival. We applied a systematic methodology in which the studies were searched, selected, and analyzed, but because allocation to a particular treatment group was based on the availability of suitable unrelated BM or CB donors, blinded or randomized controlled trials were not available. To randomize patients in a study...
comparing unrelated UCBT and UBMT, each patient would need an unrelated CB and BM donor available at the point of randomization. Conducting such a study has not been possible to date. As such, nonrandomized comparative studies were selected for this meta-analysis. The baseline characteristics of patients were comparable in these studies; therefore, the studies were pooled to estimate the overall treatment effect. Because these were all retrospective studies, an intention-to-treat analysis was impossible. Although it is true that patient characteristics were similar for both UBMT and UCBT and that the lack of availability of fully matched unrelated donors often predicted the need for less well-matched CB grafts, we cannot fully exclude the possibility of center biases in treatment and selection of patients for UBMT or UCBT. Some studies had no absolute numbers for data, and HRs could not be derived for some studies. There were, however, explicit statements of intent, as evident in the studies of Barker et al. [26], Takahashi et al. [27], and Dalle et al. [25] that patients were eligible for UCBT if fully matched siblings or fully matched unrelated BM donors were not available immediately or within a satisfactory time frame (in the case of Barker et al. [26], within 3 months of search initiation). In Dalle et al. [25], this intention-to-treat analysis is reasonably well laid out; of 91 patients who initiated a search, 85 completed a 3-month search process, and 84 found suitable grafts. A total of 64 went on to undergo transplantation after 20 cancelled their transplantations for various reasons. Of these 64 patients, 37 had a suitable BM donor, although 9 of these had CB grafts because of more rapid availability, leaving 28 who went on to receive a BM transplant. Nine patients who had an urgent need for transplantation, as well as 27 who had not suitable BM donors, all received CB transplants.

In the 3 adult studies, recipients of CB weighed less, were more likely to have advanced leukemia at the time of transplantation, and received grafts with lower cell doses and greater HLA disparities than patients who received BM transplants. TRM, DFS, and OS were dramatically better in CB recipients in Takahashi et al. [27]. This may be explained by a significantly shorter donor search to transplantation times in CB recipients (median, 2.8 months; range, 0.7–36.3 months vs median, 10.8 months; range, 4.4–52.1 months; \( P < .01 \)). Donor search to transplantation time was not reported in the other 2 studies. There may also be relevance in the fact that CB recipients tended to be older than BM recipients in Takahashi et al. [27], in contrast to the other 2 studies, in which the converse was true. Finally, differences in patient ethnicity may be significant.

All 3 pediatric studies demonstrated significantly slower neutrophil and platelet engraftment in CB recipients, with the exception of Barker et al. [26], in which the platelet engraftment rate was similar to that
of the BM recipients. No significant difference in relapse rate and OS between CB and BM recipients was found in these studies. Regarding acute and chronic GVHD development, Rocha et al. [24] reported lower risk in the CB group, in contrast with the other 2 studies, which reported similar risk. It is noteworthy, however, that 20% of unmanipulated BM recipients in this study received HLA-mismatched grafts. Mismatched BMTs have been associated with a very high risk of GVHD in pediatric recipients [30]. Nevertheless, all 3 studies did not find an increased risk of acute (aGVHD) or chronic GVHD (cGVHD) development despite markedly greater HLA disparity in CB transplants compared with BM transplants.

The comparison here is between UCBT and UBMT; peripheral blood stem cell transplantation (PBSC) is not included in the analysis. In PBSC, hematopoietic engraftment is generally faster, but GVHD (especially cGVHD) is somewhat more severe. However, numerous comparisons have found no differences in survival between UBMT and unrelated donor PBSC (UPBSC) except in patients in a late disease stage, in whom UPBSC appears to be better [31,32]. Thus, although UCBT would be expected to have even more pronounced difference in engraftment and GVHD compared with UPBSC, survival outcomes are likely to be similar, although any variance in outcomes of patients in late disease stage will be interesting to study. Finally, it is important to note that the patients in our meta-analysis all underwent myeloablative preparative regimens for their transplantation. Reduced-intensity conditioning regimens [33,34] would probably reduce the dependency on engraftment for survival, although any differences in a graft-versus-tumor effect probably would be more obvious in that setting. Interestingly, a study on patients with advanced Hodgkin’s lymphoma found comparable results between UBMT and HLA-matched sibling donor HSCT after a reduced-intensity preparative regimen [35].

This meta-analysis was performed using aggregate patient data (APD) as opposed to individual patient data (IPD) [36-38]. Whereas IPD is most suitable for time-to-event or survival data because of its ability to update data, provide longer follow-up, and study the impact of individual patient characteristics, it is not always possible. This is especially true when time or resources are limited and when the original study data are not available or are available from only a biased sample of studies. We performed this meta-analysis based on APD because of limitations in sourcing original study data from all sources.

Because of the unavailability of randomized and controlled clinical trials, we performed pooled analysis of retrospective comparative studies and confirmed that UCBT in children and adults had equivalent outcomes compared with UBMT despite the greater donor-recipient HLA disparity with UCBT. Consequently, for patients without a BM donor who is optimally matched and readily available (especially in cases of urgent need for transplantation), and even for patients with potential unrelated donors, 1 or 2 antigen-mismatched UCBT is a viable, equally effective alternative for patients needing matched donor UBMT.

REFERENCES