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Cost-effectiveness and clinical outcomes of double versus single cord blood transplantation in adults with acute leukemia in France

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*ML and AR contributed equally to this work.

ABSTRACT

Double cord blood transplantation extends the use of cord blood to adults for whom a single unit is not available, but the procedure is limited by its cost. To evaluate outcomes and cost-effectiveness of double compared to single cord blood transplantation, we analyzed 134 transplants in adults with acute leukemia in first remission. Transplants were performed in France with reduced intensity or myeloablative conditioning regimens. Costs were estimated from donor search to 1 year after transplantation. A Markov decision analysis model was used to calculate quality-adjusted life-years and cost-effectiveness ratio within 4 years. The overall survival at 2 years after single and double cord blood transplants was 42% versus 62%, respectively (P=0.03), while the leukemia-free-survival was 33% versus 55%, respectively (P=0.03). The relapse rate was 21% after double transplants and 42% after a single transplant (P=0.006). No difference was observed for non-relapse mortality or chronic graft-versus-host-disease. The estimated costs up to 1 year after reduced intensity conditioning for single and double cord blood transplantation were €165,253 and €191,827, respectively. The corresponding costs after myeloablative conditioning were €192,566 and €213,050, respectively. Compared to single transplants, double cord blood transplantation was associated with supplementary costs of €21,302 and €32,420 up to 4 years, but with increases in quality-adjusted life-years of 0.616 and 0.484, respectively, and incremental cost-effectiveness ratios of €34,581 and €66,983 in the myeloablative and reduced intensity conditioning settings, respectively. Our results showed that for adults with acute leukemia in first complete remission in France, double cord transplantation is more cost-effective than single cord blood transplantation, with better outcomes, including quality-adjusted life-years.

Introduction

Allogeneic stem cell transplantation (HSCT) is effective treatment for patients with various hematologic disorders. It is, however, a complex, resource-intensive and costly procedure. The cost of HSCT has been previously evaluated, mainly in the setting of HLA identical sibling and matched unrelated donor transplants.

The first studies on the cost-efficacy of HSCT compared allogeneic HSCT to chemotherapy in patients with acute leukemia. Despite the high cost of HSCT, the results demonstrated the advantages of the procedure due to the impact on long-term survival adjusted to the quality of life. In the first published studies, the estimated costs for HSCT varied greatly (Online Supplementary Table S1) depending on the country in which they were performed, type of donor, transplant center procedures and year of transplantation. A recent comparative study of autologous and allogeneic HSCT for patients transplanted for hematologic malignancies in the USA estimated a 100-day total cost of US$ 203,026 for allogeneic HSCT.

Unrelated donor cord blood transplantation (UCBT) has become a widely accepted transplant modality in the absence of an HLA-matched donor. However, the delay of engraftment and the increased risk of graft failure remain problems in adults transplanted with a single cord blood unit. The possibility of using two cord blood units has extended the use of UCBT to patients for whom a single unit containing a minimal of 2.5x10⁷/kg total nucleated cells is not available. Studies have been performed comparing outcomes after single (s) UCBT and double (d) UCBT, but, none focused on a homo-
geneous population.

To date, few studies have been published evaluating the cost of UCBT. The acquisition cost of two cord blood units is one of the main limitations of using dUCBT. The median cost for the first 100 days after UCBT was estimated to be around US$ 80,407 in Canada in 2007 and around US$ 137,564 in the USA in 2009, not including the cost for the donor search. In a more recent study from the Erasmus University, the cost of UCBT over 1 year was estimated to be around € 250,000.

The French healthcare system is mainly financed by the French government. Approximately 75% of health expenditure is covered by government-funded agencies. In 2011, in France, total health expenses added up to € 225.5 billion, or 11.6% of the gross domestic product (GDP) in 2010. According to the World Health Organization (WHO) this figure places France in the higher range among countries that are members of the Organization for Economic Co-operation and Development (OECD) (The World Health Report 2000: WHO).

Since almost all healthcare expenses in France are covered by a common system, we were able to perform a cost-effectiveness study comparing dUCBT and sUCBT in France, by evaluating the cost over a year and outcomes of adult patients transplanted for acute leukemia in first complete remission.

Methods

To estimate cost-effectiveness, which was the primary outcome of the study, we analyzed clinical outcomes and the cost of the transplant procedures.

We analyzed outcomes and cost of UCBT in 134 consecutive patients transplanted for acute leukemia in first complete remission. The transplants were performed in 26 centers between 2002 and 2009. Patients received a single or a double unmanipulated cord blood unit as a first graft, after myeloablative conditioning (MAC) or reduced intensity conditioning (RIC). The Institutional Review Board of the Eurocord-Netcord scientific committee approved this study.

The primary endpoint for clinical outcome was overall survival. Other endpoints were leukemia-free survival, neutrophil recovery, graft-versus-host disease (GVHD), relapse, and non-relapse mortality. The characteristics of the patients and their transplants were compared with appropriate statistical tests. Cox proportional-hazard was used for multivariate analyses. Hospital costs were estimated from the search for a donor to 1 year after UCBT, according to the French public health system. Major resources considered were stem cell procurement, initial hospitalization for the transplant, readmissions to hospital and outpatient clinics. The cost for the search for and acquisition of the graft included expenses related to the donor request, typing, and cost of the cord blood unit, and varied by country and cord blood bank (Online Supplementary Table S2). The daily cost of hospitalization was estimated using the average cost published by the French National Scale of Costs (Online Supplementary Table S3).

Resources were estimated in euros, adjusted to the 2010 French consumer price index. Cost-effectiveness was estimated by the incremental cost-effectiveness ratio (ICER), which is the extra cost generated by an additional (quality-adjusted life-year (QALY)). ICER per capita was calculated by dividing ICER by French GDP per capita in 2010.

Following the recommendation of the WHO, the GDP was used as the indicator to derive the categories of cost-effectiveness. The cost-effectiveness of a health technology can be categorized as follows: (i) very cost-effective: ICER below the per capita GDP; (ii) cost-effective: ICER between one and three times the per capita GDP; (iii) not cost-effective: ICER above three times the per capita GDP. A QALY can be used to compare claims for finite healthcare resources. One QALY corresponds to 1 year spent in perfect health.

Results

Patient, disease and transplant characteristics

The characteristics of the patients, their diseases and transplants are shown in Table 1. Forty patients were transplanted for acute lymphoblastic leukemia and 94 for acute myeloid leukemia in first complete remission. The median age of the patients was 42 years and the median time from diagnosis to UCBT was 180 days. Sixty-one patients received a sUCBT and 73 a dUCBT. There was no statistical difference between poor-risk cytogenetic groups for patients with acute lymphoblastic or myeloid leukemia receiving single or double UCBT (P=0.73 and P=0.5, respectively). Twenty-eight percent of the cord blood units were HLA identical to the recipient (at the antigen level for HLA-A, HLA-B and HLA-C).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>sUCBT n=61</th>
<th>dUCBT n=73</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up, months</td>
<td>49</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Median age; years (range)</td>
<td>41 (19-66)</td>
<td>43 (18-66)</td>
<td>0.39</td>
</tr>
<tr>
<td>Diagnosis; AML (%)</td>
<td>43 (70%)</td>
<td>51 (70%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Gender; female (%)</td>
<td>35 (57%)</td>
<td>34 (47%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Type of conditioning; RIC, n. (%)</td>
<td>36 (59%)</td>
<td>43 (59%)</td>
<td>0.99</td>
</tr>
<tr>
<td>HLA disparities; ≥2 mismatches, n. (%)</td>
<td>42 (71%)</td>
<td>51 (70%)</td>
<td>0.94</td>
</tr>
<tr>
<td>TNC infused x10^7/Kg</td>
<td>2.7 (1-6.1)</td>
<td>3.8 (1.1-6.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

sUCBT: single umbilical cord blood transplant; dUCBT: double umbilical cord blood transplant; AML: acute myeloid leukemia; RIC: reduced intensity conditioning; HLA: human leukocyte antigen; TNC: total nucleated cells.

Table 1. Patient and disease characteristics.
A and B and the allelic level for DRB1) or had one HLA disparity and 72% had two or three HLA disparities (for dUCBT the highest number of HLA disparities between the unit and the recipient was considered). The median infused total nucleated cell count was 2.7×10^7/kg for patients receiving a sUCBT and 3.8×10^7/kg for those receiving a dUCBT (P<0.001). The conditioning regimen was reduced intensity in 55 (84% total body irradiation in 79 patients (97% total body irradiation <6 Gy) and myeloablative in 55 (84% total body irradiation ≥6 Gy). The median follow-up was 49 months after sUCBT and 47 months after dUCBT.

Outcomes and risk factors

Neutrophil recovery, graft-versus-host disease and infections

Ninety-nine patients achieved neutrophil engraftment (42 of 61 patients who received a sUCBT and 57 of 73 of those who received a dUCBT) in a median time of 23 days (range, 6-55). The cumulative incidence of neutrophil engraftment was 70±6% and 84±4% for sUCBT and dUCBT, respectively (P=0.28). The cumulative incidence of acute GVHD grade II-IV was higher after dUCBT than after sUCBT: 52% versus 34%, respectively (P=0.05). No difference was found in the cumulative incidence of acute GVHD grade III-IV between the single and double transplants (sUCBT 17%, dUCBT 20%) (P=0.63). At day +100, 53% of patients experienced cytomegalovirus reactivation (37% after sUCBT and 71% after dUCBT; P=0.01), 46% had a viral infection other than cytomegalovirus infection and 47% had bacterial infections. The cumulative incidence of chronic GVHD was 18% versus 25% after sUCBT and dUCBT, respectively (P=0.22). Twelve patients (11%) had a further allogeneic transplant: seven because of graft failure (4 in the sUCBT group and 3 in the dUCBT group) and five because of relapse (4 in the sUCBT group and 1 in the dUCBT group).

Non-relapse mortality and relapse

The cumulative incidence of non-relapse mortality at 2 years was 25±6% and 26±5% after sUCBT and dUCBT, respectively (P=0.79). In adjusted multivariate analysis, the non-relapse mortality rate was lower for patients receiving a RIC regimen [hazard ratio (HR) 0.21, 95% confidence interval [95% CI] 0.08-0.52; P=0.001] and for patients younger than 50 years at the time of transplantation (HR 0.35, 95% CI 0.15-0.76; P=0.02) (Table 2).

The cumulative incidence of relapse at 2 years was 21±5% after dUCBT and 42±6% after sUCBT (P=0.006). The cumulative incidence of relapse at 2 years was 20±6% and 34±5% for patients with acute lymphoblastic leukemia and acute myeloid leukemia, respectively (P=0.14). In mul-

![Figure 1](image-url)  
Figure 1. (A) The probability of overall survival after dUCBT and sUCBT; (B) The probability of leukemia-free survival after dUCBT and sUCBT.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall survival</th>
<th>Leukemia-free survival</th>
<th>Relapse incidence</th>
<th>Non-relapse mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% CI</td>
<td>Hazard ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>dUCBT vs. sUCBT</td>
<td>0.53</td>
<td>0.33-0.86</td>
<td>0.01</td>
<td>0.21-0.80</td>
</tr>
<tr>
<td>ALL vs. AML</td>
<td>0.54</td>
<td>0.30-0.97</td>
<td>0.31</td>
<td>0.21-0.50</td>
</tr>
<tr>
<td>Age &lt; 50 years</td>
<td>0.53</td>
<td>0.29-0.96</td>
<td>0.75</td>
<td>0.43-1.31</td>
</tr>
<tr>
<td>RIC vs. MAC</td>
<td>0.56</td>
<td>0.31-1.01</td>
<td>0.57</td>
<td>0.33-1.40</td>
</tr>
<tr>
<td>dUCBT vs. sUCBT</td>
<td>0.67</td>
<td>0.39-1.13</td>
<td>0.67</td>
<td>0.39-1.20</td>
</tr>
<tr>
<td>Age &lt; 50 years</td>
<td>0.69</td>
<td>0.39-1.20</td>
<td>0.75</td>
<td>0.43-1.31</td>
</tr>
<tr>
<td>RIC vs. MAC</td>
<td>0.75</td>
<td>0.43-1.31</td>
<td>0.63</td>
<td>0.33-1.40</td>
</tr>
</tbody>
</table>

Table 2. Multivariate analysis for outcomes after single and double cord blood transplantation.

CI: confidence interval; OS, overall survival; dUCBT: double umbilical cord blood transplant; vs.: versus; sUCBT: single umbilical cord blood transplant; AML: acute myeloid leukemia; ALL: acute lymphoid leukemia; RIC: reduced intensity conditioning; MAC: myeloablative conditioning.
tivariate analysis, dUCBT (HR 0.41, 95% CI 0.21-0.80; P=0.009) and use of MAC (HR 0.45, 95% CI 0.19-0.83; P=0.06) were independently associated with a lower relapse incidence.

Overall survival and leukemia-free survival

The estimated overall survival at 2 years was 42±6% and 62±6% after sUCBT and dUCBT, respectively (P=0.05) (Figure 1A). In adjusted multivariate analysis, use of dUCBT (HR 0.53, 95% CI 0.38-0.86; P=0.01), a diagnosis of acute lymphoblastic leukemia (HR 0.54, 95% CI 0.30-0.97; P=0.04) and age younger than 50 years at transplantation (HR 0.53, 95% CI 0.29-0.96, P=0.04) were independently associated with higher overall survival.

The leukemia-free survival rate at 2 years was 33±6% in the sUCBT group versus 53±6% in the dUCBT group (P=0.03) (Figure 1B). In the multivariate analysis, the use of dUCBT was the only factor independently associated with a higher leukemia-free survival rate (HR 0.56, 95% CI 0.36–0.89; P=0.01).

Cost analysis

Cost up to 1 year after umbilical cord blood transplantation

The data on duration of hospitalization and costs by type of graft and conditioning regimen are detailed in Table 3. The mean duration of hospitalization for patients undergoing sUCBT and dUCBT after MAC was 61 and 68 days, respectively, while for those receiving a RIC regimen, it was 48 and 53 days, respectively. The mean cost per day of hospitalization in the transplant unit was € 2,019 while that for the out-patient clinic was € 858.

The mean cost for identifying a donor and obtaining the cord blood was € 28,164 for sUCBT and € 48,929 for dUCBT. Up to 1 year, the estimated cost for MAC sUCBT was € 192,566 and that for RIC sUCBT was € 165,253. For dUCBT, the estimated cost was € 213,050 with MAC and € 191,827 with RIC.

Chronic GVHD required a mean of 12 additional days of hospitalization, leading to an incremental cost of € 9,180. The occurrence of disease relapse was associated with a mean additional 15 days of hospitalization and, in 12% of the patients, with a second transplantation, leading to a supplemental cost of € 29,775.

Cost-effectiveness up to 4 years

In the MAC group, dUCBT was associated with a supplementary cost of € 21,302 up to 4 years and with an improvement in terms of QALY of 0.616. The ICER was € 34,581 after dUCBT versus sUCBT. In the RIC group, dUCBT was associated with an additional cost of € 32,420 up to 4 years and with an improvement in term of QALY of 0.484. In this case, the ICER was € 66,983 after dUCBT versus sUCBT (Table 4).

Considering that in France in 2010, the per capita GDP was € 32,000, the ICER per capita was 1.08 in MAC transplants and 2.09 in RIC ones. In sensitivity analysis varying the utility values, the ICER ranged from € 31,679 to € 47,647 for MAC and from € 59,243 to € 99,386 for RIC.

Discussion

In our study we showed an advantage of dUCBT compared to sUCBT in terms of lower relapse rate and better survival, despite a higher incidence of acute GVHD.

Recently, the Center of International Blood and Marrow Research (CIBMTR) in collaboration with the New York Cord Blood program reported no significant differences in relapse or leukemia-free survival for adults with acute leukemias in all disease states, transplanted after single or double UCBT after MAC or RIC regimens.2" There are several differences between that study and the one we report here. The CIBMTR study analyzed patients in all disease states while we focused only on patients given UCBT for acute leukemia in first complete remission. Another important point regarding this French...
study is that the protocols for induction, consolidation therapy, transplant procedures and supportive care were highly standardized throughout the country.

Our study is the first of its kind to address the cost and cost-effectiveness of sUCBT and dUCBT. The total cost up to 1 year for sUCBT was €192,000 when MAC was used and €165,000 when RIC was given. The corresponding costs for dUCBT were €213,000 and €192,000, respectively.

The cost of H SCT has been previously evaluated mainly in the setting of transplants from HLA identical siblings and matched unrelated donors. The reported costs varied greatly, from US$ 60,000 to 200,000. This difference in costs may be explained by differences in methodologies, inclusion periods, countries, populations, health coverage policies and graft type. In 2002, van Aghoven reported that, for patients with acute leukemia, the cost over a period of 2 years, including the donor search, was €151,754 per patient and increased to €173,587 for patients still alive 2 years after transplantation. More recent studies have estimated the 1-year cost of related and unrelated donor H SCT using bone marrow or peripheral blood stem cells as €159,414 in Sweden and €128,000 in the USA.

Cordonnier et al. reported the total cost of HLA identical sibling H SCT after RIC and MAC in France. The cost for 1 year after H SCT was around €60,000. It should, however, be noted that the study included very few patients (n=25), from only two transplant centers. In another study, conducted by Esperou et al. in 2004 on 85 patients from five transplant centers, the mean cost for the first 6 months after transplantation, restricted to a specific protocol, was €76,000.

The average cost for initial hospitalization for UCBT in Canada and in the USA was consistent with that in our series. However in both studies, only costs up to 100 days were included whereas in other studies costs were considered over a much longer period. For instance, Svanh et al. analyzed costs of allogeneic transplantation up to 5 years and the study by Saito et al. relates to 1-year costs. However, when making comparisons with other countries, it is important to point out that the average cost of transplantation in France and other European countries may be lower, because of different salaries and different healthcare systems, than in countries such as the USA and Canada.

The cost for graft acquisition is an important issue, especially when a double UCBT is necessary. In France, the cost of buying a cord blood unit was highly dependent on the country and the bank of origin of the unit (less than €7,000 for a unit from Taiwan, approximately €10,000 for one from France and more than €30,000 for a cord blood unit from some American banks) (Online Supplementary Table S2).

One could argue that the possible difference in costs may be due to the conditioning regimens. There was no difference in the 1-year cost in Cordonnier’s study, whereas Saito et al. reported lower costs for patients receiving RIC than those given MAC: €80,499 versus €128,254, respectively. In our study, we also found a cost increase of approximately €50,000 for patients receiving MAC.

With regards to the complications considered, chronic GVHD and disease recurrence required additional days of hospitalization, leading to further costs. The role of complications in increasing costs of transplantation has been described previously. In 2007, Costa et al. reported a cost increment of US$2,716 for chronic GVHD and US$10,576 for relapse. The additional cost for chronic GVHD reported by Esperou et al. was much higher, at around €20,000, but also included costs due to transplant-related complications and infections.

Importantly in our study, the survival advantage found for dUCBT allowed us to perform a cost-effectiveness analysis to determine the ICER of dUCBT versus sUCBT. Our results showed that dUCBT was cost-effective according to the WHO’s definition when MAC was used (ICER per capita: 1.08) and also when RIC was used (ICER twice the per capita GDP: 2.09).

By sensitivity analysis, even considering the worst scenario (low utility for chronic GVHD and higher utility for relapse for dUCBT), the ICER remained below €50,000. The ICER of dUCBT increased when the utility value of chronic GVHD decreased and when the utility value of relapse increased.

In summary, this analysis was performed to evaluate the outcomes and cost-effectiveness of dUCBT compared to sUCBT in the treatment of adults with acute leukemia in France. The results suggest that, in both the MAC and RIC settings, dUCBT is associated with better outcomes than sUCBT and is a more cost-effective strategy for adult patients with acute leukemia in first complete remission.

Based on 1-year cost calculations, dUCBT was associated with higher costs than sUCBT. In the long-term analysis, with the estimation of QALY, dUCBT was more cost-effective, regardless of the conditioning regimen.

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References


