PLENARY LECTURE

Advances in unrelated cord blood transplants
in malignancies

E Gluckman

Cord blood is an unlimited source of hematopoietic stem cells (HSCs) for allogeneic HSC transplant. Since the first human cord blood transplant performed 20 years ago, cord blood banks have been established worldwide for collection and cryopreservation of cord blood for allogeneic HSC transplant. More than 500 000 cord blood units are now available for international exchange of cord blood units. A global network of cord blood banks and transplant centers has been established for a common inventory and study of clinical outcomes. Results of unrelated allogeneic cord blood transplants in malignant and nonmalignant diseases, in adults and children, show that, compared with HLA-matched unrelated bone marrow transplant, cord blood has several advantages including prompt availability of the transplant, decrease of graft versus host disease and better long-term immune recovery resulting in a similar long-term survival. Several studies have shown that the number of cells is the most important factor for engraftment while some degree of HLA mismatches is acceptable. Progresses in this field are expected to facilitate engraftment including *ex vivo* expansion of stem cells, intra-bone injection of cord blood cells and double cord blood transplants.

Leukemia Supplements (2012) 1, S10–S11; doi:10.1038/leusup.2012.8

Keywords: cord blood allogeneic stem cell transplant; hematological malignancies

Allogeneic hematopoietic stem cell (HSC) transplant is widely used to treat patients with hematological malignant and nonmalignant disorders. The choice of the donor and the source of HSCs have changed, extending the indications of transplant to more patients, especially in adults. Nowadays, transplant physicians must choose between bone marrow cells, G-CSF-mobilized peripheral blood stem cells (PBSC) or umbilical cord blood (UCB) cells. The donor can be either an HLA-identical sibling, an unrelated matched donor, an haploidentical family PBSC or a HLA-mismatched unrelated UCB donor. Many studies had shown that HLA-mismatched UCB transplants are feasible and might, in the future, achieve results similar to those of HLA-matched transplants. This is an evolving field that must be evaluated carefully with more comparative studies, which can be achieved by multicenter registry comparisons. In addition, early toxicity and transplant-related mortality (TRM) have diminished with the use of reduced-intensity conditioning regimens, infusion of two UCB, improvement of supportive care and better control of graft versus host disease (GVHD) and infectious complications. The choice of the best stem cell source to be used is not always easy, as each stem cell source has advantages and disadvantages that must be taken into consideration before making a definitive choice.

At present, a global network of cord blood banks and transplant centers has been established for a common inventory, an estimated 600 000 UCB units have been banked and more than 25 000 UCB units distributed worldwide for adults and children with severe hematological diseases. Eurocord registry has collected and analyzed outcomes data from more than 8500 patients from European and non-European centers. The number of UCB transplants in adults has been increasing in recent years, also because of the use of double cord blood transplant and reduced-intensity conditioning. In the United States, UCB grafts are used for about 20% of unrelated donor transplantations for hematologic malignancies, and in Europe for about 12%. Most UCBTs are performed for hematological malignancies.

Recent Eurocord data show that among 8500 UCBT collected from 53 countries and 525 transplant centers, 4393 were for pediatrics and 3396 for adult patients. Since 2005, the number of adults is superior to children, with 989 patients aged more than 51 years. This increase is mostly due to the use of reduced-intensity conditioning and the use of double cord blood to achieve an adequate number of cells. In adults, most transplants are performed for malignant diseases (AML 37%, ALL 21%, MDS/MPD 13%, CML 7%, CLL 3% and lymphoma 12%). A recent survey shows that there has been an improvement of results over time. In children with AML, ALL or MDS, probability of survival after UCBT is 54% in transplants performed from 2006 to 2011 compared with 37% for those performed before 2005; similarly, in adults, survival for AML, ALL and MDS is 36% in transplants performed from 2006 to 2011 and 26% for those performed before 2000. Similar results were found in patients from North America (CIBMTR data).

In *de novo* AML in first complete remission (CR1), Eurocord analyzed 134 adults (>18 years) who received UCBT as first transplant after a myeloablative-conditioning regimen (MAC). Patients were transplanted from 2000 to 2010 in EBMT centers. Median age at UCBT was 33 years (range 18–63) and median weight was 65 kg (range 46–112). On the basis of available cytogenetic and molecular markers at diagnosis ($n = 111$), 45% of patients were classified in the intermediate-risk group and 31% in the unfavorable-risk group. Twenty-six patients had a FLT3/ITD-positive mutation status. The median time from diagnosis to UCBT was 5.9 months, and the median duration of remission before transplant was 104 days. Grafts were composed of one (sUCBT; $n = 100$) or two (dUCBT; $n = 34$) CB units. In all, 32% of CB units were identical to the recipient or had one HLA disparity (antigen level for HLA-A and B allelic level for DRB1), whereas 68% had two to three HLA disparities. Median total nucleated (TNC) cell dose at infusion was $2.7 \times 10^7/\text{kg}$ in sUCBT and $3.9 \times 10^7/\text{kg}$ in dUCBT. All patients were transplanted using a MAC, from which 60% were

busulfan based ($n=80$). Overall, the median follow-up was 22 months (range 3–120; median follow-up 28 months). The cumulative incidence (CI) of 60 days neutrophil recovery was $90 \pm 3\%$ (median time of 23 days), and it was 87% for sUCBT and 90% for dUCBT. At day 100, chimerism test showed full donor chimerism in 92% of patients. At day 100, CI of acute GVHD (grade II–IV) was $19 \pm 3\%$, and it was 12% and 38% for patients transplanted with sUCBT and dUCBT, respectively ($P=0.001$). Among 34 patients who received a dUCBT, 14 experienced grade II–IV acute GVHD (grade II ($n=10$), grade III ($n=3$), grade IV ($n=1$)); of those transplanted with a sUCBT, 10 out of 17 had grade II, 4 had grade III and 3 grade IV acute GVHD. CI of chronic GVHD at 1 year was $20 \pm 3\%$, and CI of TRM at 1 year was $32 \pm 3\%$. In the multivariable analysis, a TNC dose at infusion $>2.9 \times 10^7/\text{kg}$ ($P=0.02$) was associated with decreased TRM; however, in spite of higher incidence of aGVHD, dUCBT was not associated with higher TRM. A total of 58 patients died. The causes of death were infection, other transplant-related events ($n=45$) or relapse ($n=13$). CI of 2-year relapse was $16 \pm 4\%$: 15% for those patients with sUCBT ($n=100$) and 18% for those with dUCBT ($n=34$). Out of 26 FLT3/ITD-positive patients, 7 relapsed at a median time of 96 days after UCBT. The 2-year probability of leukemia-free survival (LFS) was $52 \pm 2\%$. There was a trend toward a higher LFS in patients with a longer duration of remission (>66 days, 27 versus 61%, $P=0.07$). In multivariable model, the use of busulfan in conditioning regimen (HR 2.2, $P=0.006$) and the use of double UCBT (HR 1.9, $P=0.06$) were independently associated with better LFS. In fact, LFS was 58% for those patients receiving the busulfan-based regimen compared with 42% for those receiving a TBI-based regimen, and it was 58% for dUCBT and 50% for sUCBT. This study shows that UCBT using one or two CB units is a valid treatment option for adults with high-risk AML in CR1 without an HLA-identical donor. The best conditioning regimen for single or double UCBT has to be assessed in prospective clinical trials.

In children AML, Eurocord analyzed the outcomes and prognostic factors after UCBT for pediatric AML, with a special emphasis on cytogenetic and molecular abnormalities. We performed a retrospective multicenter study on 376 AML children, who received a single UCBT. Transplants were performed from 1994 through 2010 in EBMT centers. Median age was 5 years and median weight 20 kg at the time of transplant. At the time of UCBT, 40% of patients were in CR1, 42% in CR2 and 18% in a more advanced disease status. In addition to hematological disease status classification, 303 children (81%) were stratified in unfavorable (37%), intermediate (48%) and favorable (15%) groups based on cytogenetic and molecular biology whenever possible. The majority of grafts were HLA 5/6 (47%) or 4/6 (37%), and 6% of patients received UCBT as a second transplant. Median infused TNC and CD34+ cells were 5.2×10^7 and $1.8 \times 10^5/\text{kg}$ of recipient body weight, respectively. The majority of patients (90%) received MAC with TBI (27%) or busulphan (69%); ATG was used in 80% of cases. GVHD prophylaxis was included: CSA + others

in 89%, MTX + others in 8% and others in 11% of patients. Median follow-up time was 36 months. The median time to achieve neutrophil and platelet recoveries was 24 and 42 days, respectively. CI of ANC recovery was 86%; in a multivariate model, it was favorably associated with a higher TNC dose ($>$ median, HR: 1.40, $P=0.007$) and transplantation in CR1 or CR2 (HR: 1.25, $P=0.003$). At day +100, CI of grade II–IV acute GVHD was 32% (13% grade III, 4% grade IV). At 3 years, CI of nonrelapse mortality (NRM) was 27%. Multivariate analysis showed that TNC dose ($>$ median, HR: 0.5, $P=0.01$) was associated with decreased NRM. There was a trend toward a decreased NRM in patients transplanted with a 6/6 or 5/6 HLA graft ($P=0.05$). CI of relapse at 3 years was 16% for patients transplanted in CR1, 28% for those transplanted in CR2 and 42% for those transplanted in more advanced disease. Estimated 3-year LFS was 65% in CR1, 43% in CR2 and 22% in more advanced disease patients. The multivariate analysis identified disease status at time of UCBT (advanced, HR: 0.5, $P<0.001$) as factors independently associated with LFS. Fifty-five children transplanted in CR1 with unfavorable disease had LFS of $75 \pm 6\%$; not statistically different from the overall CR1 group. For those transplanted in CR2, 3-year LFS was $67 \pm 8\%$, $31 \pm 7\%$ and $40 \pm 8\%$ in the favorable, intermediate and unfavorable subgroups, respectively. Multivariate analysis demonstrated the following significant prognostic factors: favorable cytogenetic and molecular risk group (reference group), intermediate (HR: 4.5, $P<0.001$), adverse (HR: 2.8, $P=0.002$) and previous CR1 duration longer than 10 months (median, HR: 0.5, $P=0.009$). These data demonstrate that UCBT is an attractive stem cell source for children with AML when no HLA-identical donor is available. The cell dose remains an important factor for engraftment and NRM. The results are particularly encouraging for the use of UCBT in patients with unfavorable cytogenetic and molecular biology risk classification diseases in CR1.

In conclusion, unrelated cord blood transplant is a reasonable option in patients with leukemia who have no HLA-identical donor. Future studies aim at improving engraftment and accelerate immune reconstitution. Several strategies are being explored to lower TRM after UCB transplantation, with most efforts focused on delivering higher TNC either with co-infusion of two unmanipulated UCB units, direct intra-bone transplantation of UCB cells and co-infusion of expanded hematopoietic progenitor cells with a single UCB unit.

CONFLICT OF INTEREST

The author declares no conflict of interest.

This article was published as part of a supplement that was supported by Novartis, MSD Italia, Roche, Celgene, GlaxoSmithKline, Sanofi, Gilead, Adienne, Italfarmaco, Pierre Fabre Pharmaceuticals with an unrestricted educational contribution to AREO—Associazione Ricerche Emato-Oncologiche (Genoa) and AMS—Associazione Malattie del Sangue (Milan) for the purpose of advancing research in acute and chronic leukemia.