Impact of Myeloablative and Reduced Intensity Conditioning on Outcomes After Unrelated Cord Blood Transplantation for Adults with Acute Lymphoblastic Leukemia

Luciana Tucunduva 1, Annalisa Ruggeri 1, Guillermo Sanz 2, Sabine Furst 3, Bernard Rio 4, Gerard Socié 5, William Arcese 6, Mauricette Michaller 7, Ibrahim Yakoub-Agha 8, Jan Cornelissen 9, Miguel A. Sanz 10, Pau Montesinos 11, Duncan Purtill 12, Eliane Gluckman 12, Vanderson Rocha 13, 1 Eurocord International Registry, Paris, France; 2 Service de Hématologie, Hopital La Fe, Valencia, Spain; 3 Institut Paoli Calmettes; 4 Service d'Hématologie, Hôtel Dieu, Paris, France; 5 Service d’Hématologie, Hospital Universitario La Fe, Valencia, Spain; 6 CHU de Lille; 7 Department of Hematology, Dr. Daniel Den Hoed Cancer Center, Rotterdam, Netherlands; 8 Service de Hématologie, Hospital Universitario La Fe, Valencia, Spain; 9 Hematology/Transplantation, Chaim Sheba Medical Center, Tel-Hashomer, Israel; 10 Hematology Dpt, CHU de Nantes - Hotel-Dieu, Nantes, France; 11 Service d’Hématologie et Thérapie Cellulaire, AP-HP, Hôpital Saint Antoine; 12 Eurocord International Registry, Paris, France; 13 Haematology, Eurocord, Paris, France

Allogeneic hematopoietic stem cell transplantation is the only curative option for high risk adult acute lymphoblastic leukemia (adALL). In the absence of an HLA identical sibling donor, HLA matched unrelated donor or HLA mismatched cord blood are alternative stem cell sources. However, very few data on the outcomes after umbilical cord blood transplantation (UCBT) for adALL using myeloablative (MAC) or reduced intensity (RIC) conditioning regimens have been reported. We conducted a retrospective survey on the outcomes after UCBT for adALL and a more specific analysis for patients with cytogenetic data transplanted in remission with either MAC or RIC. From 1996 to 2011, 433 adult patients (pts) received a UCBT for ALL. Overall 2-year LFS was 37% for pts in first complete remission (CR1, n=199), 32% for CR2 (n=138) and 9% for advanced disease (n=96). Complete cytogenetic data at diagnosis was available for 316 pts, of whom 251 were transplanted in CR1 (63%, n=157) or CR2 (37%, n=94). Median age at UCBT was 33 years (18 to 66) and 76% of the pts (n=191) had an abnormal karyotype at diagnosis. Pts were analyzed according to the presence of t(9;22) as Ph+ (n=115) and Ph- (n=136). Double CBT was performed in 109 pts (43%) and the median total nucleated cell dose at freezing was 4.02x10^7/kg. Most pts received CBUs with 1 (n=74) or 2 (n=136) HLA disparities. MAC was given to 177 pts (70%) and 73 (30%) received RIC. Overall 2-year leukaemia-free survival (LFS) was 36±3%; 37% for Ph- and 35% for Ph+ pts (p=NS). On multivariate analysis, 3 factors were associated with improved LFS: age <44 years (HR: 0.6, p=0.004), CR1 at transplant (HR: 0.6, p=0.005) and use of RIC (HR: 0.6, p=0.015).

In pts transplanted with MAC (n=177), most used regimens were Cy-TBI (27%) and Bu+Flu+TBI (25%). Median follow-up (FU) was 26 and 35 months for CR1 (n=107) and CR2 (n=70). Cumulative incidence (CI) of 60-day neutrophil recovery was 87% (CR1) and 83% (CR2); acute GVHD was 43% and 37%, respectively. Two-year CI of NRM was 41% and 49%; 2-year RI was 24% and 22% for CR1 and CR2, respectively. Two-year LFS was 35% for CR1 and 30% for CR2. No factor was found to be associated with LFS, relapse or NRM.

In pts transplanted with RIC (n=73), Cy+Flu+TBI was used in 74% (n=54). Median FU was 31 and 34 months and median age was 50 and 39 years for CR1 (n=49) and CR2 (n=24), respectively. At 2 years, CI of NRM was 22% (CR1) and 17% (CR2). Two-year RI was 30% and 47%, respectively. Two-year LFS was 49% (CR1) and 36% (CR2). For pts in CR1, univariate analysis showed that younger age (<50 years) was associated with improved LFS (62% vs 36%, p=0.042) and lower NRM.

UCBT is an option to treat high risk adALL. MAC was associated with a LFS comparable with that reported with other stem cell sources, but strategies to reduce toxicity are still needed. Results with RIC are encouraging and may be considered in younger pts. Importantly, in this large series outcomes after UCBT were similar for Ph+ and Ph- ALL.

Outcomes After Double Cord Blood Transplantation Compared to Single Cord Blood Transplantation in Adults with Acute Leukemia Given a Reduced Intensity Conditioning Regimen

Vanderson Rocha 1, Myriam Labopin 2, Annalisa Ruggeri 3, Didier Blaise 4, Bernard Rio 5, Jan Cornelissen 6, Noel Milpied 7, Luciana Tucunduva 1, Arnon Nagler 8, Mohamad Mohty 9, Eliane Gluckman 10, 1 Haematology, Eurocord, Paris, France; 2 Service d’Hematologie, Hotel Dieu, Paris, France; 3 Division of Hematology and Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel-Hashomer, Israel; 4 Bone Marrow Transplant Unit, Institut Paoli Calmettes, Marseille, Cedex 9, France; 5 Service d’Hematologie, Hôtel Dieu, Paris, France; 6 CHU de Lille; 7 Department of Hematology, Dr. Daniel Den Hoed Cancer Center, Rotterdam, Netherlands; 8 BMT unit, Bordeaux, France; 9 Haematology Dpt, CHU de Nantes - Hotel-Dieu, Nantes, France; 10 Hospital Saint Louis, Eurocord, Paris, France

Unrelated cord blood (UCB) is an alternative source of allogeneic hematopoietic stem cell transplantation (HSCT) for adults with acute leukemia lacking a HLA matched donor. Double cord blood unit (dUCBT) has been increasingly used over single CB unit (sUCBT) after reduced intensity conditioning regimen (RIC). We analyzed 360 adults with ALL (n = 77) or AML (n = 238) in CR1 (n = 212) and CR2 (n = 148) transplanted with a sUCBT (n = 131) or a dUCBT (n = 229) after RIC. Only patients (pts) transplanted with a sUCBT with a minimum of 2.5x10^7/kg total nucleated cells (TNC) were included. Pts were transplanted from 2005-2011 in EBMT centers. Comparing the recipients of sUCBT and dUCBT in CR1, there were no statistical differences according to age, diagnosis (AML or ALL), weight, CMV serostatus, cytogenetic risk, number of HLA incompatibilities. However, TNC were performed more recently (2009 vs 2008), the time from CR1 to transplant was longer (142 days vs 121 days), more frequently transplanted with Cy+Flu+TBI (87% vs 68%), lower frequency of ATG use (21% vs 35%) and they received higher number of TNC collected (5x10^7/kg vs 3.9x10^7/kg) or infused (4x10^7/kg vs 3.1x10^7/kg). Median follow-up was 23 months in both groups.

Cumulative incidence (CI) of 60 days neutrophil recovery was 82% for dUCBT and 76% for sUCBT (p=0.86); frequency of full donor chimerism at day 100 was not statistically different between dUCBT (81%) and sUCBT (86%). At day 100, CI of acute GVHD (grade II-IV) was 35% in both groups, however there was a trend of increased incidence of grade
Cytomegalovirus (CMV) is a major cause of mortality and morbidity in hematopoietic stem cell transplantation (HSCT). Transfer of CMV-specific T-cells from the donor is important for the control of CMV replication after HSCT. In this study, we compared incidence and kinetics of CMV infection and CMV disease between T-cell depleted (TCD) and unmodified (CONV) HSCT.

**Methods:** The cohort consisted of 714 adult HSCT recipients of bone marrow or peripheral blood stem cell allografts from September 1999 to March 2010 at Memorial Sloan-Kettering Cancer Center. Patients were followed until July 2012. TCD recipients did not receive any additional prophylactic medicinal immunosuppression for graft-vs-host disease (GvHD). CMV infection was monitored by PPS5 antigenemia assay (CMV Ag) if recipient or donor were CMV seropositive and the information was prospectively stored in a computerized database. Prior to 2007, recipients of mismatched or unrelated allografts were eligible for CMV prophylaxis if recipient or donor were CMV seropositive. Anti-CMV agents were given to patients who had >= 2 cells per slide (cps) on 1 occasion or 1 cps on >= 2 consecutive occasions. Relapse, second transplant, death, and study termination (April, 2012) were considered as competing risk for CMV reactivation.

**Results:** Four hundred and three (56.5%) patients received TCD grafts and 311 (43.6%) received unmodified grafts (CONV). Recipient CMV seropositivity was 48.3% in TCD and 50.8% in CONV (p=0.5219). There are 221 (54.8%) TCD and 140 (45.0%) CONV patients received allograft from mismatched or unrelated donors (p=0.0092). Sixty-four (15.9%) TCD and 45 (14.5%) CONV patients received CMV prophylaxis (p=0.6031). CMV infections occurred in 135 (33.5%) TCD and 86 (27.7%) CONV patients. Two hundred and five (92.8%) of the 221 infections developed by day +100 post-transplant. CMV infections requiring antiviral treatment occurred in 111 (27.5%) TCD and 64 (20.6%) CONV patients (p=0.0319). Days from HSCT to first CMV infection were median 31 in TCD and 41.5 in CONV (p=0.0001). Maximum cps were median 5 (range 1 to 100) cps in TCD and 3 (1 to 100) cps in CONV (p=0.0159). Duration of reactivation was median 11 days in TCD and 8 days in CONV patients (p=0.0042). CMV disease was diagnosed in 4% in TCD patients and 2.3% in CONV patients (p=0.197).

**Conclusion:** 1) Rates of CMV infection were similar in TCD and CONV allogeneic HSCT; 2) In contrast, the kinetics of CMV replication were different between the 2 groups: In TCD, CMV infection occurred earlier, with higher peak level, and longer duration of viremia 3) Rates of CMV disease were low and similar between TCD and CONV (4% and 2.3% respectively) Our data suggests that preemptive treatment based on antigenemia is similarly effective for prevention of CMV disease in TCD and CONV allografts.