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

Myriam Labopin,[1,21,22]* Annalisa Ruggeri,[2,3,22]* Norbert Claude Gorin,[4] Eliane Gluckman,[2] Didier Blaise,[5] Lionel Mannone,[6] Noel Milpied,[7] Ibrahim Yakoub-Agha,[8] Eric Deconinck,[9] Mauricette Michallet,[10] Nathalie Fegueux,[11] Gerard Socié,[12] Stephanie Nguyen,[13] Jean Yves Cahn,[14] Thierry de Revel,[15] Federico Garnier,[16] Catherine Faucher,[16] Namik Tarighat,[17] Chantal Kenzey,[2] Fernanda Volt,[2] Dominique Bertrand,[18] Mohamad Mohty,[1,21,22] and Vanderson Rocha[2,20] on behalf of Eurocord and Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC).

[1]Sorbonne Universités, UPMC Univ Paris 06, UMR-S938, CDR Saint-Antoine, Paris, France; [2]Eurocord, Hôpital Saint Louis, University Paris VII, France; [3]Rome Transplant Network, University Tor Vergata, Rome, Italy; [4]Saint Antoine Hospital, UPMC Univ Paris 06, UMR-S938, CEREST-TC EBMT, Paris, France; [5]Paoli Calmettes Hospital, Marseille, France; [6]L'Archet Hospital, Nice, France; [7]Haut-Lévêque Hospital, Pessac, France;[8]Claude Huriez Hospital, Lille, France; [9]Jean Minjoz Hospital, Besancon, France; [10]E. Herriot Hospital, Lyon, France; [11]Lapeyronie Hospital, Montpellier, France; [12]Saint Louis Hospital, Paris, France; [13]Pitié Salpetriere Hospital, Paris, France; [14]Albert Michallon Hospital, Grenoble, France; [15]Percy Hospital, Clamart, France; [16]Agence de la Biomedecine, Paris, France; [17]DIM, Paris, France; [18]Centre National Gestion, Paris, France; [19]CHU Nantes, Hematology Department, Nantes, France; [20]Churchill Hospital, University of Oxford, UK; [21]INSERM, UMR-S938, CDR Saint-Antoine, Paris, France; and [22]Hématologie Clinique et Thérapie Cellulaire, Hôpital Saint-Antoine, Paris, France

**ML and AR contributed equally to this work.*

 doi:10.3324/haematol.2013.092254
Manuscript received on May 27, 2013. Manuscript accepted on October 14, 2013.
Correspondence: annalisa.ruggeri@sat.aphp.fr

Supplemental 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 clinical results and cost of UCBT in 134 consecutive patients transplanted for AL in CR1. UCBT were performed in 26 French transplant centres between 2002 and 2009. All patients received a single or a double unmanipulated CB unit as their first graft, after myeloablative (MAC) or reduced intensity conditioning regimen (RIC). The Institution Review Board of Eurocord-Netcord scientific committee approved this study. Transplant centres performed single or double UCBT according to their centre policies. The main endpoint for clinical outcome was overall survival (OS). MAC was defined as a regimen containing either total body irradiation (TBI) with a dose greater than 6 Gy, a dose of oral busulfan greater than 8 mg/kg, or a dose of intravenous busulfan greater than 6.4 mg/kg.

Clinical Outcomes

The primary endpoint was overall survival (OS). The secondary endpoints studied were leukemia free survival (LFS) neutrophil recovery, graft versus host disease (GVHD), relapse (RI) and non-Relapse Mortality (NRM). OS was defined as the time elapsed from allo-SCT to death, regardless of the cause of death. LFS was defined as survival with no evidence of relapse. NRM was defined as death without evidence of relapse. Patient-, disease-, and transplant-related variables of the sUCBT and dUCBT were compared, using Chi-square or Fischer exact test for categorical variables and Mann-Whitney test for continuous variables. Cumulative incidence functions (CIF) were used to estimate RI and NRM in a competing risks setting, since death and relapse are competing together.(24, 25) In order to study acute and

chronic GVHD, we considered death in remission as a competing event. Probabilities of LFS and OS were calculated using the Kaplan-Meier estimate. Univariate analyses were done using log rank test for OS and LFS, Gray's test for CIF. Multivariate analyses were performed using Cox proportional-hazard model.(26) Factors differing between two groups in terms of distribution and all factors significantly associated with one of the outcome studied were included in the model. All tests are two-sided with type I error rate fixed at 0.05. Statistical analyses were performed with SPSS 19 (SPSS Inc, Chicago, IL), and R 2.13.2 (R Development Core Team, Vienna, Austria) software packages.

Outcomes and economic data collection

Data on patients, graft characteristics, and outcomes were collected using the Eurocord forms (registration 100 days, CBU infusion and yearly follow-up forms). For the purpose of this study, each transplant center was requested to complete missing data on length of hospitalization and update patient's follow-up. All hospital costs were estimated from donor search to 1 year after UCBT, according to the French public health system. Major resources considered were stem cell procurement, initial hospitalization for transplantation, all further readmissions to the hospital in transplant unit and outpatient clinics. The cost for the CBU search and graft acquisition included expenses related to donor samples request, sample typing, and the actual cost of the CB unit. The cost of the individual CBU was provided by the French national donor registry (Agence de la Biomédecine). The costs of graft acquisition were highly dependent on the country and the cord blood banks delivering the graft and are listed in supplemental table 2 (Data as for 2010 from Agence de la Biomédecine). The information on number and duration of hospitalizations were collected through the

national health care administrative data (defined as PMSI in France) and through an additional questionnaire sent to each participating center. Daily cost of each hospitalization was estimated using the average cost published by the French National Scale Costs. Each center participating to the French National Scale Costs reports yearly all the individual costs related to the procedure. The details of the resources considered are listed in supplemental table 3, including all treatment procedures, housekeeping, human resources, supplies, room costs, and overhead costs including maintenance, logistics, administration, billing, and amortization. The costs were obtained from analytic accounting system of French hospitals. Costs pertaining to pre-transplant clinical biologic and radiologic evaluation of recipient, family HLA-typing, rehabilitation facilities after transplantation and indirect costs, such as transportation, loss of incomes, etc, were not taken in consideration.

Resources were estimated in euros (€), adjusted to the 2010 French consumer price index.

Cost-effectiveness analysis

The cost-effectiveness was estimated by the ICER (Incremental cost effectiveness ratio), which represents the additional cost generated by an additional QALY (quality adjusted life years). ICER per capita was calculated by dividing ICER by French GDP per capita in 2010. Following the recommendation of the World Health Organization, GDP was used as the indicator to derive the categories of cost-effectiveness.(27, 28) Cost-effectiveness of health technology was defined as follow: 1) very cost-effective: ICER below the per capita GDP; 2) cost-effective: ICER between one and three times per capita GDP; 3) not cost-effective: ICER above three times per capita GDP. The QALY is the way to compare claims for finite healthcare resources and one

QALY corresponds to one year spent in perfect health.(27) The ICER is the difference between average costs divided by the difference in average effects. Events occurring after transplantation that were considered for their impact on quality of life were the occurrence of chronic GVHD and disease relapse. A Markov(28) decision analysis model was used to calculate the ICER within 4 years. For cost-effectiveness analysis, RIC and MAC were studied separately. The model started at 1 year post transplantation and allowed 36 cycles of 1 month each. At any time point, the model considered a patient to be in one of the 4 following clinical states: alive and well, alive with chronic GVHD, alive in relapse, and death. For the Markov model, only cGVHD occurring prior to relapse was considered for the cGVHD group. Patients who experienced relapse prior to cGVHD were considered to be in the "relapse group"

Patients who developed cGVHD prior to relapse were initially considered in the group “cGVHD”; once the relapse occurred they were, then, considered in “relapse group”. In order to calculate the QALY, time spent in each state was weighted for the quality of life experienced while in that state.(29) The utility values used were 0.979, 0.9, 0.5 and 0.0 for the four health states, respectively. They were derived from the literature to define the states of “alive without complication” and “alive with cGvHD”. For relapse, the utility value was estimated using the “standard gamble question” asked to 10 transplant physicians. All transitional probabilities included in the model were estimated on our population.

Sensitivity analyses were conducted around some of the utility values used to weigh survival to calculate QALYs. The utility values for the health states ‘alive without complication’ ranged from 0.8 to 1, for health state ‘alive with GVHD’ ranged from 0.7 to 1, for health state ‘relapse’ ranged from 0.3 to 0.7. After performing the Markov

cohort analysis, we conducted a first-order Monte Carlo microsimulation of 1000 trials to obtain point estimates, 95th percentile confidence intervals (95% CI), for cost and QALYs.

Cost effectiveness analyses (CEA) were done with TreeAge Pro 2012 Software, Inc., Williams-town, Massachusetts.

Supplemental Table 1. Cost and cost effectiveness of HSCT- review of the literature

Country	*Authors; year*	*Nr of patients*	*Type of transplant*	*Period study*	*Total cost/ patient*
USA	Welch HG; 1989	41	allogeneic BMT	5 years	193 000 USD
France	Dufoir T; 1992	40	allogeneic BMT	5 years	424 696 FF
Canada	Barr R,1996	18	allogeneic BMT	18 months	100 600 CAND
USA	Lee SJ; 2000	181	allogeneic SCT	100 days	105300 USD
Norvege	Mishra V; 2001	17	10 MSD, 7UD	1 year	106 825 USD
The Netherlands	van Agthoven M; 2002	97	HLA id PBSCT	2 years	98977 Euros
			HLA id BMT	2 years	98334 Euros
			UD transplantation	2 years	151745 Euros
France	Cordonnier C; 2005	23	12 MAC	1 year	64600 Euros
			11 NMA	1 year	60000 Euros
France	Espérou H; 2005	85	MRD MAC	6 months	76237 Euros
Japan	Yu YB ; 2006	18	allogeneic PBSCT	whole treatment period	76423 USD
Sweden	Svahn BM; 2006	93	36 MSD, 57 UD	5 years	139414 Euros
USA	Saito AM; 2007	132 MRD, 143 UD	185 MAC	1 year	128253 USD
			90 RIC	1 year	80499 USD
USA	Saito AM; 2008	315	158 MDS, 157 UD	1 year	128800 USD
USA	Majhail NS; 2009	294	121 MRD	100 days	83583 USD
			173 UCBT	100 days	137564 USD
USA	Majhail NS; 2013	1320		100 days	203026 USD

Supplemental Table 2 : Cost of Cord Blood Units by country and cord blood banks (without shipping costs)

Country	City or CBB	Price of one CB Unit (2010)
France		10 000 €
GERMANY	Düsseldorf ZKRD	21 000 €
BELGIUM	MBPB	22 450 €
	Leuven	20 000 €
SPAIN	REDMO	23 500 €
	BCB Barcelone	23 000 €
FINLAND		22 491 €
ITALY		17 462 €
NETHERLANDS		22 450 €
SWITZERLAND		25 385 €
ENGLAND	A.NOLAN	21 000 GBP
	BBMR	19 051 GBP
AUSTRALIA		39 000 AUD
ISRAEL	Haddasah	26 000 USD
	Sheba	22 000 USD
TAIWAN	Healthbanks Biotech	10 000 USD
	BIONET Corp	4 500 USD
USA	CRIR Cryobanks Intl	28 800 USD
	Gift of Life	20 000 USD
	Colorado -Aurora	25 000 USD
	Michigan	32 000 USD
	New-York	35 000 USD
	Paramus	25 000 USD
	Stem Cyte Inter.	32 000 USD
	Gainesville	29 490 USD
	Denver	29 490 USD
	San Diego	24 240 USD

	St Louis	29 805 USD
	Glenview	32 115 USD
	San Antonio	34 215 USD
	Orange	24 765 USD
	Camden	42 615 USD
	Grand Rapids	37 365 USD
	Seattle	36 840 USD
	Arcadia	34 165 USD
	Detroit	37 365 USD
	Durham	37 365 USD
	Altamonte Springs	36 840 USD
	Allendale	42 615 USD
	Houston	35 790 USD
	Seattle	36 840 USD
	Glenview	32 115 USD
	Orlando	37 365 USD
	Boca Rocton	23 715 USD
	Aurora	32 115 USD
	Taipei -Taiwan	34 165 USD
	New-York	40 585 USD
	Warrensville Heights	37 995 USD

Supplemental Table 3. Resources and expenses taken in account by the French National Scale of Costs

Clinical analysis expenses	Clinical expenses including personnel, maintenance and amortization
	Intensive care expenses including personnel, maintenance and amortization
	Monitoring costs including personnel, maintenance and amortization
	Resuscitation expenses including personnel, maintenance and amortization
Medico-technical expenses	Emergency service expenses including personnel and ambulance services
	Dialysis expenses including personnel
	Laboratory expenses including personnel
	Operating Room expenses including personnel
	Radiology/Radiotherapy expenses including personnel
	Anaesthesiology expenses including personnel
	Other medical-technical expenses
General logistics and managerial expenses	Laundry
	Food/Restaurant services
	General administrative services
	Personnel administration
	Patient receptionist service
	Room and boarding services
	Maintenance
	Patient transport other than ambulance
	Patient navigation service (stretcher, wheelchair, etc…)
Medical logistics expenses	Pharmacy
	Sterilization
	Biomedical engineering

	Hygiene and surveillance
	Other medical logistics
Follow-up expenses	Pharmaceutical specialties billable charges
	Pharmaceutical specialties in addition to non-billable
	Blood products
	Drugs
	Other medical consumables
	Medical outsourcing. medical imaging
	Medical outsourcing. laboratories
	Ambulance subcontracting
	Medical outsourcing. hospitalization outside hospital
	Medical outsourcing. other
	Fees of outside medical personnel
	Cost of medical act
Comprehensive	Full cost (excluding structure)