Engraftment kinetics and graft failure after single umbilical cord blood transplantation using a myeloablative conditioning regimen

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Patients and methods

The study included all patients (n=1268) with a diagnosis of acute leukemia in complete remission, transplanted with a single, unrelated UCB unit following a MAC between 1994 and 2011 at EBMT centers and reported to Eurocord. Data on patient and donor characteristics and transplant outcomes were collected through EBMT and Eurocord databases. Consistency of data for this study was checked by two physicians to ensure quality. Missing data and supplemental questions specific to this study were requested directly to the transplant centers.

Definitions and Endpoints

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. HLA compatibility was defined at antigen level for HLA-A and -B loci and at allelic level for HLA-DRB1 locus. Neutrophil engraftment was defined as an absolute neutrophil count (ANC) greater than 0.5 x 10^9/L for three consecutive days. Full donor chimerism was defined as >95% of donor cells and mixed chimera between 5% and 95% of donor cells. Methods of chimerism analysis varied among transplant centres. Graft failure was defined as failure to achieve an ANC greater than 0.5 x 10^9/L or as achievement of ANC greater than 0.5 x 10^9/L without evidence of donor engraftment (autologous reconstitution). . Transplant-related mortality (TRM) was defined death in remission and considered the competing event for engraftment. OS was defined as the probability being alive, regardless of disease status, at any time point; surviving patients were censored at last follow-up, while only death was considered an event. Leukemia-free survival (LFS) was defined as the probability of being alive and disease free at any time point; both death and relapse were considered events, and patients who were alive and leukemia-free were censored at last follow-up.

Statistical analysis

Median values and ranges were used for continuous variables and percentages for categorical variables. For each continuous variable, the study population was initially split into quartiles and in two groups by the median. Patient-, disease-, and transplant-related variables of the groups were compared using Chi-square or Fischer exact test for categorical variables, and Mann-Whitney test for continuous variables. The probabilities of OS and LFS were calculated using the Kaplan-Meier method and the log-rank test for univariate comparisons.(9)

The probability of neutrophil engraftment was investigated through both the conditional probability and the probability density. The probability density function for neutrophil engraftment was estimated differentiating the cumulative incidence (CI) engraftment curve, therefore describing the probability to engraft at each time point from UCBT, and taking in consideration competing events,

such as early deaths. The conditional probability is the probability of neutrophil engraftment at each time point from UCBT, on condition of having still not engrafted at that specific time point, and it is estimated as the ratio between engrafted patients within each time interval and patients at risk entering that interval. In this study, time intervals of five days were chosen. The overall incidence of GF and TRM were calculated with the CI estimator.

The following variables were tested in univariate analyses: age at UCBT, type of leukemia, disease status, year of UCBT, CMV serostatus, HLA compatibility, ABO compatibility, total nucleated cell (TNC) count at cryopreservation, use of TBI, and use of ATG. The time to engraftment was used as time-dependent covariate for TRM. Multivariate analyses adjusted were performed using Cox proportional hazards regression model for LFS and OS, and Fine and Gray's proportional hazards regression model for engraftment, GvHD, NRM and relapse.(10, 11) Variables that reached a p-value of 0.15 in the univariate analysis were included in the initial models for multivariate analysis and variables were eliminated one at a time in a stepwise fashion in order to keep only those variables that reached a p-value of 0.05 or less in the final model. Statistical analyses were performed with SPSS version 19 (Inc., Chicago, IL) and Splus (MathSoft, Inc., Seattle, WA).