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Early CD4+ Immune Reconstitution Predicts Probability of Relapse in Pediatric AML after Unrelated Cord Blood Transplantation: Importance of Preventing in Vivo T-Cell Depletion Using Thymoglobulin®

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Background: Relapse of leukemia after pediatric hematopoietic cell transplantation (HCT) is a frequent cause of treatment failure. Immune reconstitution (IR) early after HCT is pivotal to generate a potent graft-versus-leukemia effect. We studied the association between IR of various lymphocyte subsets and outcomes in children receiving a cord blood HCT for hematological malignancies.

Methods: All consecutive patients with a hematological malignancy receiving a cord blood HCT between 2004-2014 at Great Ormond Street Hospital London and at the UMC Utrecht were included. Patients received a myeloablative regimen ± Thymoglobulin. Primary endpoint was relapse; secondary endpoints were overall survival, non-relapse mortality (NRM), acute GvHD (grade 2-4) and chronic GvHD. Lymphocyte-subsets (CD3+, CD4+, CD8+, NK and B-cells) were monitored every other week after engraftment. Various definitions of IR were analyzed including one in line with a reported association: CD4+ T-cell count >50/μL in 2 consecutive measurements within 100 days post-HCT (Bartelink et al, BBMT 2013). Cox proportional hazard models and logistic regression models were used.

Results: 89 patients were included, with a median age of 7.1 years (range 0.7-18): 36 ALL (19 CR1, 14 CR2, 3 CR3), 49 AML (14 refractory, 35 CR) and 4 other malignancies. 36 patients received Thymoglobulin (Utrecht only). CD4-IR (count >50, twice <100 days) was the best predictor for endpoints; in multivariate (MV) analyses, CD4-IR was a predictor for lower probability of relapse in AML patients (MV: HR 0.29, 95% CI 0.03-0.98, p=0.04; figure 1), but not in ALL (p=0.14). CD4-IR was also a predictor for NRM (MV: HR 0.13, 95% CI 0.03-0.52, p=0.004; figure 2). CD4-IR predicted OS in AML (MV: HR 0.17, 95% CI 0.06-0.53, p=0.002), but not in ALL. However, CD4-IR did not have an impact on acute grade 2-4 (p=0.41) or chronic GvHD (p=0.12). Successful CD4-IR was less frequent in patients receiving Thymoglobulin (MV: OR 0.04, 95% CI 0.002-0.27, p=0.005). Associations with the endpoints for the other lymphocyte-subsets were less predictive.

Conclusion: Early CD4-IR post cord blood HCT predicts the probability of relapse in AML as well as NRM in all patients. Thymoglobulin negatively impacts CD4-IR post cord blood HCT, hence the use and/or the dosing of Thymoglobulin should be carefully re-considered.

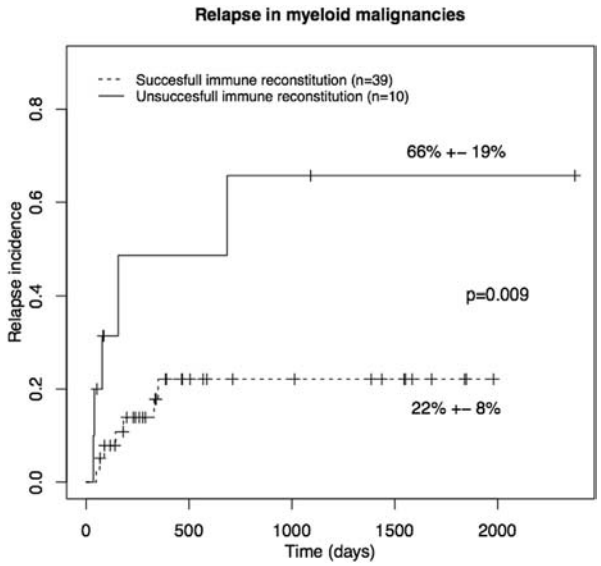

Figure 1. Cumulative incidence of relapse according to CD4+ immune reconstitution in myeloid leukemia

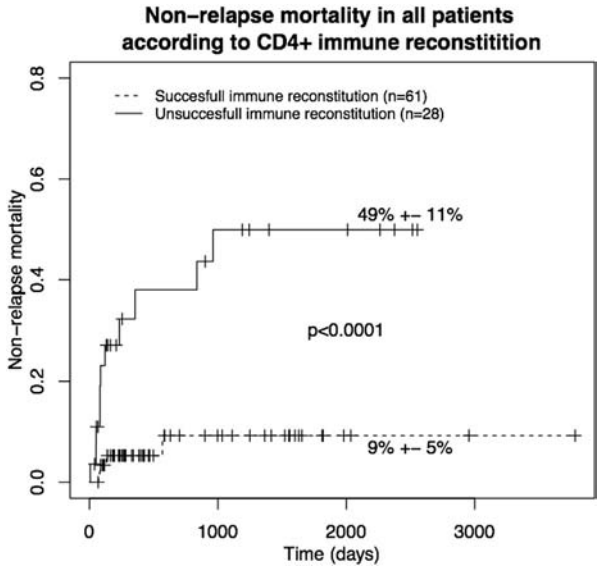

Figure 2. Non-relapse mortality according to CD4+ immune reconstitution in all patients

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Higher Incidence of Grade III and IV Toxicities in Adolescents Undergoing Allogeneic Hematopoietic Cell Transplantation and Its Impact on Mortality at One Year Post-Transplant: A Retrospective Cohort Study of Pediatric Patients Undergoing Allogeneic Stem

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