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Oral Session

Clinical Care: Transplantation Regimen Toxicities and Engraftment-Donor Issues and Transplant Centers

What Is the Role for Donor NK Cells after Nonmyeloablative Conditioning?

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Abstract

Background: The potential role of donor NK cells after nonmyeloablative conditioning for allogeneic hematopoietic cell transplantation (HCT) is not defined. We investigated the impact of the kinetics of donor NK cell engraftment as well as the impact of missing recipient KIR ligands and the number of donor inhibitory and activating KIR genes on HCT outcomes in 282 patients (153 with HLA-matched related donors and 129 with unrelated donors) conditioned with 2 Gy TBI +/– fludarabine. Postgrafting immunosuppression consisted of cyclosporine and mycophenolate mofetil. Diagnoses were hematological malignancies (n=274) or solid tumors (8).

Methods: NK cells were isolated from peripheral blood by flow cytometry on days 14, 28 and 42 after HCT. The proportions of cells of donor and host origin were assessed by FISH or by VNTR-PCR. High-resolution HLA-typing was performed using oligonucleotide probe and/or direct sequencing methods. Donor KIR genotyping was performed using a commercial PCR-SSP kit (Invitrogen) following manufacturers protocol.

Results: High numbers of T (P=0.01) and CD34+ (P=0.009) cells in the graft, as well as lower numbers of donor inhibitory KIR genes (P=0.01) were each associated with higher levels of donor NK cell chimerism. There was a suggestion of an association between lower numbers of activating KIR genes and higher CD56 chimerism, however this was not statistically significant. NK cell chimerism levels were comparable in patients who had all KIR ligands present vs. in those who were missing any ligand, and there was no association between the specific missing ligand and NK chimerism. A day-14 NK cell chimerism level of < 50% was associated with increased risks of graft rejection (*P*=.009). Modeling chimerism levels as a continuous linear variable, there was no association between NK cell chimerism levels on day 14 and occurrence of grade II-IV acute GVHD. In contrast, high levels of donor NK cell chimerism on days 14–42 were associated with a lower risk of relapse (P=0.006) and better progression-free survival (P=0.003) in time-dependent analyses. The qualitative associations between donor NK cell chimerism and graft rejection, GVHD, relapse or progression-free survival did not change after adjustment for the presence of recipient KIR ligands nor after adjustment for the number of donor inhibitory or activating KIR genes. Finally, the 3-year cumulative incidence of relapse was 42% in patients who have all ligand for donor NK cell KIR, versus 38% in patients who miss one or more ligand for donor NK cell KIR (adjusted hazard ratio = 1.05; 95% confidence interval 0.65–1.68; p=0.85).

Conclusions: Robust engraftment of donor NK cells correlated with low risk of graft rejection, low risk of relapse and high progression-free survival but not with acute GVHD. The clinical importance of donor KIR inhibitory and activating genes on post-transplant donor NK chimerism merits further study.

Footnotes

Disclosure: Off Label Use: Fludarabine, Mycophenolate mofetil, Cyclosporine.