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A 2-Step Approach to Myeloablative Haploidentical Stem Cell Transplantation with Optimized T-Cell Dosing: Early Immune Reconstitution Leads to Better Outcomes

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Track: BMT Tandem "Scientific" Meeting

Saturday, February 16, 2013, 4:45 PM-6:45 PM

Ballroom A-D (Salt Palace Convention Center)

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We developed a 2-step approach to myeloablative haploidentical HSCT in which patients receive a large fixed dose of cyclophosphamide (CY)-tolerized T cells separately from the HSC infusion in the hopes of accelerating post HSCT immune reconstitution (IR). The uniformity of the T cell dosing facilitates comparison of patients without (low risk) and with (high risk) active malignancy at HSCT to ascertain the impact of disease status at HSCT on IR with fewer confounding effects from conditioning or T cell dosing.

We analyzed IR at day +28 in patients receiving 2 step myeloablative haploidentical HSCT. All patients received 12 Gy of total body irradiation followed by 2×10^8 CD3+ cells/kg donor T cells (HSCT step 1). CY 60 mg/kg/d x 2 was given starting 2 or 3 days after the T cell infusion in the low and high risk groups respectively. Tacrolimus and MMF were begun on day -1. A CD 34 selected product was infused on day 0 (HSCT step 2) with median CD34 doses of 5.8 and 5.2×10^6 /kg in the low and high-risk groups respectively.

19 patients with AML (9), ALL (7), MDS (1), and NHL (2) without disease, and 16 patients with AML (10), ALL (2), MDS (3), and T cell NHL (1) with active disease at HSCT were analyzed.

A 17th patient in the high risk group died prior to engraftment and was not fully evaluable. Outcomes for the low and high risk groups respectively with 2-24 months follow-up (median of

9 in each group) were: no rejections; ANC >500: 11 versus 12 days; grades III-IV GVHD: 5.2% versus 18.7%; mortality from GVHD 0% versus 6.2%; infectious mortality: 0% versus 12.5%; non-infectious regimen-related mortality: 0% versus 11.7%; mortality from relapse; 5.2% versus 18.7%; Overall survival: 94.8% versus 52.9%. By day +28, all patients had achieved CR and >95% donor marrow chimerism. Compared to our experience with T cell depleted (TCD) HSCT, improved T and NK cell IR was observed, although the low risk group had higher median numbers of T cells. Conversely, higher numbers of CD56^{bright} NK cells were present in the high risk group.

Compared to TCD approaches at our institution and others, the 2 step approach allows for stronger early IR with low infectious mortality in patients without and with active malignancy at HSCT. IR was more robust in patients without active disease. IR in the higher risk group may be hindered by less hospitable marrow stroma and a greater baseline inflammation related to the active malignancy and exacerbated by the HSCT. The increased rate of significant GVHD and the prominence of NK^{bright} cells, which are strong producers of cytokines, may reflect this higher state of inflammation. In addition, differences in the degree of T cell eradication by CY, based on T cell responses to malignancy or the longer period of T cell activation in the high risk regimen, may account for variations in IR between the groups. Recognition of the differences in early IR amongst specific patient populations may help optimize post HSCT care.

