Sarita Rani Jaiswal et al., J Blood Disorders Transf 2014, 5:8
http://dx.doi.org/10.4172/2155-9864.S1.006

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Hematology & Blood Disorders
September 29-October 01, 2014 DoubleTree by Hilton Baltimore-BWI Airport, USA

Impact of natural killer (NK) cell KIR ligand mismatch and B score on the outcome of haploidentical transplantation with post-transplantation cyclophosphamide (PTCY) in aplastic anemia

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NK Cell KIR ligand mismatch (KIRLMM) has been shown to reduce the risk of relapse in acute myeloid leukemia (AML) following myeloablative T cell depleted (TCD) Haploidentical BMT (HAPLO). However, there is no data on the impact of KIRLMM or KIR B-score based on centromeric and telomeric distribution of inhibitory and activating genes in HAPLO for Severe Aplastic Anemia (SAA) with or without TCD. We prospectively evaluated the impact of KIRLMM and B-score in 10 consecutive patients undergoing HAPLO with PTCY for SAA following unmanipulated PBSC graft, and compared with 15 patients undergoing the same for AML. Donors were not selected based on KIRLMM initially. The patients with High-Risk (HR) AML (n=15) received myeloablative conditioning with Flu-IVBu6.4-Mel140 (n=10) and those with SAA received Flu-ATG-Cy- Mel120. In patients with AML, 11 were transplanted with active disease and 4 with HR cytogenetics were transplanted in CR1/CR2. The median age was 41 (6-46) years for SAA and 32 years (8-48 yrs) for AML. Patients with SAA were heavily transfused (median 35 vs. 10 in AML). All but one engrafted in both groups within 2 weeks. aGVHD/cGVHD occurred in 2/2 and 1/1 patient in AML and SAA groups respectively. The incidence of relapse was 10% in patients receiving transplant from a KIRLMM donor with a B-score >2 (n=8), versus 90% in patients without the same (n=7), with a DFS at 2 years of 80% versus 10% (p=0.04). In patients with SAA, all 4 patients with KIRLMM donors with B-score >2 had early alloreactivity and TRM within 100 days, whereas those without the same (n=6) had 100% DFS at 2yrs (n=0.007). We documented early lymphocyte proliferation with full donor chimerism in patients with SAA between days 2 and 5 post transplant, compared to muted proliferation in patients with AML with mixed chimerism (p=0.01). This pilot study on HAPLO PBSCT with PTCY highlights the favourable impact of KIRLMM donor with high B-score for patients with HR-AML undergoing intensive conditioning. On the other hand the same donor profile adversely impacted the outcome in patients with SAA. Based on these findings, we hypothesise that the lack of previous cytotoxic therapy and less intense conditioning spares recipient dendritic cells which are matured rather than inhibited in a high DC:NK ratio, promoting proliferation of donor alloreactive T cells. This process is enhanced further by NK cell mediated killing of host T cells (more effective as there is no leukemic target) as demonstrated by complete donor chimerism of T lymphocytes before day 5 in patients with SAA, compared to mixed chimerism in patients with AML. We suggest patients with SAA with KIRLMM donor should receive a TCD graft, whereas those with non KIRLMM donors can receive unmanipulated graft with PTCY with excellent outcome.

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