The Impact of Reduced Dose of Posttransplant Cyclophosphamide in HLA-Haploidentical Peripheral Blood Stem Cell Transplantation

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HLA-haploidentical stem cell transplantation using posttransplant cyclophosphamide (PTCy-haploPBSCT) ensures good graft-versus-host disease (GVHD) controls and low non-relapse mortality (NRM), however, it remains to be elucidated whether dose-reduction of cyclophosphamide (CY) could be feasible.

We conducted a prospective, multicenter, phase II study to evaluate the efficacy and safety of reduced-dose of PTCy in reduced-intensity conditioning (RIC) based PTCy-haploPBSCT (Haplo16 RIC, UMIN000020656). Conditioning regimen was fludarabine (150 mg/m2), busulfan (6.4 mg/kg), and total body irradiation (4 Gy). GVHD prophylaxis consisted of CY, tacrolimus and mycophenolate mofetil (MMF). The dose of CY was 40 mg/kg on days 3 and 4 (total 80 mg/kg). Tacrolimus was started from day 5, and MMF was started at a dose of 45 mg/kg/day from day 5 and discontinued with rapid taper after day 35. The primary endpoint was the incidence of grade III-IV acute GVHD.

Fiftyseven patients with a median age of 61 (range, 18 to 60) were enrolled in this study between 2016 and 2017. Diagnoses included AML (n=14), ALL (n=7), MDS (n=13), lymphoma (n=16), and others (n=7). Thirty-six patients (63%) were not in remission and 16 patients (28%) had a history of prior allogeneic stem cell transplantation (allo-SCT). According to the refined disease risk index, 28 patients (49%) were classified as high / very high risk. Neutrophil engraftment was achieved in 97% with a median of 15 days. The incidence of grades IIIV and III-IV acute GVHD at days 100 were 26% and 7% (95%CI, 2-16%), respectively. The incidence of grade III-IV acute GVHD was clearly below the predefined threshold as the primary endpoint. All grade and moderate to severe chronic GVHD at 1-year were 35% and 19%, respectively. In the median follow-up period of 393 days (365-826), overall survival (OS), disease-free survival (DFS), NRM, and relapse rate (RR) at 1-year were 70%, 51%, 14%, and 35%, respectively.

In our previous Haplo14 RIC study using CY at a dose of 50 mg/kg on days 3 and 4 (Sugita et al, BMT 2018), the incidences of grade II-IV and III-IV acute GVHD were 14% and 5%, respectively. All grade and moderate to severe chronic GVHD at 1-year were 23% and 17%, respectively. OS, DFS, NRM, and RR at 1-year were 52%, 43%, 18%, and 39%, respectively.

We performed a retrospective comparison of the incidences of acute and chronic GVHD between Haplo16 RIC and Haplo14 RIC study. Although there was a trend for higher grade II-IV acute GVHD in Haplo16 RIC study (26% vs 14%, P=0.07), there was no significant difference in grade III-IV acute GVHD (7% vs 5%, P=0.41), all grade chronic GVHD (35% vs 23%, P=0.19), and moderate to severe chronic GVHD (19% vs 17%, P=0.81).

Our results suggest that the reduction of PTCy is feasible in RIC based PTCy-haploPBSCT, although prospective studies are required to confirm our results.