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ORAL ABSTRACTS

723.ALLOGENEIC TRANSPLANTATION: LONG-TERM FOLLOW-UP AND DISEASE RECURRENCE

Long-Term Outcomes after Unrelated Marrow Transplantation for Aplastic Anemia with Optimized Cyclophosphamide Dose (BMT CTN 0301)

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Background: Seventy-nine patients (aged ≤65 years) with aplastic anemia received HLA-matched or single locus mismatched unrelated donor marrow transplantation (BMT) on a clinical trial (*BMT CTN 0301; NCT00326417*) between 02/2006 and 12/2013 (*Lancet Haematol. 2015, 2:e367-75*). The median ages of patients enrolled on the cyclophosphamide (Cy) 50 mg/kg and 100 mg/kg strata were 25 and 18 years, respectively, and 80% were Caucasians. That trial determined the minimum dose of Cy required for engraftment when added to total body irradiation (TBI 2 Gy), anti-thymocyte globulin (rabbit-ATG 9 mg/kg) and fludarabine (120 mg/m ^{2}). Graft versus host disease (GVHD) prophylaxis was cyclosporine and methotrexate. Although Cy at 50 mg/kg (n=38) and 100 mg/kg (n=41) were both effective for day 100 and 1-year outcomes, the computed optimum Cy dose by Bayesian method was 50 mg/kg. Early results showed a 1-year incidence of graft failure after Cy 50 mg/kg and 100 mg/kg of 12% and 15%, respectively. The corresponding probabilities of 1-year survival were 92% and 76%.
Methods: Thirty-seven patients who received Cy at 50 mg/kg and 31 patients who received Cy at 100 mg/kg were alive ≥1 year after BMT. These patients now have median follow ups of 7 and 8.7 years, respectively. The incidence of graft failure and chronic GVHD was calculated using the cumulative incidence estimator and the probability of survival using the Kaplan-Meier estimator.
Results: In the trial cohort, 31 of 38 patients (82%) who received Cy 50 mg/kg were HLA-matched to their donor at HLA-A, B, C and DRB1, compared to 27 of 41 (66%) receiving Cy 100 mg/kg. **Table 1** shows outcomes of the 38 and 41 patients who received Cy at 50 mg/kg and Cy at 100 mg/kg. With Cy 50 mg/kg there was 1 late graft failure at 4 years (cumulative total 5). Five deaths occurred at 1.5, 1.8, 4.2, 5.2 and 12.2 years after BMT (cumulative total 6). All chronic GVHD occurred within 2 years. Late toxicities (n=8; 22%) included liver cirrhosis (n=1, 1.25 years), myocardial infarction (n=1, 3.8 years), congestive heart failure (n=1, 8.7 years), acute renal failure requiring dialysis (n=1, 3.8 years), avascular necrosis (n=1, 9 years), gonadal dysfunction in pre-pubertal children at BMT (n=2, 1.4 and 3.9 years), and secondary cancer (n=1, pancreatic adenocarcinoma 3.1 years). The 8-year survival among the 38 patients receiving Cy 50 mg/kg was 85% despite late toxicities, including death, being more common beyond the first year after BMT. With Cy 100 mg/kg, there were no late graft failures. There was 1 death at 8.6 years (in a patient with underlying dyskeratosis congenita (cumulative total 11). One patient was diagnosed with chronic GVHD at 7 years. Late toxicities (n=6; 19%) included pulmonary (n=2, ARDS 8 years and restrictive airway disease 1.9 years), chronic renal failure requiring dialysis (n=1, 15 years), avascular necrosis (n=1, 1.5 years), gonadal dysfunction (n=1, 2.6 years), and secondary cancer (n=1, myelodysplastic syndrome 8.9 years). The 8-year survival among the 41 patients receiving Cy 100

mg/kg was 76% and all except 1 death occurred within the 1 st year after BMT. Causes of death after the first year of BMT are shown in **Table 2.**

Conclusion: Eight-year survival ≥75% and sustained engraftment confirm both Cy at 50 mg/kg and Cy at 100 mg/kg with TBI 2 Gy, ATG and fludarabine are effective conditioning for unrelated BMT for aplastic anemia but life-long surveillance for late complications is required. Chronic GVHD was common and proved fatal in several patients despite most donor-recipient pairs who received Cy at 50 mg/kg being HLA-matched at the allele-level.

Disclosures Nakamura: *Omeros:* Consultancy; *Blue Bird:* Consultancy; *BMT CTN Steering Committee:* Membership on an entity's Board of Directors or advisory committees; *Mt. Sinai:* Other: Acute GVHD; *International Consortium:* Other: consortium chair; *Sanofi:* Consultancy; *Jazz Pharmaceuticals:* Consultancy, Other: research collaboration; *Napajen:* Consultancy; *NCCN:* Other: guideline panel for HCT; *Miyarisan:* Research Funding; *Leukemia & Lymphoma Society:* Other: grant reviewer; *NCTN Lymphoma Steering Committee:* Membership on an entity's Board of Directors or advisory committees. **Pulsipher:** *Adaptive Biotechnologies:* Research Funding; *GentiBio:* Membership on an entity's Board of Directors or advisory committees; *Bluebird Bio:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *CARGO Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Vertex Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *Miltenyi Biotec:* Research Funding.

Table 1. Outcomes

Outcome	Cy 50 mg/kg N=38	Cy 100 mg/kg N=41
Chronic GVHD		
2 years	47% (95% CI 31 – 62)	39% (95% CI 24 – 54)
5 years	47% (95% CI 31 – 62)	39% (95% CI 24 – 54)
8 years	47% (95% CI 31 – 62)	43% (95% CI 27 – 58)
Graft failure		
2 years	11% (95% CI 3 – 23)	24% (95% CI 13 – 38)
5 years	14% (95% CI 5 – 27)	24% (95% CI 13 – 38)
8 years	14% (95% CI 5 – 27)	24% (95% CI 13 – 38)
Overall survival		
2 years	92% (95% CI 77 – 97)	76% (95% CI 59 – 86)
5 years	89% (95% CI 72 – 96)	76% (95% CI 59 – 86)
8 years	85% (95% CI 67 – 94)	76% (95% CI 59 – 86)

Table 2. Causes of late death

Causes	Cy 50 mg/kg	Cy 100 mg/kg
Chronic GVHD	3	-
Pancreatic adenocarcinoma	1	-
Multi-organ failure	1	-
ARDS (Dyskeratosis congenita)	-	1

Figure 1

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