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POSTER ABSTRACTS

721.ALLOGENEIC TRANSPLANTATION: CONDITIONING REGIMENS, ENGRAFTMENT AND ACUTE TOXICITIES

Regimen Intensity and Age Affect Transplant-Related Outcomes after Matched Related Donor Hematopoietic Cell Transplantation for Sickle Cell Disease: A STAR Registry Study

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Background: Serotherapies such as anti-thymocyte globulin (ATG) and alemtuzumab (AL) are added to conditioning chemotherapy for matched related donor (MRD) hematopoietic cell transplantation (HCT) for sickle cell disease (SCD) to facilitate engraftment and prevent graft-vs-host disease (GVHD). Most reports show ATG added to myeloablative (MA) conditioning; however, the use of AL has increased with investigation of different intensity regimens. The aim of this study was to compare HCT-related outcomes across common conditioning approaches to determine superiority.
Methods: Retrospective data on baseline patient and HCT characteristics, and HCT outcomes were collected on 352 SCD patients >1 yr post-HCT at 14 Sickle cell Transplant Advocacy and Research (STAR) Alliance centers. Patients with a non-MRD (n=117) or without serotherapy (n=26) were excluded, leaving 209. MA included busulfan (BU) cumulative dose (CD) >8mg/kg or TBI ≥800 cGy; other regimens were termed non-MA (nMA). Summary statistics were presented as median (IQR) for continuous variables and count (%) for categorical variables. Comparisons were made using two-sample hypothesis tests, with p-value of < 0.05 as significant. Time-to-event analyses followed out to 3 years (censored after) and considered 4 outcomes. The first 3 were estimated via the Kaplan-Meier method: (1) overall survival (OS); (2) rejection-free survival (RFS); with death and rejection as events; (3) severe GVHD-free, RFS (GRFS), with death, RFS and severe GVHD as events; and (4) GVHD was estimated by Fine-Gray competing risk analyses, considering death as a competing event and censoring for rejection.

Results: 209 patients received MRD HCT with MA+AL (66, 32%), nMA+AL (49, 23%), MA+horse (hATG) (71, 34%), or MA+rabbit (rATG) (23, 11%). Median recipient and donor age at HCT were 8.4yr (IQR: 5.1, 13.0) and 9.3 (5.1, 15.0) and similar across cohorts. MA+AL had a less severe clinical phenotype and nMA+AL had decreased pulmonary function; other baseline characteristics were similar (data not included). Conditioning for MA+AL included bu/cyclophosphamide (cy) (64%) or bu/fludarabine (flu) (36%), for MA+hATG bu/cy (68%) or bu/cy/flu (32%), for MA+rATG bu/cy (83%) or bu/flu (17%), and for nMA+AL melphalan/flu (92%) plus thiotepa (TT) (8%). GVHD prophylaxis was primarily calcineurin inhibitor and methotrexate or mycophenolate mofetil (91.4%). In MA, serotherapy was proximal timed with AL starting day -5 or -6 at a median (IQR) CD of 1.05mg/kg (0.8, 1.5), hATG starting day -3 at 90mg/kg (90), or rATG starting day -5 at 10mg/kg (9.6, 10.1); in nMA, AL was distal timed starting day -22 at a CD of 1.98mg/kg (1.0, 2.8). Stem cells were bone marrow in all, and GCSF primed in 15.4% of MA+AL and 4% of nMA+AL. Total nucleated and CD3 cell doses were similar across cohorts. nMA+AL had shorter median follow up at 2y (1, 4) vs 3y (2, 6) overall. nMA+AL had earliest time to neutrophil engraftment, required less platelet infusions, and had a shorter hospital stay at median 13d (12, 15), 8 infusions (4,13), and 21d (18, 26), respectively. Readmissions were highest for MA+AL at 77% (vs 64% overall). Graft rejection occurred only in nMA+AL (4, 8.2%) and MA+rATG (2, 8.7%). **Table**
3-yr CI of grade III/IV aGVHD was highest in nMA at 12% (CI: 0.05, 0.23) vs 0-7%, *p=0.130* and for any cGVHD was significantly higher in nMA+AL at 33% (0.19, 0.46) vs 9-19%, *p=0.*001. 3-year OS was excellent at 94.4% (91.3, 97.7) and comparable per cohort. 3-year RFS was lowest though not significantly in nMA+AL at 87% (0.78, 0.97) vs 91-97%, *p=0.260*. 3-year GRFS was significantly lower in nMA+AL at 69% (0.57, 0.83) vs 83-94%, *p=0.001*. When age controlled GRFS in nMA+AL ≥13y was significantly lower at 59% (0.40, 0.88) vs 74-100%, *p=0.007*. **Figure**
Conclusions: Despite small cohort sizes and retrospective nature, this study allowed for direct comparison of common approaches to MRD HCT for SCD. Outcomes were collectively excellent. nMA had earlier engraftment, less transfusion needs, and shorter hospital stay, although significantly more cGVHD and lower 3-yr GRFS influenced by older age. Current clinical trials in nMA+AL include TT and abatacept to mitigate this difference. We previously reported an association between MA and cardiac dysfunction (Stenger et al. Transplant Cell Ther 2023). Potential benefit of nMA must be balanced against risk of rejection and GVHD, thus providers should carefully consider such when selecting conditioning.

Disclosures John: *bluebird bio:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *vertex:* Membership on an entity's Board of Directors or advisory committees. **Eckrich:** *Vertex:* Consultancy. **Guilcher:** *Bristol Myers Squibb:* Research Funding; *bluebird bio, Inc.:* Research Funding. **Kasow:** *Aruvant:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Stenger:** *bluebird bio, Inc.:* Research Funding.

Table: Patient baseline characteristics and HCT outcomes after MRD HCT for SCD by conditioning approach

Characteristic	Overall N = 209[1]	MA Alemtuzumab N = 66[1]	nMA Alemtuzumab N = 49[1]	MA Horse ATG N = 71[1]	MA Rabbit ATG N = 23[1]	p-value[2]
Age at BMT (yr)	8.4 (5.1, 13.0)	8.6 (4.30, 13.3)	9.3 (6.2, 15.2)	8.0 (5.4, 11.)	7.8 (4.6, 15.3)	0.563
Donor Age (yr)	9.3 (5.1, 15.0)	9.5 (3.7, 15.7)	11.50 (5.8, 15.0)	9.0 (5.1, 13.6)	8.4 (6.0, 14.7)	0.792
Yrs from HCT to last visit	3 (2, 6)	4 (3, 6)	2 (1, 4)	3 (2, 7)	3 (2, 7)	**0.003**
Myeloablative						**<0.001**
No	49 (23%)	0 (0%)	49 (100%)	0 (0%)	0 (0%)	
Yes	160 (77%)	66 (100%)	0 (0%)	71 (100%)	23 (100%)	
Days to neutrophil engraftment	16 (13, 20)	19 (17, 21)	13 (12, 15)	17 (12, 21)	15 (13, 17)	**<0.001**
Platelet transfusions (#)	11 (7, 17)	11 (6, 22)	8 (4, 13)	12 (8, 17)	15 (10, 18)	**0.011**
Days to discharge	25 (20, 30)	28 (23, 32)	21 (18, 26)	24 (20, 28)	24 (21, 29)	**<0.001**
Any Readmission	133 (64%)	50 (77%)	39 (61%)	40 (57%)	13 (57%)	**0.076**
Graft rejection	6 (2.9%)	0 (0%)	4 (8.2%)	0 (0%)	2 (8.7%)	**0.003**
Acute GVHD						0.285
No	170 (81%)	56 (85%)	36 (73%)	57 (80%)	21 (91%)	
Yes	39 (19%)	10 (15%)	13 (27%)	14 (20%)	2 (8.7%)	
Chronic GVHD						**0.017**
No	172 (82%)	60 (91%)	34 (69%)	57 (80%)	21 (91%)	
Yes	37 (18%)	6 (9.1%)	15 (31%)	14 (20%)	2 (8.7%)	
Chronic GVHD grade						**0.047**
Limited or Mild	16 (44%)	5 (83%)	5 (33%)	4 (31%)	2 (100%)	
Moderate, Severe, or Extensive	20 (56%)	1 (17%)	10 (67%)	9 (69%)	0 (0%)	
Death	11 (5.3%)	2 (3.0%)	3 (6.1%)	6 (8.5%)	0 (0%)	0.388

[1]Median (IQR); n (%); [2] Kruskal-Wallis rank sum test, Pearson's Chi-squared test; Fisher's exact test; [3] Myeloablative (MA) = busulfan cumulative dose >8mg/kg or total body irradiation (TBI) ≥800 cGy, all others = non-MA (nMA); [4] Graft rejection = graft failure or donor chimerism <5% after initial engraftment. Abbreviations: HCT, hematopoietic stem cell transplant; yr, years; GVHD, graft-versus-host disease.

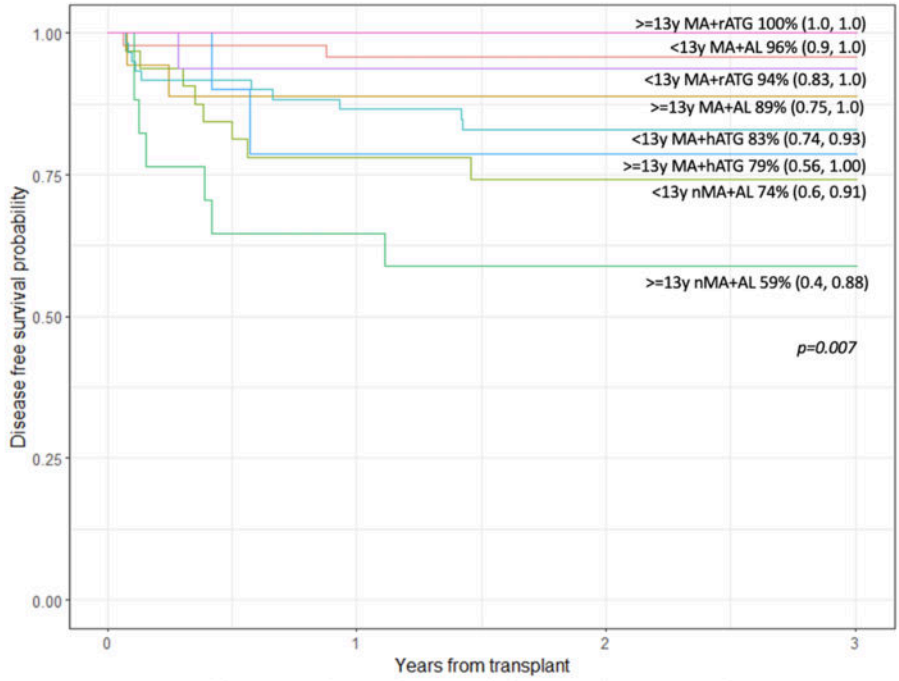

Figure: 3-year severe GVHD-free, Rejection-free Survival (GRFS) following HCT for SCD by serotherapy and conditioning intensity. Events included death, disease recurrence defined as Hb S >50% with acute SCD related complications, rejection including graft failure or donor chimerism <5% after initial engraftment, and severe GVHD defined as acute grade III/IV and chronic severe/extensive.

Figure 1

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