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POSTER ABSTRACTS

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

High Exposure of Rabbit Anti-Thymocyte Globulin (ATG) Is Strongly Associated with Inferior DFS in Pediatric Patients with Malignancy Undergoing Alpha-Beta T-Cell Depleted Haploidentical HCT

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The PTCTC ONC1401 trial reported a 75% 2-year disease-free survival (DFS) for pediatric patients with acute leukemia or MDS undergoing AB-TCR/CD19 depleted (AB-TCD) haploidentical HCT. Patients ≥10 years had significantly worse DFS. Conditioning for AB-TCD HCT typically includes rATG (Thymoglobulin®) 3 mg/kg/day on days -12 to -10. Models of rATG pharmacokinetics (PK) show slower clearance in older children. We hypothesized worse DFS seen in older patients may be due to excessive *in vivo* T-cell depletion by residual rATG post HCT.

Patients undergoing first AB-TCD haploidentical HCT with rATG as the sole serotherapy agent for treatment of malignancy from Dec 2015 to Jan 2023 were included. Patients were treated on PTCTC ONC1401 or institutional prospective trials of AB-TCD. Minimal residual disease (MRD) was determined by the best-available method (multi-parameter flow or next-generation sequencing) for each patient. Predicted pre- and post-HCT AUC of rATG (in AU*day/mL) were retrospectively determined using the software platform InsightRx© (InsightRx, Inc., San Francisco, CA) and a validated PK model for rATG clearance. Quadratic regression was used to identify optimal target windows of rATG exposure for cumulative incidence and Kaplan-Meier estimations. Multivariate analysis (MVA) Cox regression models were built using all covariates with a univariate p-value <0.2.

The dataset included 134 patients (**Table 1**); median (range) follow-up of survivors was 3.4 years (0.5-7.6). The median age at HCT was 12.3 years (0.4-27.4), and median donor age was 32 years (5-61). The median infused cell doses for CD34 and AB-T-cells were 15.2 (2.5-45.8) x10^6/kg and 7.0 (0.1-27.6) x10^4/kg. The 100-day incidence of rejection was 11.3% (5.8-16.8) with a 3-year EFS of 59% (50.2-67.8). The 3-year incidence of non-relapse mortality (NRM) and relapse were 13.8% (6.9-20.7) and 21.4% (13.8-29). The 100-day incidence of grades 2-4 and 3-4 aGVHD were 24.4% (16.2-32.6) and 8.5% (3.4-13.6), while 3-year incidence of cGVHD was 16.7% (9.1-24.3). The 3-year DFS and OS were 67.6% (59.2-76) and 73.8% (64-83.6).

Increased 3-year NRM was seen in patients ≥10 years: 19.9% (10.6-31.4) vs. 5.6% (0.1-13.4) (p=0.03); in those with sibling vs. parent donors: 27.3% (12.4-42.2) vs. 8.5% (1.6-15.4) (p=0.008); and CMV mismatched donors: 25.5% (9.1-41.3) vs. 10.4% (3.3-17.5) (p=0.03). There was no difference in relapse between MRD-techniques, so these were combined for subsequent analyses. Lower 3-year relapse was seen in patients who were MRD-negative: 12.6% (5.5-19.7) vs. 45.7% (26.7-64.7) (p<0.001); and who received targeted small-molecule therapy post-HCT: 0% (0-19.8) vs. 24.1% (15.5-32.7) (p=0.04).

The median predicted pre-HCT AUC of rATG was 63.7 AU*day/mL (16.4-109). A pre-HCT exposure of ≥40 AU*day/mL was associated with decreased rejection: 8.1% (3-13.2) vs. 27.3% (8.8-45.9; p=0.008). A pre-HCT exposure of <80 AU*day/mL was associated with lower 3-year TRM: 8% (1.7-14.3) vs. 33.4% (14.8-52; p<0.001). The 3-year EFS for patients with a pre-HCT AUC

of 40-79.9 AU*day/mL was 69.7% (58.7-80.7) vs. 45.4% (31.9-58.9) for those not in goal range (p=0.004). The median post-HCT AUC of rATG was 9.5 AU*day/mL (1-42.5). There was no different in grade 2-4 (p=0.61) or grade 3-4 (p=0.25) aGVHD or cGVHD (p=0.9) between those with low (<13 AU*day/mL) vs. high (≥13 AU*day/mL) exposure. A low post-HCT AUC was associated with both lower 3-year NRM: 7.2% (0.9-13.5) vs. 28.1% (11.6-44.6) (p=0.002), and lower 3-year relapse incidence: 15.5% (7-23.7) vs. 34.3% (18.6-50) (p=0.01).

In MRD-negative patients, low vs. high post-HCT rATG AUC was associated with a 3-year DFS of 81.2% (71-91.4) vs. 60.2% (42-78.4) (p=0.03); in MRD-positive patients, low vs. high post-HCT rATG AUC was associated with a 3-year DFS of 69.3% (47.9-90.7) vs. 17.9% (0.1-39.5) (p<0.001). MVA showed that high post-HCT rATG exposure, MRD-positivity, and CMV-mismatched donors were associated with worse 3-year DFS (**Table 2**).

We identified optimal windows for rATG exposure - pre-HCT of 40-79.9 AU*day/mL, post-HCT <13 AU*day/mL - associated with lower rates of rejection, NRM, relapse, and improved DFS. Validation with prospective drug levels and an independent cohort would strengthen these conclusions. Our data indicates that model-based dosing of rATG to target pre- and post-HCT exposure may be superior to weight-based dosing in patients undergoing AB-TCD HCT.

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OffLabel Disclosure: Rabbit ATG - for conditioning prior to haploidentical HCT.

Table 1. Patient Demographics & Transplant Characteristics: Univariate Impacts on 3-Year DFS

Patient or Transplant Factor	Overall (%)	3-year DFS (95% CI)	*p* value
	134	67.6% (59.2-76%)	
Age at HCT: <10 years	50 (37.3%)	76.4% (64.1-88.7%)	0.11
Age at HCT: ≥10 years	84 (62.7%)	62.3% (51.1-73.5%)	
Sex: Male	80 (59.7%)	74.1% (63.9-84.3%)	0.08
Sex: Female	54 (40.3%)	58.7% (44.8-72.6%)	
Race & Ethnicity			
White/Non-Hispanic	28 (21%)	72.3% (54.5-90.1%)	0.92
White/Hispanic	59 (44%)	66.6% (54.3-78.9%)	
Black/African-American	16 (11.9%)	65.6% (40.3-90.9%)	
Asian	15 (11.2%)	71.5% (47.6-95.4%)	
Other/More-than-one Race	16 (11.9%)	64.1% (51.2-77%)	
Body Mass Index[1]			
Underweight	6 (4.5%)	83.3% (53.5-99.9%)	0.48
Heathy weight	71 (53%)	72.4% (61.2-83.6%)	
Overweight	16 (11.9%)	67.5% (43.8-91.2%)	
Obese	30 (22.4%)	57% (38.2-75.8%)	
Diagnosis			
ALL	80 (59.7%)	66.3% (55.3-77.3%)	0.59
AML/MDS	39 (29.1%)	65.9% (49.6-82.2%)	
Other[2]	15 (11.2%)	78% (55.7-99.9%)	
Remission Status			
Active Disease	7 (5.2%)	71.4% (37.9-99.9%)	0.87
CR1	70 (52.2%)	70.5% (59.1-81.9%)	
CR2	46 (34.3%)	62.5% (47.8-77.2%)	
CR3+	11 (8.2%)	72.7% (46.4-99%)	
MRD Status: Positive	36 (26.9%)	49.3% (31.3-67.3%)	*0.006*
MRD Status: Negative[3]	93 (69.4%)	74.2% (64.8-83.6%)	
Donor: Parent	89 (66.4%)	68.7% (58.5-78.9%)	0.83
Donor: Full or half-sibling[4]	41 (30.6%)	64.2% (48.1-80.3%)	
CMV Serostatus			
Matched (R+/D+ or R-D-)	95 (70.9%)	73.9% (64.5-83.3%)	*0.02*
Mismatched (R+/D- or R-/D+)	39 (29.1%)	51.5% (34.1-69.9%)	
Conditioning			
Melphalan-based	58 (43.3%)	70.8% (58.5-83.1%)	0.28
Busulfan-based	24 (17.9%)	55.3% (34.1-76.5%)	
TBI-based	52 (38.8%)	70.1% (56.6-83.6%)	
Infused CD34 dose: <12.5x10^6/kg	46 (34.3%)	55.6% (39.7-71.5%)	0.13
Infused CD34 dose: ≥12.5x10^6/kg	88 (65.7%)	73.8% (64.2-83.4%)	
Targeted Agent post-HCT: No	115 (85.8%)	64.8% (55.4-74.2%)	0.18
Targeted Agent post-HCT: Yes[5]	19 (14.2%)	84.2% (67.7-99.9%)	
Pre-HCT AUC of rATG			
<80 AU*day/mL	97 (72.4%)	73.1% (63.7-82.5%)	*0.012*
≥80 AU*day/mL	37 (27.6%)	52% (34-70%)	
Post-HCT AUC of rATG			
<13 AU*day/mL	87 (64.9%)	78.4% (69.2-87.6%)	*<0.001*
≥13 AU*day/mL	47 (35.1%)	47.2% (31.5-62.9%)	

[1]Eleven patients <2 years of age not included in BMI calculations.
[2]Other diseases included: MPAL (n=7), NHL (n=5), JMML (n=2), CML AP (n=1).
[3]Five patients were not tested for MRD.
[4]Four other donors included: Uncle (n=2), Cousin (n=1), Daughter (n=1).
[5]Including: Dasatinib (n=13), Sorafenib (n=6).

Table 2: Multivariate Analysis of Factors Impacting on 3-year NRM, Relapse, and DFS

Factor	3-year NRM HR estimate (95% CI)	*p* value	3-year Relapse HR estimate (95% CI)	*p* value	3-year 1-DFS HR estimate (95% CI)	*p* value
MRD Positive	-	-	4.1 (1.8-9.3)	<0.001	2.6 (1.4-4.9)	0.004
Parent Donor	3.5 (1.2-10.4)	0.02	0.3 (0.8-0.9)	0.03	-	-
CMV Mismatched Donor	2.6 (1.3-10.3)	0.02	-	-	1.9 (1.01-3.6)	0.049
Post-HCT AUC of ATG ≥13 AU*day/L	5.3 (1.8-15.2)	0.001	4.4 (1.9-10.1)	<0.001	3.2 (1.7-6.1)	<0.001

Figure 1

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