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POSTER ABSTRACTS

722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION

Zinc Status Affects T Cell Reconstitution in Patients Receiving Naïve T Cell Depleted Allogeneic HSCT

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Delayed immune reconstitution (IR) is a major clinical problem contributing to post-allogeneic hematopoietic stem cell transplant (allo-HSCT) morbidity and mortality. Specifically, CD4 T cell reconstitution is linked with improved clinical outcomes. As the primary organ of T cell production, the thymus is a crucial contributor to T cell reconstitution after HSCT generating a broad T cell receptor (TCR) repertoire selected through central tolerance However, T cell reconstitution can be hindered by poor thymus function as a consequence of age, transplant conditioning, or graft versus host disease (GVHD). At present, no drugs are available to boost T cell recovery, while many of the factors limiting IR are still unknown.

Zinc (Zn), the second most abundant trace element in our body, is important for normal T cell development. Zn deficiency (ZD) in humans and mice is characterized by poor circulating T cells and depressed thymic function, which are both restorable after reintroduction of Zn with the diet. Despite having multiple risk factors for ZD, there are no published data focusing on ZD prevalence among allo-HSCT recipients. Based on our previous observations, we hypothesized that peri-HSCT Zn levels correlate with IR.

In this study, we analyzed serum Zn levels of allo-HSCT patients who received naïve T cell (T_N) depleted grafts as a strategy to prevent aGVHD (Bleakley et al., 2022, NCT00914940). This population is particularly interesting for studying IR because in these patients, circulating T_N at d+365 after HSCT will primarily be of donor hematopoietic stem cell origin generated in the recipient thymus. Samples and clinical data were prospectively collected.

Fifty-two patients had peri-HSCT serum samples available for Zn measures, as pre-HSCT and/or day +80 samples. Zn measures were performed through mass-spectrometry at the University of Washington Hospital-Biochemistry Lab. ZD was defined for Zn<70ug/dL as defined by the WHO. T cell populations ($CD4^+$, $CD8^+$, T_N $CD4^+$ and $CD8^+$, T regulatory cells, NK cells, B cells) were analyzed by flow cytometry at day+365. DNA was extracted from PBMC pellets collected at d+365 and were analyzed in qPCR for the expression of signal-joint T cell receptor excision circles (sjTRECs), being the gold standard for measuring thymic-derived T cells. We studied the association between Zn levels at baseline and day+80 and parameters of IR through linear regression. Comparisons between two groups were analyzed by t-test.

Median age at transplant was 47 (range 6-61). Twenty-eight patients received myeloablative conditioning with total body irradiation (TBI) of 13.2 Gy (53.8%) and 24 (46.2%) received an intermediate intensity conditioning regimen with 4Gy TBI. Forty-one patients (78.8%) had pre-HSCT and 46 (88.5%) had day+80 Zn measures; 38 patients (73.1%) had both pre-HSCT and day+80 Zn measures. Median pre-HSCT and day+80 Zn levels were, respectively, 71 (range 60-105) and 80 (range 36-112); at baseline, 13 patients (25%) had ZD (<70ug/dL, according to WHO), whereas seven (13.3%) were ZD at day+80. Median sjTRECs at day +365 were 3.33/mg of DNA (range 0.00-16,704.54).

As expected, sjTRECs at day+365 significantly correlated with age at transplant (r^2=0,3824; p<0.0001), whereas Zn levels preHCT or day80 did not. The number of circulating $CD4^+$ and $CD8^+$ T_N at day+365 showed significant correlation with age. Zinc levels did not correlate with IR of absolute $CD4^+$, $CD8^+$, NK, T regs, and B cells at day+365, although we observed a trend for lower $CD4^+$ counts at day 365 with lower day+80 Zn levels. Day+80 serum Zn levels was associated with sjTRECs at day+365 (Figure 1A. r^2=0.2643; p=0.0019) and lower pre-HSCT Zn significantly correlated with worse $CD8^+T_N$ reconstitution

at day+365 (Figure 1B. r^2=0.1433; p= 0.0327), with clear trends in the same direction also for pre-HSCT Zn and $CD4^+$ T_N and day+80 Zn and $CD4^+$ T_N.

In conclusion, we found that a non-negligible population of patients undergo allo-HSCT with unrecognized ZD. Peri-transplant Zinc status negatively affects IR, especially on the thymic-derived T cell compartment. Early recognition of ZD and zinc supplementation might help prevent morbidity related to poor IR in a proportion of patients. A multivariable analysis looking at other clinical data and outcomes is ongoing. Validation of these findings is needed on a larger number of patients, including a cohort of patients receiving T_N-replete HSCT.

Disclosures Iovino: *Mustang Bio:* Current equity holder in publicly-traded company. **Bleakley:** *Orca Bio:* Consultancy; *Miltenyi Biotec:* Research Funding.

Table 1: Baseline characteristics, serum zinc levels, and immune parameters at day +365. P values are reported for simple linear regressions.

Patients' characteristics		Association with pre-HSCT serum Zn (p value)	Association with day +80 serum Zn (p value)
Age (years), Median (Range)	47 (6-61)	0.3890	0.9683
Serum zinc measures (ug/dL), Median (range)			
Pre-HSCT	71 (60-105)		
Day +80	80 (36-112)		
Disease subtype, n(%)			
AML	27 (51.9%)		
ALL	21 (40.4%)		
Other	4 (7.7%)		
Conditioning regimen, n (%)			
TBI 13.2 Gy	28 (53.8%)		
TBI 4 Gy	24 (46.2%)		
Donor, n(%)			
MRD	24 (46.2%)		
MUD	28 (53.8%)		
sjTRECs day +365, Median (Range)	3.33 (0.00-16,704)	0.2946	***0.0019***
PB lymphoid populations at day +365			
Absolute CD4+	343 (65-478)	0.7198	0.1846
Absolute CD8+	376 (51-949)	0.7779	0.1750
CD4+ naïve	8,5 (0-63)	0.2243	0.0822
CD8+ naïve	9 (0-88)	***0.0327***	0.1778
T regulatory cells	19 (6-59)	0.8064	0.2368
B cells	172 (7-1077)	0.8045	0.2469
NK cells	208 (99-608)	0.9796	0.9796

Figure 1: linear regression of day +80 serum zinc and sjTRECs and pre-HSCT zinc levels and CD8+ naive T cells at day +365

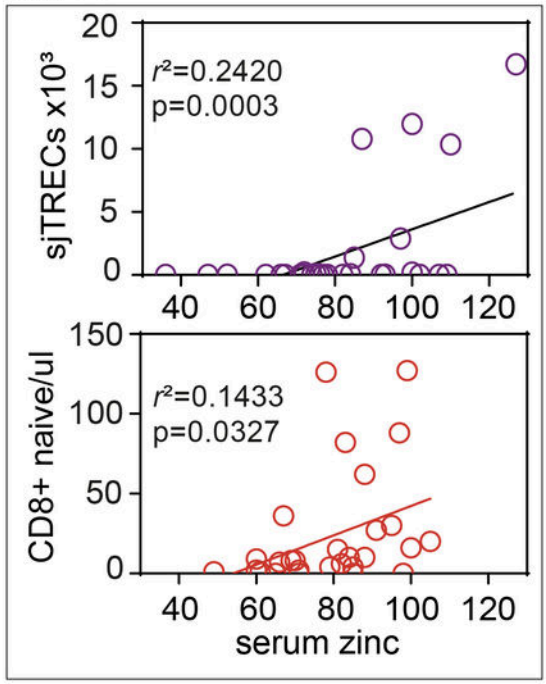

Figure 1

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