Conclusion: Counts of T cells, B cells and myeloid DCs early posttransplant depend on the number of these cells infused with the graft. Naive T cell counts late posttransplant depend on recipient age. GVHD appears to hamper the recovery of B cells, regulatory NK cells and plasmacytoid DCs. Day 7 ATG serum levels have a significant impact on T cell counts in the first 3 months posttransplant.

226

KGF PROMOTES CD4+ T CELL RECOVERY AFTER T-CELL DEPLETED ALLOGENEIC HEMATOPOEITIC STEM CELL TRANSPLANTATION IN PATIENTS CONDITIONED WITH TOTAL BODY IRRADIATION: IMPACT ON OVERALL SURVIVAL

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Delayed immune recovery (IR) after allogeneic HSCT (allo-HSCT) is associated with increased risks of infection and relapse, which can impact survival. Studies by others and us have shown in pre-clinical mouse models that pre-HSCT administration of KGF resulted in increased thymopoiesis and peripheral T-cell numbers post allo-HSCT. Therefore, we performed a retrospective study to evaluate the effect of KGF (Palifermin, Biovitrium) on IR in allo-HSCT recipients. We conducted a review of 241 consecutive patients who underwent an ablative T-cell depleted allo-HSCT from 2005-2009. The conditioning regimen was TBI-based in 114 patients and chemotherapy-based in 127 patients. 160 patients (66.4 %) received KGF peri-transplant. IR data (CD4, CD8, NK, CD45RA, PHA response) were collected for one year after HSCT and censored following DLI (n = 49), 2nd transplant (n = 21) or Interleukin 7 treatment (n = 8). A joint longitudinal survival model was used to characterize the profile of IR data over time (longitudinal model) and the association between immunologic data and survival (survival model; overall survival (OS) and event-free survival (EFS)). In the joint OS model analysis of TBI recipients, administration of KGF was marginally significantly associated with recovery of CD4 count (slope = 0.29, p = 0.059) and there was a trend for an association between CD4 recovery and OS (HR = 0.69, p = 0.077). With a similar association between administration of KGF and recovery of CD4 count, CD4 recovery was not found to be associated with EFS. For patients who received chemotherapy-based preparative regimens, KGF had no impact on CD4 recovery. However, in these patients, CD4 recovery was associated with an increased OS (HR = 0.61, p = 0.006) and EFS (HR = 0.56, p = 0.023).

Table 1. Joint Longitudinal Survival Model

		Longitudinal Model, effect of KGF – CD4			Survival Model – CD4		
Regimen	Survival Parameter	Slope (of log transformed CD4 count)	95% CI	P-value	HR	95% CI	P-value
TBI	OS	0.29	-0.01~0.59	0.059	0.69	0.46~1.04	0.077
TBI	EFS	0.29	-0.02~0.60	0.063	0.69	0.41~1.17	0.171
Chemo	OS	NS	NS	NS	0.61	0.43~0.87	0.006
Chemo	EFS	NS	NS	NS	0.56	0.34~0.92	0.023

For the combined group of patients, CD4 recovery was associated with improved OS (HR 0.65, p0.002), but not EFS; KGF did not impact CD4 recovery. Administration of KGF did not impact the recovery of other immune subsets. This analysis is potentially limited by its retrospective nature and the length of the study time frame. However, our data suggest that KGF improves CD4 recovery in recipients of TBI-based conditioning regimens, which in turn is associated with increased OS. This data is consistent with the pre-clinical data and clinical mucositis data suggesting the effect of KGF may depend on the preparative regimen. A prospective trial is warranted to further investigate these promising findings.

227

RECOVERY OF FUNCTIONAL T CELLS SPECIFIC FOR PERSISTING VIRUS IS NOT IMPAIRED IN PATIENTS WITH CHRONIC GRAFT-VS-HOST DISEASE

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Introduction: T cell expression of PD-1, a marker of functional exhaustion manifested by inability to produce cytokines upon stimulation, is upregulated in patients with acute graft-vs-host disease (GHVD). This is thought to explain at least in part why patients with acute GVHD have frequent infections. Here we wished to evaluate whether this is true also for chronic GVHD.

Patients and Methods: We studied 17 allogeneic hematopoietic cell transplant recipients who have not developed acute or chronic GVHD by day 84. Between day 84 and 365, 7 patients did and 10 patients did not develop chronic GVHD needing systemic immunosuppressive therapy (de novo, ie, without preceding acute GVHD). We studied total CD4 and CD8 T cells as well as Epstein-Barr virus (EBV)-specific CD4 and CD8 T cells. Blood mononuclear cells were stimulated with EBV lysate or EBNA3A+B+C overlapping peptides. After overnight incubation, expression of IFNγ, TNFα, IL2 and PD-1 on $CD3^+CD4^+CD8^-$ or $CD3^+CD4^-CD8^+$ cells was determined by flow cytometry.

Results: PD-1 expression on total, EBV lysate-specific or EBNA3-specific CD4 or CD8 T cells was not significantly higher among patients who did vs did not develop chronic GVHD. On the contrary, there was a trend toward lower PD-1 expression on EBV lysate-specific CD4 and CD8 T cells and EBNA3-specific CD4 T cells in patients who developed chronic GVHD. This was significant ($p < .05$, Mann-Whitney test) for EBV lysate-specific CD4 T cells on day 84, EBV lysate-specific CD8 T cells on day 180, EBV lysate-specific CD4 and CD8 T cells on day 365, EBNA3-specific CD4 T cells on day 84 and EBNA3-specific CD4 T cells on day 365. Consistent with that, absolute counts of total, EBV lysate-specific or EBNA3-specific T cells were not significantly lower in patients who did vs did not develop chronic GVHD. On the contrary, there was a trend toward higher EBV lysate-specific and EBNA3-specific CD4 or CD8 T cell counts in patients who developed chronic GVHD. This was significant on day 84 for total EBV lysate-specific CD4 and CD8 cells, EBV lysate-specific $CD4^+IFN\gamma^+$ cells and $CD8^+IFN\gamma^+$ cells, and total EBNA3-specific CD4 cells, EBNA3-specific $CD4^+IFN\gamma^+$ cells, $CD4^+IL2^+$ cells, $CD4^+IFN\gamma^+TNF\alpha^+IL2^+$ cells and $CD8^+IFN\gamma^+$ cells.

Conclusion: De novo chronic GvHD and its treatment do not adversely affect the counts of functional T cells specific for EBV and, perhaps, for persisting viruses in general.