View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

(95% CI 16 – 44%) by one year. The cumulative incidence of primary disease relapse was 23% (95% CI 13 – 41%) at 1 year. CMV reactivation differed according to recipient and donor CMV serostatus. EBV reactivation occurred in 54% (95% CI 40% - 71%). Preemptive rituximab therapy controlled EBV in the majority of cases; however, PTLD was diagnosed in 5 cases, and was fatal in one. A regimen of ATG 7.5mg/kg today ending on day -1 effectively prevents grade III-IV acute GVHD and severe chronic GVHD in 6-7/8 mismatched unrelated donor HCT.

519

INFLUENCE OF GENOMIC STRUCTURAL VARIANTS ON GVHD AND RELAPSE RISK IN LYMPHOMA PATIENTS TREATED WITH ALLOGENEIC HSCT

Larson, G.P.[1], Palmer, J.[2], Qian, D.[2], Forman, S.[3], Senitzer, D.[4], Nakamura, R.[3] [1] Beckman Research Institute of the City of Hope, Duarte, CA; [2] Division of Biostatistics; [3] Hematology; [4] Histocompatibility Laboratory

Copy number variants (CNV) contribute to the risk of multiple common diseases and are implicated in unfavorable clinical outcomes in HSCT. The role of CNVs bearing immuno-tolerance genes (mHAg) has been demonstrated for *UGT2B17* in HLA-matched siblings after HSCT (McCarroll, et al *Nat Genet* 2009). Homozygous CNV deletion transïplant donors mismatched with CNV+ recipients may harbor immune systems naïve to proteins present within the recipient eliciting GVHD demonstrating a growing role for CNVs in transplant medicine. Allogeneic HSCT, a potentially curative therapy for recurrent non-Hodgkin lymphoma (NHL), is often compromised by transplant-mediated GVHD thereby jeopardizing patient survival. Owing to known differences in CNV allele frequencies in ethnically diverse populations combined with the racially diverse composition of NHL patients seen at our institution, the incidence of CNV-mediated GVHD may very widely. To test this premise, we are examining the affect of population-specific CNVs on GVHD in a cohort of NHL patients.

We are investigating GVHD in 292 patients who underwent HSCT to 1) determine the genetic admixture of our patients, 2) subsequently use genetic ancestry to guide the selection of CNVs for GVHD association testing, and 3) develop a novel mass spectrometry based platform to genotype CNVs. In our initial group of 85 patients who underwent allo-HSCT (64 related and 21 unrelated donors), grade II-IV acute GVHD occurred in 43 patients, and 21 experienced NHL relapse. Forty-eight patients self-reported as non-Hispanic Caucasian, 3 African American, 5 Asian, and 29 Hispanic or Latino. Genetic admixture estimates with a panel of ~100 Ancestry Informative Markers were used to define genetic ancestry and correlate to self-reported ethnicity. Admixture analysis on self-reported Hispanics showed that 69% (20/29) contained > 10% AmerIndian ancestry. Weighted ancestry estimates in 3 HapMap populations based on genetic proportions observed in our patients indicate numerous CNV alleles as potential targets, 48 of these have allele frequencies > 10% in our cohort and represent possible targets for donor-recipient mismatches.

We are genotyping donor/recipient pairs for a select group of CNVs in conjunction with *UGT2B17* using mass spectroscopy to correlate CNV discordant pairs with GVHD. Approaches like this are applicable to the racially diverse patient populations commonly seen at institutions performing HSCT and may improve clinical outcomes.

520

A PHASE I/II STUDY OF CHEMOTHERAPY FOLLOWED BY DONOR LYMPHOCYTE INFUSION PLUS INTERLEUKIN-2 FOR RELAPSED ACUTE LEUKEMIA AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Inamoto, Y., Fefer, A., Sandmaier, B.M., Gooley, T.A., Warren, E.H., Petersdorf, S.H., Sanders, J.E., Storb, R.F., Appelbaum, F.R., Martin, P.J., Flowers, M.E.D. Fred Hutchinson Cancer Research Center, Seattle, WA

Introduction: Efficacy of donor lymphocyte infusion (DLI) for relapsed acute leukemia after allogeneic hematopoietic cell transplantation (HCT) is limited. We hypothesized that interleukin-2 (IL-2) combined with DLI after chemotherapy might augment graft-versus-leukemia effects. To identify a safe and effective IL-2 regimen, a phase I/II study of DLI plus IL-2 therapy was performed.
Methods: Patients with relapsed acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) after allogeneic HCT were eligible for this study. After chemotherapy, patients received DLI ($1x10^8$ CD3/kg for patients with related donors, and $0.1x10^8$ CD3/kg for those with unrelated donors) and an escalating dose of induction IL-2 (Aldesleukin, Chiron, CA; 1.0, 2.0, or $3.0x10^6$ IU/m^2/day representing levels I, Ia and II) for 5 days followed by maintenance ($1.0x10^6$ IU/m^2/day) for 10 days as a continuous intravenous infusion. Study toxicities were prespecified. An excess study toxicity rate was defined as any incidence where the lower limit of the 80% one-sided confidence interval exceeded 25%. To examine the potential efficacy of this therapy, disease-free survival (DFS) was estimated according to diagnosis and remission status at time of DLI.
Results: A total of 17 patients (11 with AML and 6 with ALL) with median age 33 years (range 19-61) were enrolled in this study. Donors were related siblings for 13 patients and unrelated volunteers for 4 patients. Sixteen patients had a prior history of GVHD. The median time from HCT to chemotherapy was 11.8 months (range 3-121). The median time from chemotherapy to DLI was 61 days (range 36-91). Outcomes are summarized in the Table. IL-2 related toxicities were reversible in all except in 1 patient at level II who died of capillary leak syndrome. Grades III-IV acute GVHD developed in 5 patients, and extensive chronic GVHD developed in 8. Study toxicities developed in 1 patient at IL-2 dose level I, 2 patients at level Ia and 1 patient at level II. Eight patients had a complete remission after chemotherapy prior to DLI, and 2 additional patients had a complete remission after DLI plus IL-2 therapy. DFS at 1 year was 40% for patients with AML in complete remission at DLI (n = 5) and 8% for those with AML not in remission (n = 6) or ALL in any stage at DLI (n = 6).
Conclusion: The maximal tolerated induction dose of IL-2 combined with DLI appears to be $1.0x10^6$ IU/m^2/day. IL-2 administration after DLI might increase the incidence of chronic GVHD.

Table 1. GVHD, study toxicity and remission duration after DLI according to IL-2 dose level

Patient#	Diagnosis	IL-2 Dose Level	Acute GVHD	Chronic GVHD	Study Toxicity*	Remission Duration after DLI (Month)
1	AML	I	0	NA	N	0
2	AML	I	III	Extensive	N	33
3	AML	I	III	Extensive	N	35
4	AML	I	0	Extensive	N	0
5	ALL	I	0	0	N	0
6	ALL	I	III	Extensive	Y (GVHD)	8
7	ALL	I	0	0	N	5
8	AML	Ia	0	NA	N	0
9	AML	Ia	0	0	N	0
10	AML	Ia	II	Extensive	N	9
11	AML	Ia	0	Extensive	N	5
12	AML	Ia	IV	Extensive	Y (GVHD)	47
13	AML	Ia	0	0	N	6
14	AML	Ia	0	0	N	3
15	ALL	Ia	0	Limited	N	0
16	ALL	Ia	III	Extensive	Y (IL-2)	12
17	ALL	II	0	NA	Y (IL-2)	0

*Death related to acute or chronic GVHD, development of acute or chronic GVHD with inability to decrease the dose of prednisone to less than 1mg/kg/day within 1 month after initiating treatment for GVHD, or life threatening or fatal organ toxicity attributable to IL-2.

521

INTERFERON-GAMMA PRODUCTION BY ALLOGENEIC FOXP3+ REGULATORY T CELLS PROMOTES SURVIVAL IN EXPERIMENTAL GVHD

Koenecke, C.[1,2], Lee, C.-W.[1,2], Föhse, L.[2], Ganser, A.[1], Förster, R.[2], Prinz, I.[2] [1] Hannover Medical School, Hannover, Germany; [2] Hannover Medical School, Hannover, Germany

Background and Aims: Adoptive transfer of natural FoxP3+ regulatory T cells (Tregs) has been shown to prevent lethal GvHD. It is emerging that Tregs are a stable lineage that do not revert into harmful FoxP3 effector cells. However, we have recently found that Tregs