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POSTER ABSTRACTS

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

Prediction of Graft-Versus-Host Disease (GVHD) in Recipients of Hematopoietic Cell Transplant(alloHCT) from a Single Mismatched Unrelated Donor Using a Highly Multiplexed Proteomics Assay: MHC-Pepseq

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Introduction: Graft-versus-host disease (GVHD) remains a major barrier of allogenic hematopoietic stem cell transplantation (HCT). While direct recognition of mismatched HLA molecules is believed to be the major driver of alloimmune T cell response, indirect presentation of mismatched host class I or class II proteins may also contribute to CD4 T cell-mediated GVHD or graft-versus-leukemia (GVL). Using a novel highly multiplexed peptide-MHC binding assay (MHC-PepSeq), we developed a score of HLA-DRB1 restricted and binding allogeneic peptide sequences for each donor/recipient pair in a CIBMTR cohort of mismatched adult HCT recipients with hematological malignancies. We hypothesized that the risk score derived from the MHC-PepSeq assay is associated with the incidence and severity of acute and chronic GVHD.
Methods: Using public population allele frequencies (allelefrequencies.net), we identified a set of alleles that covers >95% of HLA genotypes of 3 major US populations (European Caucasian, African American, Mexican Chicano) at 9 HLA-loci (-A, -B, -C, -DRA1, -DRB1, -DQA1, -DQB1, -DPA1, -DPB1) and converted their sequences to 7,744 unique, densely-tiled 15-mer peptides. A highly multiplexed synthesis protocol ("PepSeq") was used to generate a library of DNA-barcoded peptides of the corresponding sequences, which we used to generate experimental binding measurements of each peptide against 12 common HLA-DRB1 molecules. The resulting data were then used to enumerate DR-binding peptides present in recipient HLA but not donor HLA genotype ("allopeptide score"), for each donor-recipient pair in a cohort of HLA-A, B, C and DRB1 (8/8) matched unrelated donors with a mismatch in HLA-DPB1 and a cohort of 7/8 Class I mismatched unrelated donors. Univariate analysis was used to compare clinical demographics and allopeptide association with clinical outcomes. In multivariable analysis, a logistic regression model was used to analyze aGVHD II-IV at day 100 (primary outcome), and Cox proportional hazards were applied for OS, relapse, chronic GVHD (cGVHD) and non-relapse mortality (NRM) (secondary outcomes).
Results: In the 8/8 cohort, 6679 matched unrelated pairs were identified with allopeptide detected in 1563 (30.5%). In the 7/8 cohort, 1133 pairs were identified with allopeptide detected in 156 (15.9%). Patient characteristics were balanced in both cohorts and described in **Table 1**.

In the 8/8 cohort, the cumulative incidence of aGVHD II-IV at day 100 post HCT was 42.3% (95% CI: 40.9-43.7%) in patients with a detectable allopeptide and 45.5% (95%CI: 43.0-48.0%) in patients with non-detectable allopeptide, respectively (p=.069). No significant differences were observed in univariate analysis for cGVHD, NRM, OS. In multivariate analysis there were no significant associations between presence of detectable allopeptide (Y/N) and aGVHD II-IV, cGVHD, OS, and NRM. However, a significant interaction between disease and allopeptide status was detected in the relapse model (P=0.0020), with allopeptide presence associated with a decreased risk of relapse in ALL (HR 0.71; 95%CI:0.54-0.94, p=0.0168) and an increased risk of relapse in AML (HR 1.23; 95%CI:1.05-1.43, p=0.0085). Allopeptide presence was not significantly associated with relapse in MDS (HR 0.89; 95% CI:0.74-1.06 p=0.1901). Adjusted cumulative incidence of relapse is shown in **Figure 1**.
In the 7/8 cohort, cumulative incidence of aGVHD II-IV at day 100 post HCT was 43.4% (95% CI: 40.2-46.5%) and 41.8% (95% CI: 34.1-49.7%) (p=.77) in the allopeptide-detectable and non-detectable groups, respectively. In univariate analysis there were no statistically significant differences noted in cGVHD, NRM, OS. In multivariate analysis allopeptide presence was not significantly associated with any of the endpoints aGVHD II-IV, cGVHD, OS, relapse or NRM.
Conclusion: In a large CIBMTR 8/8 and 7/8 matched unrelated donor cohort, allopeptide scores derived from MHC-pepseq were not predictive of aGVHD, possibly due to the limitation of the assay (i.e., low sensitivity, limited to class II presentation - HLA-DRB1 in this analysis) and/or low antigenicity in HLA molecules when indirectly presented as minor histocompatibility antigens. The observed reverse association of allopeptide presence with relapse in AML and ALL requires further investigation, and subgroup analyses for individual HLA-DRB1 presenting allele are currently underway.

Disclosures Sandhu: *Autolus Therapeutics:* Consultancy; *City of Hope Medical Center:* Current Employment. **DeFilipp:** *Sanofi:* Consultancy; *MorphoSys:* Consultancy, Honoraria; *Inhibrx:* Consultancy; *PharmaBiome AG:* Consultancy; *Ono Pharmaceuticals:* Consultancy; *Incyte:* Consultancy, Honoraria, Research Funding; *Regimmune:* Research Funding; *Taiho Oncology:* Research Funding. **Kitko:** *Horizon:* Membership on an entity's Board of Directors or advisory committees. **Lee:** *Janssen:* Other: Study medication provider; *Novartis:* Other: Steering Committee member; *Amgen, AstraZeneca, Incyte, Kadmon, Pfizer, Syndax:* Research Funding; *Equillium, Kadmon, Mallinckrodt:* Consultancy. **MacMillan:** *Talaris:* Other: DSMB; *Equillium:* Other: DSMB; *NMDP:* Other: Chair NMDP IRB. **Nakamura:** *Miyarisan:* Research Funding; *Leukemia & Lymphoma Society:* Other: grant reviewer; *Mt. Sinai:* Other: Acute GVHD; *BMT CTN Steering Committee:* Membership on an entity's Board of Directors or advisory committees; *NCTN Lymphoma Steering Committee:* Membership on an entity's Board of Directors or advisory committees; *Napajen:* Consultancy; *International Consortium:* Other: consortium chair; *NCCN:* Other: guideline panel for HCT; *Jazz Pharmaceuticals:* Consultancy, Other: research collaboration; *Omeros:* Consultancy; *Sanofi:* Consultancy; *Blue Bird:* Consultancy.

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Table 1. Patient and alloHCT characteristics				
	8/8 unrelated donor		7/8 unrelated donor	
Allopeptide	0(N=5116)	≥1(N=1563)	0(N=977)	≥1(N=156)
Median follow up months- median (range)	69.5(6.5-172.3)	70.9(3.7-170.3)	69.2(12.0-170.9)	71.4(12.0-168.3)
Age at alloHCT, years Median (Range)	57.6(18-83.5)	57.9(18-79.4)	54.4(18.1-78.3)	51.9(18.2-71.7)
Patient Gender-N (%)				
Female	2207(43.1)	668 (42.7)	459(47.0)	67(42.9)
Male	2909(56.1)	895(57.3)	518(53.0)	89(57.1)
Donor/Recipient Sex match-N (%)	2269(44.4)	663(42.4)	350(35.8)	60(38.5)
M-M	1467(28.7)	448(28.7)	253(25.9)	37(23.7)
M-F	640(12.5)	232(14.8)	168(17.2)	29(18.6)
F-M	740(14.5)	220(14.1)	206(21.1)	30(19.2)
F-F				
Disease-N (%)				
AML	2682(52.4)	835(53.4)	522(53.4)	84(53.8)
ALL	927(18.1)	288(18.4)	194(19.9)	34(21.8)
MDS	1507(29.5)	440(28.2)	261(26.7)	38(24.4)
GVHD prophylaxis-N (%)				
PTCy +/- others	373(7.3)	123(7.9)	187(19.1)	25(16)
CNI +MMF	788(15.4)	233(14.9)	159(16.3)	24(15.4)
CNI +MTX	3486(68.1)	1046(66.9)	578(59.2)	96(16.5)
CNI +/- others	438(8.6)	149(9.5)	48(4.9)	11(7.1)
Other/missing	31(0.6)	12(0.8)	5(0.5)	0(0.0)
Graft type- N (%)				
Bone Marrow	830(16.2)	253(16.2)	158(16.2)	40((25.6)
Peripheral blood	4286(83.8)	1310(83.8)	819(83.8)	116(74.4)
Conditioning regimen-N (%)				
Myeloablative	3043(59.5)	940(60.1)	563(57.6)	109(69.9)
Reduced intensity	2073(40.5)	623(39.9)	414(42.4)	47(30.1)
ATG-N (%)				
No	3183(62.2)	973(62.3)	498(51.0)	72(46.2)
Yes	1722(33.7)	531(34.0)	428(43.8)	78(50.0)
Not reported	211(4.1)	59(3.8)	51(5.2)	6(3.8)
Number of allopeptides-N (%)				
0	5116(100)	0(0.0)	977(100)	72(46.2)
1-2	0(0.0)	1302(83.3)	0(0.0)	78(50.0)
≥2	0(0.0)	261(16.7)	0(0.0)	6(3.8)

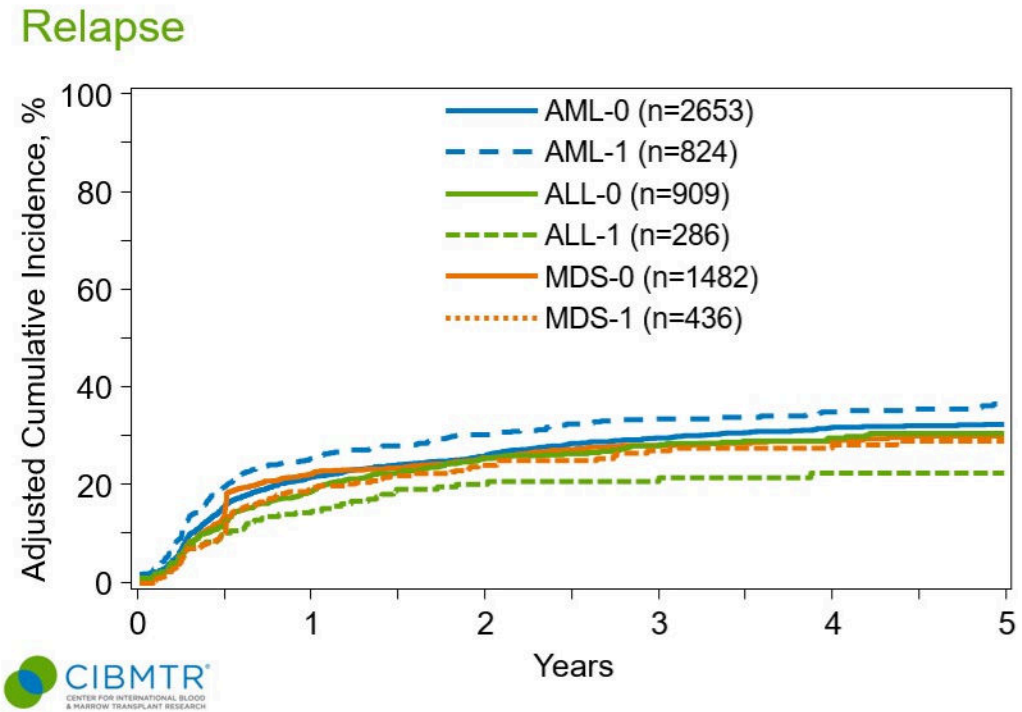

Figure 1