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Research Article

Autoimmune HLA Alleles and Neoepitope Presentation Predict Post-Allogenic Transplant Relapse

Andrea Castro,[1,2] Aaron M. Goodman,[3] Zachary Rane,[4] James V. Talwar,[1,2] Garrett M. Frampton,[5] Gerald P. Morris,[6] Scott M. Lippman,[4,7] Xinlian Zhang,[8] Razelle Kurzrock,[9] Hannah Carter[2,7]

[1]Bioinformatics and Systems Biology Program, University of California San Diego, La Jolla, CA, USA
[2]Division of Medical Genetics, Department of Medicine, University of California San Diego, La Jolla, CA, USA
[3]Division of Blood and Marrow Transplantation, Department of Medicine, University of California San Diego, La Jolla, CA, USA
[4]School of Medicine, University of California San Diego, La Jolla, CA, USA
[5]Foundation Medicine, Cambridge, MA, USA
[6]Department of Pathology, University of California San Diego, La Jolla, CA, USA
[7]Moores Cancer Center, University of California San Diego, La Jolla, CA, USA
[8]Division of Biostatistics and Bioinformatics, Herbert Wertheim School of Public Health, University of California San Diego, La Jolla, CA, USA
[9]Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

Andrea Castro and Aaron M. Goodman are co-first authors.

Razelle Kurzrock and Hannah Carter are co-senior authors.

Address correspondence to Aaron M. Goodman (a1goodman@ucsd.edu).

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ABSTRACT

Introduction: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) can cure patients with high-risk myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). However, many patients relapse or develop debilitating graft-versus-host disease. Transplant restores T-cell reactivity against tumor cells, implicating patient human leukocyte antigen (HLA)-dependent antigen presentation via the major histocompatibility complex as a determinant of response. We sought to identify characteristics of the HLA genotype that influence response in allo-HSCT patients. **Methods:** We collected HLA genotype and panel-based somatic mutation profiles for 55 patients with AML and MDS and available data treated at the University of California San Diego Moores Cancer Center between May 2012 and January 2019. We evaluated characteristics of the HLA genotype relative to relapse-free time and overall survival (OS) post-allo-HSCT using univariable and multivariable regression. **Results:** In multivariable regression, the presence of an autoimmune allele was significantly associated with relapse-free time (hazard ratio [HR], 0.25; $p = 0.01$) and OS (HR, 0.16; $p < 0.005$). The better potential of the donor HLA type to present peptides harboring driver mutations trended toward better relapse-free survival (HR, 0.45; $p = 0.07$) and significantly correlated with longer OS (HR, 0.33; $p = 0.01$) though only a minority of cases had an HLA mismatch. **Conclusion:** In this single institution retrospective study of patients receiving allo-HSCT for relapsed AML/MDS, characteristics of an individual's HLA genotype (presence of an autoimmune allele and potential of the donor HLA to better present

peptides representing driver mutations) were significantly associated with better outcomes. These findings suggest that HLA type may guide the optimal application of allo-HSCT and merit evaluation in larger cohorts. **ClinicalTrials.gov Identifier: NCT02478931**

Keywords: allo-HSCT, HLA genotype, neoantigen, relapse, acute myeloid leukemia

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the standard of care for patients with high-risk acute myeloid leukemia (AML) in first remission and for those with myelodysplastic syndromes (MDS) scored as *poor* or *very poor* per the Revised International Prognostic Scoring System. Allo-HSCT can restore T-cell reactivity against malignant cells (graft-vs-leukemia [GVL] effect),[1] which is dependent on antigen presentation by the major histocompatibility complex (MHC). Differences in recipient versus donor human leukocyte antigen (HLA) alleles may alter the potential for antigen-presenting immune cells to display tumor-associated antigens, potentially affecting T-cell reactivity. Post-allo-HSCT, evidence of immune evasion via reduction of MHC-II, but not MHC-I, allele abundance has been observed in some patients.[2] In addition, upregulation of class II–associated invariant chain peptide is associated with immune escape in AML by disrupting MHC-II antigen presentation.[3] Altogether, these studies suggest that patient HLA alleles, especially MHC-II alleles, influence AML relapse risk post-allo-HSCT and warrant further investigation.

We hypothesized that patients with improved MHC presentation of tumor mutations via donor MHC molecules posttransplantation would have better outcomes than those with a worse or identical presentation. We focused on both MHC class I and II because cross-presenting antigen-presenting cells have been identified as important for generating anti-tumor immune responses.[4,5] Analogous results have been described in solid tumors, where the ability of MHC to present mutanome-derived neoantigens is associated with therapeutic benefit or lack thereof after immune checkpoint blockade therapy.[6] Because GVL, which is generally coupled with graft-versus-host disease (GVHD), is associated with improved prognosis,[7] we further considered the potential for autoimmune alleles to improve anti-tumor immunity. Documented autoimmune alleles exist for both MHC-I and MHC-II, and current literature suggests that intrinsic MHC instability and presentation of certain self-peptides contribute to increased risk of autoimmunity, though exact mechanisms remain unclear.[8,9]

METHODS

Ethics Approval and Consent to Participate

This study was performed in accordance with University of California San Diego institutional review board guidelines for data analysis and for any investigational interventions to which patients consented. This was a reanalysis of data from a subset of patients who received Foundation Medicine profiling of their tumor as part of the PREDICT trial (ClinicalTrials.gov Identifier: NCT02478931) and were treated with bone marrow transplant as part of the standard of care for their disease.

Mutation Affinity Analysis and Assessment of Outcomes

Somatic mutations and HLA types for 55 patients were obtained from Foundation Medicine (Cambridge, MA). Eighteen patients did not have any missense or in-frame indel mutations to calculate patient harmonic-mean best-rank (PHBR) scores for and were thus excluded from mutation affinity analysis. PHBR presentation scores were calculated using NetMHCpan4.0 and NetMHCIIpan4.0,[10,11] described previously[12] for available HLA alleles with at least a two-field resolution. HLA allele frequencies were compared to observed frequencies in The Cancer Genome Atlas by Fisher Exact Test.

Univariable Cox proportional hazards (Cox PH) analysis was performed for the following 14 variables: conditioning intensity, stem-cell source, disease status at transplant, donor source, age at diagnosis, sex, chronic GVHD status, variant allelic fraction (VAF), PHBR-I, PHBR-II, PHBR-I change, PHBR-II change, MHC-I autoimmune allele status, and MHC-II autoimmune allele status. These variables were measured against relapse-free time and overall survival for all patients and matched-unrelated donor (MUD)-only patients. Multiple testing correction was performed using the Benjamini-Hochberg method. For multivariable Cox PH analysis, we performed backward selection on all 14 variables, retaining only covariates that reduced the Akaike information criterion to obtain the model that best fits the data with the minimal parameters. Recipient and donor PHBR scores were very similar, resulting in multicollinearity, and thus were evaluated separately during multivariable analysis. Analysis was performed in Python: Regression was performed using sklearn v0.24.2 and Cox PH analysis was implemented with the Lifelines package v0.26.0. All other tests used the SciPy package v1.7.1.

Autoimmune allele frequencies used for comparison were based upon data generated by the TCGA Research Network: https://www.cancer.gov/tcga.

RESULTS

Patient Characteristics

We analyzed data from 55 patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) who received a single allo-HSCT at the UCSD Moores Cancer Center between May 2012 and January 2019 and for whom we had donor and/or recipient HLA typing and next-generation sequencing mutational data. The biological and clinical characteristics and their correlation with the outcome are shown in Figure 1, Supplemental Tables S1 and S2, and Supplemental Figures S1 to S4. Overall, 43 of 55 (78.2%) patients had perfect matching between MHC-I alleles at high resolution (two-field; e.g., HLA-A*01:01) and 45 of 55 (81.8%) at low resolution (one-field; e.g., HLA-A*01). Altogether, 18 of 55 (32.7%) had perfect matching between typed MHC-II alleles at high resolution and 19 of 55 (34.5%) at low resolution, although on average, more than 90% of class I and 83% of MHC-II alleles matched within patients (Fig. 1A). Overall, 58% and 80% of patients had at least one MHC-I and one MHC-II autoimmune-associated HLA allele, respectively[13–19] (Fig. 1B, Supplemental Table S1 and S2). Of all patients, 37 had protein coding mutations detected by panel sequencing (Supplemental Table S3). To quantify putative neoepitope presentation given patient HLA type, we calculated PHBR scores, where lower scores indicate better presentation[12,20] for all mutations. Because the recipient and donor alleles were closely matched, most patients showed no differences in PHBR scores. In eight patients with differing donor/recipient HLA types, PHBR score comparison indicated that 7 of 10 mutations had improved MHC-I presentation and 3 of 10 mutations had improved MHC-II presentation (Figs. 1C, D).

MHC-I Autoimmune Allele Carrier Status Associated with Longer Relapse-Free Time Post-Allo-HSCT

We considered 14 covariates (Fig. 1E), including conditioning intensity, stem-cell source, disease status at transplant, donor source, age at diagnosis, sex, chronic GVHD status, variant allelic fraction (VAF), PHBR-I, PHBR-II, PHBR-I change, PHBR-II change, MHC-I autoimmune allele status, and MHC-II autoimmune allele status. Higher PHBR scores indicate worse HLA presentation of mutanome-derived putative neoantigens.

To evaluate a possible association between relapse-free time and HLA type, we performed backward selection on the 14 covariates for each patient's most clonal mutation (Supplemental Fig. S1). In univariable analysis, only a responsive disease status at transplant and age at diagnosis were significantly associated with relapse-free time; however, these were no longer significant after multiple testing correction (Fig. 1E). A responsive disease status at transplant was the most protective variable evaluated, as expected.

We next compared Akaike information criterion scores in a multivariable framework to remove confounding variables that did not improve the Cox PH model. After selection, six variables remained, including MHC-I autoimmune allele presence, conditioning intensity, transplant type, chronic GVHD status, PHBR-I change, and PHBR-I. Of note, responsive disease status at transplant was significantly correlated with better mutation presentation (lower PHBR-I score), and age at diagnosis was significantly correlated with decreased conditioning intensity, which led to the omission of these factors by the selection process due to redundancy (Supplemental Fig. S2). We found that the presence of an MHC-I autoimmune allele (hazard ratio [HR], 0.25; $p = 0.01$) and chronic GVHD (HR, 0.23; $p = 0.01$) were strongly associated with longer relapse-free time. These factors remained significantly protective even when we replaced donor presentation of mutations with disease status at transplant in the multivariable model (cGVHD HR, 0.24; $p = 0.01$; autoimmune allele carrier status HR, 0.3; $p = 0.03$; Supplemental Fig. S3). Poor predicted donor or recipient mutation presentation (higher PHBR scores) via MHC-I was associated with relapse (HR, 1.22; 95% CI, 0.99–1.50; $p = 0.06$) and improved presentation with the donated HLA alleles (PHBR change) was associated with longer relapse-free time (HR, 0.45; $p = 0.07$). Intensive conditioning and being a MUD were associated with relapse (HR, 3.7; 95% CI, 1.15–11.92; $p = 0.03$; and HR, 3.69; 95% CI, 0.94–14.48; $p = 0.06$, respectively) (Fig. 1F). Regarding 10 mutations in which donor HLA types resulted in a PHBR change, we found that the change in score from the recipient to the donor was more informative than the raw score for either donor or recipient HLA type.

Overall Survival Associated with Having at Least One Autoimmune Allele and Improved Neoepitope Presentation via Donated MHC-I

We repeated the multivariable analysis using overall survival as the endpoint and found that autoimmune allele status (HR, 0.16; $p < 0.005$) and improved presentation via donated MHC-I (lower PHBR-I scores, HR, 0.33; $p = 0.01$) were also significantly associated with more prolonged overall survival (Supplemental Fig. S4). Other significant protective variables include chronic GVHD (HR, 0.06; $p < 0.005$) and mutation clonality (HR, 0.0007; $p = 0.006$) while intensive conditioning (HR, 11.35; $p < 0.005$), MUD status (HR, 9.35; $p = 0.01$), and bone marrow stem cell source (HR, 5.51; $p = 0.02$) were associated with shorter overall survival.

Finally, to evaluate our findings in a more homogenous group, we removed nine patients to focus on only MUD donors and performed the same backward selection multivariable analysis with relapse-free time and overall survival (Supplemental Fig. S5). Presence of a class I autoimmune allele was once again significantly associated with more prolonged overall survival (HR, 0.14;

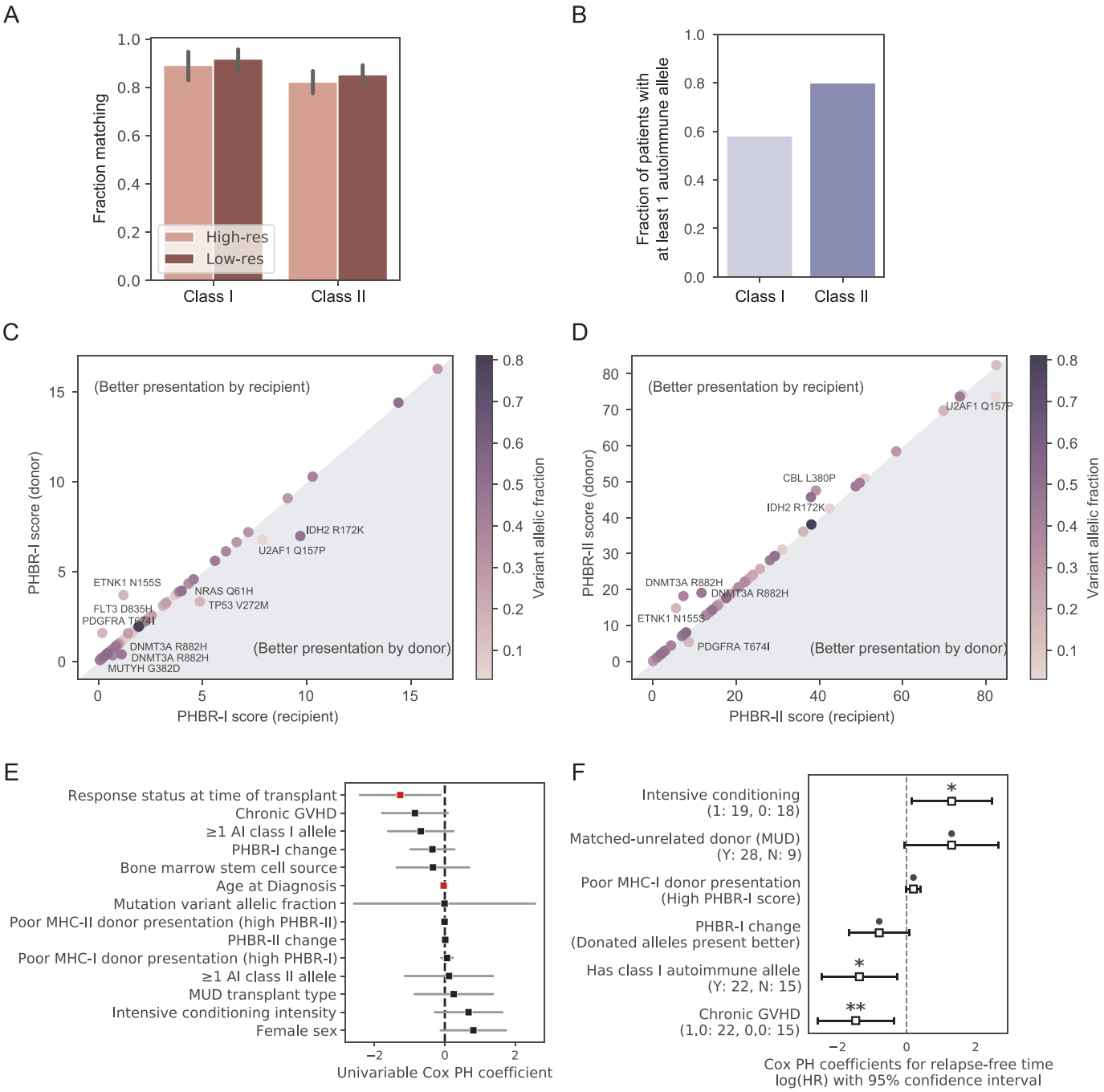

Figure 1. Cohort overview. (A) Barplot showing the number of matched HLA alleles at low-resolution, one-field (e.g., HLA-A*01) and high-resolution, or two-field (e.g., HLA-A*01:01) resolution between donor and recipient. This shows high concordance between matched donor and recipient HLA allele types. High-res: HLA types match to three-field resolution. Low-res: HLA types match to two-field resolution. (B) Barplot showing the fraction of all patients ($N = 55$) with at least one class I or II autoimmune allele. Scatterplots of (C) PHBR-I and (D) PHBR-II presentation scores for donor versus recipient HLA alleles. Lower PHBR scores indicate better presentation and vice versa. Mutations with differing PHBR presentation scores for donor versus recipient HLA types are labeled. In both C and D, mutations in the gray-shaded triangle are predicted to be better presented by the donor than by recipient HLA alleles. Points along the y-x line indicate no change in presentation, and points in the white upper triangle indicate mutations more poorly presented by the donor HLA alleles. (E) Relapse-free time Cox PH analysis in a univariable model testing independent association with relapse-free time for all 14 variables evaluated and (F) multivariable model for variables retained after backward selection for relapse-free time, for patients ($n = 37$) with mutations with PHBR scores. The number of patients in each dichotomous category is indicated; PHBR scores and changes are continuous. The box indicates log(hazard ratio), and the whiskers indicate standard error. Negative log(HR) scores correspond to a reduced risk of relapse. ** indicates $p \leq 0.01$, * indicates $p \leq 0.05$, • indicates $p \leq 0.1$. Red boxes indicate statistical significance $p < 0.05$ before multiple testing Benjamini Hochberg correction; there were no significant variables after correction. Thus, panel F indicates that in multivariable analysis, GVHD, and autoimmune allele carrier status were significantly associated with decreased relapse hazard ratio, while intensive conditioning was associated with a higher relapse hazard, and MUD status and factors related to MHC class I presentation are trending. Abbreviations: AI: autoimmune; GVHD: graft versus host disease; HLA: human leukocyte antigen; MHC: major histocompatibility complex; MUD: matched unrelated donor; PH: proportional hazard; PHBR: patient harmonic mean best rank presentation score; res: resolution.

$p = 0.01$); the association of autoimmune allele carrier status with relapse-free time did not reach significance (HR, 0.37; $p = 0.095$). Poorer potential to present somatic mutations via MHC-I was significantly associated with an increased risk of death (HR, 1.41; $p = 0.02$).

DISCUSSION

Patients with myeloid malignancies who relapse after allo-HSCT have limited therapeutic options. Here, we found that characteristics of the HLA genotype are associated with longer relapse-free time and overall survival. Specifically, individuals carrying a class I autoimmune HLA allele had longer relapse-free and overall survival, and this effect was independent of disease status at transplant. Poor presentation of driver mutations by the donor HLA type was significantly associated with worse overall survival and trended toward being a risk factor for shorter relapse-free survival ($p < 0.06$). Few patients had HLA mismatches, but in those cases, we identified some differences in the potential of the donor HLA type to present driver mutations detected via panel sequencing. The improved potential of the donor MHC I to present driver mutations trended toward better relapse-free survival ($p < 0.07$) and was significantly associated with overall survival ($p < 0.01$).

The HLA is a known factor in the dynamics of allo-HSCT response. Recognition of mismatched HLA can lead to relapse post-allo-HSCT, and loss of mismatched alleles is an established mechanism of escape from T-cell alloreactivity.[21,22] Studies have evaluated the relationship between mismatch at specific HLA genes or even alleles and patient outcomes.[23–26] Our study does not focus on individual alleles, which may be the target of immunity themselves, but rather on the potential of a given HLA genotype to mediate effective neoantigen-directed immune responses. This is made possible because we had somatic mutation profiling for most patients.

While HLA alleles must be carefully matched to avoid severe and potentially fatal GVHD, our work suggests that small differences in donor and recipient alleles may be able to improve outcomes without substantially increasing risk of immune rejection. Still, because some association has been reported between GVHD and autoimmune alleles,[27] prioritizing donor HLA types with an autoimmune allele could increase the risk of adverse effects. Autoimmune allele presence was not associated with chronic GVHD in our cohort ($N = 55$; Fisher exact odds ratio = 0.6; $p = 0.4$), and the frequency of autoimmune alleles was similar to that of other cancer cohorts (10,428 TCGA samples; Pearson R, 0.9; $p = 6.4e^{-4}$). Although none of the patients gained or lost an autoimmune-associated allele through allo-HSCT, one patient in the larger cohort gained the HLA-C12:03 autoimmune allele after the transplant. During almost 2 years of follow-up this patient did not relapse after the transplant and had chronic and acute GVHD.

Immune checkpoint blockade has been proposed as a strategy to promote GVL while carefully mitigating or maintaining patient GVHD.[28] Of note, antibodies against programmed cell death protein 1 (anti-PD-1 therapy) induced high levels of cytotoxic T-lymphocyte associated protein 4 positive (CTLA4+) lymphocytes and a delayed increase in PD-1+ cells in responding patients, suggesting that a temporary loss of PD-1-mediated self-tolerance enhanced GVL effects. In mice, genetic loss of CTLA4, a strong mediator of peripheral self-tolerance, produced fatal autoimmunity.[29]

T cell–replete allo-HSCT relies heavily on antigen-specific T-cell responses to generate a GVH effect. In this context, CTLA4 blockade could augment the GVL effect to prevent relapse. HLA differences between donor and recipient may increase the efficacy of this strategy. In a mouse model of MHC-disparate allogeneic transplantation, anti-CTLA4 given early in the transplant course increased GVHD or graft rejection (depending on conditioning intensity). Delayed anti-CTLA4 administration produced limited GVHD while triggering profound GVL effects against host-derived AML cells.[30]

Limitations

We note that our study is limited by sample size and that data were collected from a real-world cohort. The lack of availability of RNA-sequencing data limited our ability to evaluate HLA allele and mutation expression. We also did not have data on autoimmune sequelae, postconditioning lymphopenia or lymphodepletion, or non-HLA mismatch mechanisms, such as KIR haplotypes or donor HLA antibodies. Detection and interpretation of effects related to HLA class II was impeded because we only had complete class II HLA types for half of the cohort. Undetected immune evasion in our cohort may have confounded analysis of MHC-II association with relapse-free time. Because of these limitations, performing validation studies in larger and better-annotated cohorts will be critical. Even so, our study suggests the importance of MHC-based mutanome-derived neoantigen presentation and autoimmune alleles in predicting allo-HSCT response.

CONCLUSION

In this single-institution, retrospective study of patients receiving allogeneic hematopoietic stem cell transplants, patients carrying one or more autoimmune alleles had longer relapse-free and overall survival. Because of strict HLA type matching, only a minority of cases had HLA mismatch; however, for cases in which the mismatch occurred, more effective presentation of driver mutations by the donor alleles was significantly associated with longer overall survival. Follow-on studies in larger cohorts with additional covariates will be critical to further explore these findings and gain more mechanistic insight.

Acknowledgment

Autoimmune allele frequencies used here for comparison were based upon data generated by the TCGA Research Network: https://www.cancer.gov/tcga.

Data Availability

Somatic mutations and HLA donor and recipient alleles are available from the authors upon reasonable request.

Supplemental Material

Supplemental materials are available online with the article.

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