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# Scoring HLA Class I Mismatches by HistoCheck Does Not Predict Clinical Outcome in Unrelated Hematopoietic Stem Cell Transplantation

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Currently, there is no well-accepted rating system for reliably predicting which HLA-mismatched (MM) unrelated donor should be selected for a patient without an HLA allele-matched donor. We evaluated the ability of an MM ranking system, HistoCheck, to predict the risk associated with HLA class I disparity in a population of 744 single allele or antigen HLA-A, -B, or -C MM myeloablative unrelated donor hematopoietic stem cell transplantation recipients with acute myelogenous leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, or myelodysplastic syndrome, facilitated through the National Marrow Donor Program between 1988 and 2003. Multivariate models were used to adjust for other significant clinical risk factors. HLA MMs were scored using the HistoCheck Web-based tool, and the patients were divided into 4 quartiles: dissimilarity score (DSS) 1.04-2.84 (allele MM), DSS >2.84-13.75 (allele and antigen MM), DSS >13.75-19.39 (antigen MM), and DSS >19.39-36.62 (antigen MM). Using the lowest scoring quartile as the reference, the DSS groups were evaluated for associations with relapse, treatment-related mortality, acute and chronic graft-versus-host disease, leukemia-free survival, and overall survival in the entire cohort and also in subset analyses by disease and disease stage. No significant associations were found between DSS and any outcomes in the overall cohort using the quartile categories or treating DSS as a continuous variable. Higher DSS scores were associated with decreased engraftment in early-stage disease ($P = .0003$), but not in other disease stages. In summary, DSS does not correlate with transplantation outcomes, and the HistoCheck scoring system does not provide an effective technique for ranking HLA class I MM. The dataset used in this study is available to evaluate new algorithms proposed for donor selection.

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**KEY WORDS:** Unrelated donor, HLA mismatch, Transplant

## INTRODUCTION

Although HLA matching for alleles of HLA-A, -B, -C, and -DRB1 (ie, 8/8 matches) has been shown to optimize survival after hematopoietic stem cell transplantation (HCT) [1,2], 30%-40% of HCTs facilitated through the National Marrow Donor Program (NMDP) are mismatched at 1 or more loci [3]. Mismatching for a single allele (7/8 match) results in a 10% reduction in average overall survival (OS) compared with an 8/8 match; however, this risk may be acceptable compared with that from alternative therapies.

No rating system exists to reliably predict which HLA-mismatched (MM) unrelated donor should be selected for a patient who does not have an HLA allele-matched donor. Previous Center for International Blood and Marrow Transplant Research (CIBMTR) studies have evaluated MM donor selection based on serologically cross-reactive epitope groups (ie, CREGs) [4], amino acid triplets (ie, HLA MatchMaker) [5], and

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the number of amino acid differences [6,7] and found that these selection strategies do not predict outcomes. Although studies of donor–recipient pairs from the Japanese Marrow Donor Program have suggested a differential impact of specific HLA mismatches [8-10], a recent CIBMTR report discussed the difficulties in evaluating the impact of specific allele mismatches in the context of mismatches at other loci [9]. Thus, evaluating various HLA-based donor selection criteria continues to be a priority to improve the outcomes of HCT with HLA-MM donors.

In 2002, Elsner and Blasczyk [11] suggested that a rating system based on structural data of HLA class I molecules might be used to identify acceptable mismatches. Their algorithm is based on the functional similarity of amino acids using a distance matrix developed by Risler et al. [12], and on the frequency of amino acid substitutions in proteins. Risler scores are further weighted based on the position of the disparity in the HLA molecule (ie, location in the peptide binding or T cell receptor recognition site). In 2004, Blasczyk et al. [13] extended this algorithm to include evaluation of class II molecules and developed an Internet-based software tool, HistoCheck, for assigning scores (http://www.histocheck.de/).

In 2004, Shaw et al. [14] used HistoCheck to score 26 single HLA-A allele MM recipients and 9 single HLA-B allele MM recipients in the Anthony Nolan clinical database. These recipients were matched for alleles at the other key HLA loci. The investigators compared the clinical outcomes with the HistoCheck scores. No associations with neutrophil engraftment, acute or chronic graft-versus-host disease (GVHD), relapse, or survival were found in this small study. In 2011, Askar et al. [15] evaluated the correlation between HistoCheck score and high-risk HLA allele MM combinations previously described by Kawase et al. [9]. They found no difference in HistoCheck score distribution between high-risk and low-risk allele combinations, and the HistoCheck score did not correlate with mismatch risk stratification in the Japanese population. We used CIBMTR data to evaluate the HistoCheck algorithm in a larger study to provide guidance for HLA-MM donor selection.

## MATERIALS AND METHODS

### Study Population

The study included patients reported to the NMDP who underwent HCT from an unrelated donor between 1988 and 2003. All patients and their donors were fully HLA-typed at high resolution through the NMDP's ongoing retrospective high-resolution typing project. The study included 744 donor–recipient pairs with a single HLA-A, -B or -C mismatch. All cases were matched for HLA-DRB1 and -DQB1. Eligible diagnoses included acute lymphoblastic leukemia (ALL; n = 199), acute myelogenous leukemia (AML; n = 224), chronic myelogenous leukemia (CML; n = 259), and myelodysplastic syndrome (MDS; n = 62). Early-stage disease was defined as AML or ALL in first complete remission, CML in first chronic phase, and MDS subtype refractory anemia. Intermediate-stage disease was defined as AML or ALL in second or subsequent complete remission or in first relapse and CML in accelerated phase or second chronic phase. Advanced-phase disease was defined as AML in second or subsequent relapse or primary induction failure, CML in blast phase, MDS subtypes refractory anemia with excess blasts or in transformation, or unclassified MDS. All patients received a standard myeloablative conditioning regimen. The same dataset has been used to evaluate another matching algorithm, HLA Matchmaker [5].

Patients who received conditioning regimens of lower intensity, those who underwent second or subsequent HCT, or surviving patients who did not provide signed informed consent to allow analysis of their clinical data or HLA typing of stored NMDP Research Repository samples were excluded. All surviving recipients included in this analysis were contacted retrospectively and provided informed consent for participation in the NMDP research program. To adjust for the potential bias introduced by exclusion of nonconsenting surviving patients, a modeling process randomly excluded the same percentage of deceased patients using a biased coin randomization, with exclusion probabilities based on characteristics associated with not providing consent for use of the data in survivors [1].

### Evaluation of HLA Disparity

HLA class I mismatches were scored by the HistoCheck Web-based tool [13] (http://www.histocheck.de/). Patients were divided into 4 quartiles for analysis based on dissimilarity score (DSS): group 1, DSS 1.04-2.84; group 2, >2.84-13.75; group 3, >13.75-19.39; and group 4, >19.39-36.62. In addition, all analyses included an evaluation of DSS score as a continuous variable. All cases were matched for HLA-DRB1 and -DQB1. HLA-DPB1 matching was available for all cases, but was not considered in the analysis.

### Clinical Endpoints

The association between HistoCheck score and outcomes was evaluated, with disease-free survival (DFS) as the primary endpoint and acute GVHD grade II-IV, chronic GVHD, treatment-related mortality (TRM), relapse, OS, and neutrophil engraftment as secondary endpoints. DFS was defined as relapse or death from any cause, with patients who were alive and