ASBMT
American Society for Blood and Marrow Transplantation

HLA-C Antigen Mismatch Is Associated with Worse Outcome in Unrelated Donor Peripheral Blood Stem Cell Transplantation

Ann Woolfrey,[1] John P. Klein,[2] Michael Haagenson,[3] Stephen Spellman,[4] Effie Petersdorf,[1] Machteld Oudshoorn,[5] James Gajewski,[6] Gregory A. Hale,[7] John Horan,[8] Minoo Battiwalla,[9] Susana R. Marino,[10] Michelle Setterholm,[4] Olle Ringden,[11] Carolyn Hurley,[12] Neal Flomenberg,[13] Claudio Anasetti,[14] Marcelo Fernandez-Vina,[15] Stephanie J. Lee[1]

The association between HLA matching and outcome in unrelated-donor peripheral blood stem cell (PBSC) transplantation has not yet been established. In the present study, a total of 1933 unrelated donor–recipient pairs who underwent PBSC transplantation between 1999 and 2006 for acute myelogenous leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, or chronic myelogenous leukemia and received high-resolution HLA typing for HLA-A, -B, -C, -DRB1, -DQA1, and -DQB1 were included in the analysis. Outcomes were compared between HLA-matched and HLA-mismatched pairs, adjusting for patient and transplant characteristics. Matching for HLA-A, -B, -C, and -DRB1 alleles (8/8 match) was associated with better survival at 1 year compared with 7/8 HLA-matched pairs (56% vs 47%). Using 8/8 HLA–matched patients as the baseline (n = 1243), HLA-C antigen mismatches (n = 189) were statistically significantly associated with lower leukemia-free survival (relative risk [RR], 1.36; 95% confidence interval [CI], 1.13-1.64; $P = .0010$), and increased risk for mortality (RR, 1.41; 95% CI, 1.16-1.70; $P = .0005$), treatment-related mortality (RR, 1.61; 95% CI, 1.25-2.08; $P = .0002$), and grade III-IV graft-versus-host disease (RR, 1.98; 95% CI, 1.50-2.62; $P < .0001$). HLA-B antigen or allele mismatching was associated with an increased risk for acute GVHD grade III-IV. No statistically significant differences in outcome were observed for HLA-C allele (n = 61), HLA-A antigen/allele (n = 136), HLA-DRB1 allele (n = 39), or HLA-DQ antigen/allele (n = 114) mismatches compared with 8/8 HLA–matched pairs. HLA mismatch was not associated with relapse or chronic GVHD. HLA-C antigen–mismatched unrelated PBSC donors were associated with worse outcomes compared with 8/8 HLA–matched donors. The study's limited power due to small sample size precludes conclusions about other mismatches.

Biol Blood Marrow Transplant 17: 885-892 (2011)

KEY WORDS: HLA Mismatch, Hematopoietic cell transplantation, HLA-C antigen, Graft-vs-Host disease, Disease free survival

INTRODUCTION

Unrelated donors have provided a vital resource for patients who do not have an HLA-matched relative. Approximately 50% of allogeneic hematopoietic cell transplantations (HCTs) reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) use unrelated donors. Over the past decade, the number of peripheral blood stem cell (PBSC) grafts facilitated by the National Marrow Donor Program (NMDP) has grown substantially, such that currently around 75% of unrelated grafts are PBSC (NMDP

From the [1]Fred Hutchinson Cancer Research Center, Seattle, Washington; [2]Medical College of Wisconsin, Milwaukee, Wisconsin; [3]Center for International Blood and Marrow Transplant Research, Minneapolis, Minnesota; [4]National Marrow Donor Program, Minneapolis, Minnesota; [5]Europdonor Foundation, Leiden, The Netherlands; [6]Oregon Health and Science University, Portland, Oregon; [7]All Children's Hospital, St Petersburg, Florida; [8]Emory University, Atlanta, Georgia; [9]Roswell Park Cancer Institute, Buffalo, New York; [10]University of Chicago Medical Center, Chicago, Illinois; [11]Karolinska Institute, Stockholm, Sweden; [12]Georgetown University Medical Center, Washington, DC; [13]Thomas Jefferson University, Philadelphia, Pennsylvania; [14]H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida; and [15]M.D. Anderson Cancer Center, Houston, Texas.

Financial disclosure: See Acknowledgments on page 891.

Correspondence and reprint requests: Ann Woolfrey, MD, Fred Hutchinson Cancer Center, 1100 Fairview Avenue North D5-280, Seattle, WA 98109 (e-mail: awoolfre@fhcrc.org).

Received June 25, 2010; accepted September 16, 2010

1083-8791/$36.00
doi:10.1016/j.bbmt.2010.09.012

statistics). In addition, approximately 30% of all PBSC products are mismatched for one or more of the recipient's HLA loci. Previous NMDP/CIBMTR studies evaluating the effects of HLA mismatch included predominantly bone marrow (BM) recipients. Given that the number of unrelated donor PBSC transplantations in the NMDP registry has now reached sufficient quantity for preliminary analysis, the present study was designed to determine the association of HLA mismatch in PBSC transplantation with survival, relapse, graft-versus-host disease (GVHD), and transplantation-related mortality (TRM).

Previous studies from the NMDP/CIBMTR in the setting of BM transplantation have shown an association between HLA mismatch and with worse outcomes [1,2]. In particular, single mismatches at HLA-A, -B, -C, or DRB1 were associated with increased risk for TRM and acute GVHD compared with 8/8 HLA–matched pairs. Isolated HLA-DQ mismatches did not appear to be detrimental. Reports from the Fred Hutchinson Cancer Research Center and the Japanese Marrow Donor Program also support the concept that disparities involving HLA class I alleles are independent risk factors for acute GVHD, TRM, and overall survival [3,4].

In the 1990s, collection of granulocyte-colony stimulating factor (G-CSF)-mobilized PBSCs was introduced as an alternative to BM donation for volunteer unrelated donors [5]. Advantages of PBSCs over BM include more rapid engraftment of neutrophils and platelets for patients and the ability to avoid the operating room for donors and physicians. Retrospective studies have found similar rates of acute GVHD, TRM, relapse, and survival with unrelated donor PBSCs and BM, but an increased incidence of extensive chronic GVHD with PBSCs [6].

Although PBSCs have supplanted BM as the most common source of unrelated hematopoietic stem cells, the impact of HLA mismatch on outcomes after unrelated PBSC transplantation has not yet been well studied. The present study was undertaken to compare the outcomes of HLA-mismatched compared with HLA-matched unrelated donor transplantation using PBSCs as the graft source. Identification of mismatched HLA loci associated with particularly poor outcomes may help guide donor selection when an 8/8 HLA–matched donor is not available and allogeneic transplantation is recommended.

PATIENTS AND METHODS

Study Population

The study population included all patients reported to the NMDP/CIBMTR registries who received an unrelated PBSC transplant between 1999 and 2006 for acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), or chronic myelogenous leukemia (CML) for whom retrospective high-resolution HLA typing results were available for both patient and unrelated donor. Diseases were categorized as early phase (acute leukemia in first complete remission [CR1], CML in first chronic phase, and MDS-refractory anemia [RA]), intermediate phase (acute leukemia in second remission [CR2] and CML in accelerated or second chronic phase), or advanced phase (acute leukemia advanced beyond CR2 or not in remission, CML in blast crisis, MDS-RA with excess blasts [RAEB] or in transformation [RAEB-T]). Conditioning regimens were defined as "myeloablative" if the patient received total body irradiation (TBI) at a dose >500 cGy if given as a single dose or >800 cGy if given in fractions, received busulfan at a dose ≥ 9.5 mg/kg, or received melphalan at a dose >150 mg/m^2. All other regimens were considered either reduced-intensity conditioning (RIC) or nonmyeloablative (NM) conditioning [7]. All patients received T cell–replete grafts.

All patients included in this study signed informed consent for reporting of clinical information to the NMDP/CIBMTR registries in accordance with the Declaration of Helsinki. Twenty-seven (1.3%) of otherwise eligible patients were excluded to account for lack of consent to use the data of surviving patients or to adjust for potential bias by excluding appropriately 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.

HLA Typing

High-resolution typing for HLA-A, -B, -C, -DRB1, -DQA1, -DQB1, -DPA1, and -DPB1 was performed as described previously [1]. Low-resolution (serologic or antigen level) disparities involved conversion of the DNA-based typing to its lower-level serologic equivalent, usually by collapsing the 4-digit typing result back to its first 2 digits, with the exception of a few HLA-B alleles that were mapped to their corresponding serologic specificities. Antigen and allele mismatches at HLA-DRB1 were combined. Mismatches at HLA-DQ were scored if there was disparity for either the -DQA1 or the -DQB1 sequence, because both -DQA1 and -DQB1 genes contribute to the expression of a single heterodimeric HLA-DQ protein. HLA-DQA1 was not considered for determination of antigen matching. Directional mismatches (graft-vs-host or host-vs-graft) were considered appropriate in the analysis of GVHD and engraftment, as described previously [8]. Mismatches at homozygous alleles were considered single mismatches.

Biostatistical Methods

Probabilities for mortality and leukemia-free survival (LFS) were calculated using the Kaplan-Meier estimator, and survival curves were compared using the log-rank