Biology of Blood and Marrow Transplantation 14:45-53 (2008)

1083-8791/08/1409-0001$32.00/0
doi:10.1016/j.bbmt.2008.06.014

National Marrow Donor Program HLA Matching Guidelines for Unrelated Adult Donor Hematopoietic Cell Transplants

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STATEMENT OF CONFLICT OF INTEREST: See Acknowledgements on page 52.

Received February 20, 2008; accepted June 17, 2008

This commentary, sponsored by the National Marrow Donor Program® (NMDP), provides updated guidelines for unrelated hematopoietic cell donor selection in the format of frequently asked questions (FAQ). These revisions to the guidelines, initially published in 2003 [1], are based on current and relevant data that we believe represent optimal donor-recipient matching criteria.

WHAT IS THE PURPOSE OF THE NMDP DONOR-RECIPIENT MATCHING CRITERIA?

Since its inception in 1987, the NMDP has required evaluation of donor-recipient histocompatibility matching (HLA-A, -B, and -DR) prior to unrelated hematopoietic cell transplantation (HCT). The minimum acceptable match was originally defined by serologic splits (antigen level of resolution) at these 3 loci (6 possible antigens) and required at least 5 matches, that is, a 5 of 6 match. This requirement has changed little over the years. Currently, to request a donor for transplantation, the *minimal acceptable level of matching* remains a 5 of 6 match for HLA-A, -B, and -DRB1. Although only evaluated at antigen level of resolution for donor release, each of these 3 loci *must be typed at high-resolution by DNA-based methods*. High-resolution typing is defined as the identification of alleles based on differences in the antigen recognition site (ARS) domains (Exons 2 and 3 of Class I and exon 2 of Class II genes). Alleles that are identical in the ARS domain have not been shown to have immunologic differences, and the standard practice of many transplant centers is to accept these alleles as a match [2]. In 2005, a requirement for HLA-C typing was added. The most recent studies have clearly shown that transplant outcomes can be improved by matching strategies that increase the overall degree of HLA compatibility above the minimum (eg, high-resolution matching, matching for HLA-C, -DP, -DQ, and haplotypes) [3].

WHAT LITERATURE DISCUSSES THE IMPACT OF HLA ON HEMATOPOIETIC CELL TRANSPLANTATION OUTCOME?

There are many studies that evaluate the role of HLA matching in outcome. Our initial recommendations were based on large, contemporary studies from 3 groups that have evaluated most of the HLA loci using DNA testing to resolve alleles [4-9]. The number of pairs evaluated through the NMDP network has now increased to 3857, and further analysis of outcome has been published by Lee et al. [10].

OF THE SEVERAL OUTCOME MEASURES, WHICH IS THE MOST IMPORTANT TO CONSIDER?

The outcome of primary importance is survival. However, it may be important to consider the effect of HLA matching on the incidence of acute and chronic graft-versus-host disease (aGVHD, cGVHD), treatment-related mortality (TRM), or graft rejection. Although the impact of HLA matching on survival is

Table 1. *Effect of HLA Mismatching on Survival*

Study	A	B	C	DRB1
JMDP [4]	decrease* (merged A+B)		no effect†	no effect (merged DR+DQ)
FHCRC [8]	no effect	no effect	decrease	no effect
NMDP [9]	decrease	decrease	decrease	decrease
NMDP [10]	decrease	no effect	decrease	decrease

*"Decrease" means a decrease in survival caused by an HLA locus mismatch.
†"No effect" means no impact of a mismatch.

considered to be the primary determinant for donor selection, the impact on other outcome measures may be important in developing a specific risk-adapted treatment strategy for the recipient.

WHAT DO THE PUBLISHED STUDIES SUGGEST REGARDING THE ASSOCIATION BETWEEN HLA MATCHING AND PATIENT OUTCOMES?

Associations between HLA disparity and survival differ in the studies. The differences are detailed in Table 1, and are likely the result of differences in study design as described below.

WHY DO STUDIES GIVE DIFFERENT RESULTS?

Differences in the study designs are summarized in Table 2. Sample size dictated how the mismatches were classified across the multiple loci, and different studies collapsed the loci differently. For example, Morishima et al [4] combined mismatches at HLA-A and -B, and at -DR and -DQ, to get a larger sample size to detect differences among groups. Petersdorf et al [5-7] collapsed mismatches based on class I versus class II loci. In the more recent NMDP studies, Flomenberg et al [9] and Lee et al [10] looked at each locus separately. The former analysis employed multivariate modeling to evaluate mismatches across all loci studied [9]. The more recent study used "subset analysis," which means that in examining mismatches at a particular locus, all other loci were high-resolution matched [10]. Flomenberg et al [9] found a direct association between the number of mismatched HLA alleles and survival, but did not identify a locus-specific effect. In contrast, Morishima et al and Lee et al identified locus-specific effects, albeit with somewhat differing results. Morishima et al identified the combined A/B group as having a stronger effect on survival than the other loci. However, because this combined A/B group included single allelic mismatches for A or B as well as mismatches for both A and B, the observed effect may have been magnified by these multiple mismatches. Lee et al found that a single mismatch either at HLA-A or HLA-DRB1 had a more profound effect on survival compared to HLA-B or HLA-C. This study also found that a high-resolution mismatch had an effect similar to an antigen level mismatch. The differences between the findings of Morishima et al and Lee et al may be explained by the different study populations. The distribution of alleles in the U.S. and Japanese populations was quite different, with little overlap in the alleles and mismatches represented in the 2 populations. There may be other immunologic factors that vary among ethnic/racial groups and influence the relationship between HLA matching and transplant outcomes. Other patient-related factors appear to be important, particularly diagnosis and phase of disease. Both Petersdorf et al [8] and Lee et al found that the impact of HLA-mismatching was more pronounced among patients with "low-risk" disease (generally defined as chronic myelogenous leukemia (CML)-chronic phase and/or early-phase myelodysplastic syndromes (MDS) and/or acute leukemia in first remission). In contrast, for "high-risk" patients, the increase in overall mortality associated with advanced disease status appears to obfuscate the benefit of HLA matching.

Taken together, these studies support several general concepts in analyzing the effect of HLA mismatch on survival. First, there appears to be a direct association between the number of HLA mismatches and the risk for mortality. Second, mismatching between donor and recipient appears to have a greater impact on patients with "low-risk" disease. Finally, specific mismatches among the HLA-loci may be tolerated better within certain ethnic groups.

WHAT DOES THE NMDP SUGGEST AS OPTIMAL MATCH CRITERIA?

The reports reviewed above show that high-resolution matching for HLA-A, -B, -C, and -DRB1 maximizes posttransplant survival (Table 3). Thus, whenever possible, donors who are high resolution matched at these 4 HLA loci should be sought. This does not imply that the unavailability of such a well-matched donor is a contraindication for transplant. If a mismatch is unavoidable, a single mismatched donor (-A, -B, -C, or -DRB1) should be sought. From the NMDP data reviewed above, it appears that high-resolution mismatches have a negative impact similar to antigen-level mismatches [10]. The sole exception may occur at HLA-C where high-resolution

Table 2. *Similarities and Differences in Design of the Studies*

	JMDP Morishima et al. [4]	FHCRC Petersdorf et al. [8]	NMDP Flomenberg et al. [9]	NMDP Lee et al. [10]
Transplant source	Multicenter	Single center	Multicenter	Multicenter
Stem cell source	Marrow	90% Marrow	Marrow	94% Marrow
Patient diseases	AML, ALL, CML, MDS, SAA, others	CML, AML, ALL, MDS	CML, AML, ALL, MDS, SAA, others	CML, AML, ALL, MDS
Patient ages	0-51, median 23	1-62, median 35	0-66, median 30	0-65, median 33
Patient race	Japanese	Predominantly White from U. S.	Predominantly White from U. S.	Predominantly White from U.S.
No pairs evaluated	1298	948	1874	3857
HLA loci characterized*	[A,B] [C] [DRB1, DQB1]	[A] [B] [C] [DRB1] [DQB1] [DPB1]	[A] [B] [C] [DRB1] [DQA1, DQB1] [DPA1, DPB1]	[A] [B] [C] [DRB1] [DQA1, DQB1] [DPA1, DPB1]
Match criteria for patients entered into study	Antigen A, B, DR matched only	Antigen matching at A, B, DR with Dw or DRB1 allele matching; mismatching allowed within guidelines described in 1998 study	Antigen matching at A, B and antigen or high resolution level at DRB1; 5 of 6 minimum match	Antigen matching at A, B and antigen or high resolution level at DRB1:5 of 6 minimum match
Level of match investigated	High resolution	High resolution and antigen level	High resolution and antigen level for A, B, C, DRB1; any level for DQ and DP	High resolution and antigen level

SAA indicates severe aplastic anemia.
*[Brackets] indicate HLA loci grouped together for analysis.]

mismatches appear to be better tolerated; however, this particular aspect needs further study. In the NMDP data, mismatches at HLA-B and -C may be less detrimental than those at HLA-A and -DRB1, but this sense is tempered by limited numbers of transplants and by the lack of allele-specific mismatch analyses. That is, within the existing dataset, the distribution of "permissive" and "nonpermissive" mismatches at each locus may be nonuniform. For example, more permissive mismatches within the HLA-B locus mismatched dataset would diminish the negative impact of mismatching for HLA-B. Clearly, more research is needed in this area.

Of importance is the observation in the NMDP data that mismatches at HLA-DQ do not show the same overall negative impact as those at the 4 other HLA loci [10], but DQ mismatches may be important in certain disease subsets or when coupled with mismatches at other loci [3,8]. Similar to HLA-DQ, mismatches at HLA-DP do not seem to play a role in overall mortality. In the Lee et al. [10] study, HLA-DP mismatching was associated with an increased risk for aGVHD; however, there was no impact on overall survival (OS), and only a suggestion of an association with increased risk of treatment-related mortality. In addition, Shaw et al [11] showed a similar association between HLA-DP mismatches and an increased risk for aGVHD; however, this negative impact may be offset by a decreased risk for disease relapse.

WHAT HLA MATCHING IS REQUIRED FOR STEM CELL SOURCES OTHER THAN MARROW?

A recent Center for International Blood and Marrow Transplant Research (CIBMTR) analysis of unrelated donor transplantation comparing bone marrow to peripheral blood stem cells (PBSCs) as hematopoietic cell sources in adults with leukemia and myelodysplastic syndrome showed a significantly higher risk of grades II-IV aGVHD and cGVHD following unrelated donor PBSC transplantation with no survival benefit for PBSC recipients [12]. The data currently available regarding the role of HLA mismatch in transplant outcome are generated from series using bone marrow as a stem cell source. Additional analyses of transplants using PBSCs as a stem cell source are needed to determine if the same principles apply. One alternative stem cell source for cases without a suitable donor is the use of umbilical cord blood. Recent studies have established the utility of umbilical cord blood, particularly as a treatment for childhood leukemia [13]. The impact of HLA matching on outcomes following unrelated donor umbilical cord blood transplantation was recently summarized by the NMDP [14].

Table 3. *Typing and Matching of Potential Donor and Patient HLA Loci*

HLA Locus	Search Strategy	Matching	Resolution of Testing
A	Yes	Recommended	High
B	Yes	Recommended	High
C	Yes	Recommended	High
DRA	No	No	
DRB1	Yes	Recommended	High
DRB3, DRB4, DRB5	Yes (DRB1 association)*	Unknown†	
DQA1	No	No	
DQB1	Yes (DRB1 association)*	Uncertain‡	
DPA1	No	No	
DPB1	No	Uncertain	

*Certain alleles at one locus are preferentially associated with some but not other alleles at a second locus. Knowledge of the patient's HLA-DRB3/4/5 or DQB1 assignment provides a check on the patient's typing by association, can be used to select the best matched donor from potential donors equivalently matched at HLA-A, -B, -C, and -DRB1 and, for DQB1, permits HapLogic match evaluation and prediction.

†Unknown indicates that the impact of matching has not been evaluated.

‡Uncertian indicates that studies as to the importance of these loci in matching. Matching may be necessary if patient possesses anti-HLA antibodies to the mismatched antigens.

WHAT NON-HLA DONOR CHARACTERISTICS SHOULD I CONSIDER?

Other non-HLA factors are often considered when selecting donors including CMV negative serology (for CMV-negative patients), male sex, younger age, ABO compatibility, larger body weight, and matched race. In the recent NMDP analysis by Lee et al [10], none of these factors were important when compared to HLA matching. This finding contrasted with another NMDP study by Kollman et al [15], which found that, in addition to HLA matching, younger donor age was associated with better survival. In the Kollman study, there was also no significant association of donor CMV serology, sex, parity, race, or ABO matching and recipient survival. Female donors with multiple pregnancies were associated with a higher risk of cGVHD, but there was no impact on survival. Several variables likely explain the different findings in these 2 studies including the absolute patient numbers, the definitions of HLA matching, duration of follow-up, and the consideration of center effects.

HOW DO I SEARCH FOR THE BEST DONOR?

Each search should be initiated based on high-resolution HLA assignments of the patient. HLA-A, -B, -C, and -DRB1 loci should be characterized because they are important in matching; others assist in designing an efficient search strategy for the patient (Table 3). The search report received from the NMDP now contains information that indicates the likelihood of each potential donor carrying the same alleles as the searching patient. This is especially helpful when faced with a long list of potential adult or cord blood donors but only sufficient resources and/or time to type a few of the potential donors at higher resolution. The NMDP search algorithm HapLogic^{SM} uses data on the frequencies of alleles and haplotypes in human populations to predict the probability of high-resolution matches at individual HLA loci and at all key loci simultaneously (Figure 1).

The optimal number of potential donors to select from the search report should be individualized for each patient because many factors influence the likelihood of finding a compatible donor. Factors to be considered include the patient's alleles and haplotypes (ie, rare versus common), as well as clinical urgency. For patients with potential donors with a high probability of high-resolution matches as determined by HapLogic, high-resolution typing of a small number (eg, 3-5) of donors is usually sufficient. However, more than 1 donor should be selected because donors may be unavailable, mistyped, or not matched once high-resolution testing is complete. For patients with rare alleles and haplotypes where the likelihood of matching is low, 10 or more donors may be required to find the best match. In the latter situation, help should be immediately sought from in-house or NMDP histocompatibility experts to design an effective search strategy that may include evaluation of worldwide donor registries. Similarly, for a patient with clinical urgency, multiple donors should be simultaneously evaluated and typed.

WHEN SHOULD I LAUNCH AN INTERNATIONAL SEARCH FOR A DONOR?

The NMDP donor file includes volunteers from the U.S. as well as Norway, Sweden, Germany, and Israel. The NMDP also provides a general search of Bone Marrow Donors Worldwide (BMDW) as well as an automatic detailed search of certain international registries using the EMDIS (European Marrow Donor Information System) network that are readily accessible through NMDP software or by written request. The BMDW report is particularly helpful to set an optimal, but realistic, target for the donor search in relation to the number and details of the potential donors and the time and resources available for a particular patient. However, the decision on the overall search strategy and the usefulness of an extended international search must also take into account the variation of allele and haplotype frequencies in different geographic, racial, or ethnic groups. Whenever deemed useful, the NMDP can be asked to request search reports from additional registries and/or with relaxed matching criteria for difficult cases or specifically

Recipient:
NMDP RID:
Local ID:
TC Code:
Birth Date:
ABO: O +
CMV: Untested

Original Search: 2007-01-12
Date Formalized: 2007-01-23
Date of Search: 2007-08-21

Diagnosis: ACUTE MYELOGENOUS LEUKEMIA
Race (Ethnicity): White – Unspecified (NHIS)
Transfer:

Phen Seq	A	B	DRB1	DRB3	DRB4	DRB5	DQB1	C
1	0101	0702	07BPEJ		0101	0101	0202	0702
	2601	4403	15FX				0602	1601

Donor

ID Number			CMV Sts - Date	SIP = Sample at Repository/International Indicator/PBSC								Match Grade/Calculation				
S I P	Age	Sex/Pg	Status - Date													
M Cat	ABO	Prev Don	Release Code													
	Race (Ethnicity)			A	B	DRB1	DRB3	DRB4	DRB5	DQB1	C	A	B	DRB1	DQB1	C
0531-7947-9			P - 2007-02-20	0101	0702	07BPEJ		0101	0101	0202	0702	A	A	P	A	A
Y-Y	45	M	AV	2601	4403	15WU				0602	1601	A	A	P	A	A
6/6	A +	0	-									100%	100%	99%	100%	100%
White – North American (NHIS)												Pr(6)=99%			Pr(5)=0%	
0706-6535-1			U	01BMFN	07NTH	0701						P	P	P		
Y-Y	46	F	AV	26GAX	4403	1501						P	A	P		
6/6		0	-									99%	99%	99%	1%	64%
White – Northern European (NHIS)												Pr(6)=99%			Pr(5)=0%	
0320-1305-4			P - 2007-02-09	0101	0702	07BPEJ		0101	0101	0202	0702	A	A	P	A	A
N-Y	47	M	AV	2601	4403	15WU				0602	1601	A	A	P	A	A
6/6	A +	0	-									100%	100%	99%	100%	100%
White – North American or European												Pr(6)=99%			Pr(5)=0%	

Figure 1. Example of an NMDP search report. The columns labeled "Match Grade/Calculation" include a letter indicating the match status of each allele at the locus indicated (A, allele match; P, potential allele match), the probability of matching both alleles at the locus (100% for the first donor at each locus), and the probability of a 6/6 HLA-A,-B,-DRB1 allele match (Pr[6] 100% for first donor) and of at most a 5/6 allele match (Pr[5] 0%).

filtered match lists for searches with many donor candidates.

HOW LONG DO I SEARCH FOR DONORS?

For patients with common haplotypes, a suitably matched donor can usually be identified on the first match run. For patients with uncommon haplotypes, a well-matched donor may not be readily apparent on the initial match run. For these patients, we recommend that one request help from a local HLA laboratory or NMDP consultant to assist in identifying the best potential match.

If one is not able to identify an available, acceptably matched donor within the current NMDP Registry, it is very unlikely that newly recruited donors will match the patient in a useful time frame. The NMDP donor file contains nearly 7 million donors (~78% typed for HLA-A, -B, and -DR) and the NMDP search also provides a match report of an additional ~5 million donors listed in BMDW, so patients who are not able to find a suitably matched donor in this pool most likely have haplotypes that are infrequently represented. The NMDP adds an average of 30,000 new donors to the file monthly. The likelihood that a patient's type will be represented in those new recruits when it did not appear in the initial file of ~12 million is low. Therefore, it is recommended that one reevaluate the alternative treatment options for those patients and decide whether to reduce the matching requirements or select another therapy (eg, unrelated cord blood transplantation, a partially matched related donor transplantation, or nontransplant therapy). However, it should be recognized that search strategies can be significantly affected by the lack of financial resources. For some individuals, enlisting the assistance of an HLA expert can help maximize available resources by optimizing potential donor screening.

HOW SHOULD THE CLINICAL STATUS OF MY PATIENT INFLUENCE THE SELECTION OF THE DONOR?

The clinical status of the patient will influence donor selection. Patients with a relatively stable disease such as low-risk MDS or a non-SCID primary immune deficiency are less likely to deteriorate quickly, thus giving their physician time to search and identify the best matched unrelated donor. In contrast, patients with acute leukemia may have only a brief remission time in which transplant is feasible. A prolonged search time exposes patients to additional toxic chemotherapy, an increased risk of infection and risk of relapse. For these patients, a short search time and ongoing consideration of alternatives (such as using an unrelated cord blood unit, a mismatched unrelated donor, a haploidentical donor, or an investigational therapy) should be entertained. The risk from the underlying disease and the availability of therapeutic alternatives

also influences the degree of mismatch considered acceptable by the physician and patient. Besides considering differences in life expectancy, the quality of life associated with transplantation from the best available unrelated donor should be compared to the quality of life associated with alternative therapies.

HOW SHOULD POTENTIALLY MATCHED DONORS BE HLA TYPED?

Donors identified on the NMDP search report with the highest likelihood of matching the patient should undergo complete high-resolution testing to select the best HLA match. DNA-based testing methods must be used, and a reasonable effort made to identify the donor's HLA alleles (Table 3). Some loci should be characterized because they are key to matching; others (labeled unknown or uncertain) should be typed to allow selection of the best match once other donor characteristics have been taken into account. An HLA expert might recommend a strategy that initially targets selected loci for higher resolution typing to reduce the typing cost; however, this approach should be balanced against the patient's medical condition so as not to unduly delay an urgent transplant.

DOES THE RACE/ETHNICITY OF THE DONOR NEED TO BE THE SAME AS THE RACE/ETHNICITY OF THE RECIPIENT?

The direct answer to this question is no. However, some HLA alleles and haplotypes are distributed at different frequencies among different racial/ethnic groups. When searching for a donor, for some alleles, a high-resolution match is more likely to be found among persons of the same ethnicity as the patient. For alleles and haplotypes that are found frequently in several races/ethnicities, donors from these populations should be evaluated. HapLogic takes the race/ethnicity into account when predicting the likelihood of a high-resolution match. Once high-resolution matches are identified, the race/ethnicity of the matched donor should have no significant impact on the outcome of the transplant. When donor/recipient pairs matched at the antigen level for HLA-A and -B and at -DRB1 using DNA-based typing were compared, there was no advantage to being matched by race [9,10]. It should be recognized that the number of racially mismatched donor/recipient pairs in these studies was small, and further studies are needed to confirm these data.

HOW DO I SELECT THE BEST PARTIALLY MATCHED UNRELATED DONOR?

Most recently, Lee et al [10] showed that a single mismatch, antigen-level, or high-resolution, at HLA-A, -B, -C, or -DRB1 loci was associated with a higher mortality and decreased survival; however, the reduction in survival may be acceptable in comparison to the survival rates for currently available alternative treatments. In the Lee et al. study, mismatches at HLA-B and/or -C seemed to be better tolerated than mismatches at HLA-A and -DRB1. The results were somewhat different in a study by the International Histocompatibility Working Group [16]. Single mismatches at the HLA-A locus conferred an increased risk in transplantations facilitated by the Japanese Marrow Donor Program (JMDP) but not in the non-JMDP population analyzed. For the HLA-C locus, high-resolution mismatching appeared permissible within the JMDP data but was associated with increased risk in the non-JMDP transplantations.

Data from the NMDP and Fred Hutchinson Cancer Research Center [8,9] suggest that risks accompanying multiple mismatches may be cumulative or even synergistic. Although single mismatches at HLA-DP or -DQ were not associated with increased mortality; both studies found a small but statistically insignificant impact on survival when a DQ mismatch occurred in combination with other mismatches. Therefore, HLA-DQ matched donors should be favored if other matching criteria are equal.

For patients who do not appear to have well-matched donors based on an initial search, more complex strategies are required to identify donors with specific mismatches. Such strategies are needed to limit the number of high-resolution mismatches at other loci. For these searches we recommend that one request help from a local HLA expert or NMDP consultant to assist in finding the best mismatch.

It is hoped that in the future it may be possible to identify "permissible" mismatches; however, currently there are insufficient data to support this idea as a standard of practice. For example, in an analysis of NMDP data, HLA mismatching within a serologic crossreactive group (CREG) was not associated with a survival benefit in comparison to mismatches outside a CREG [17]. Likewise, algorithms for selecting less immunogenic mismatches have not predicted improved outcome [18]. However, a few studies have provided some information on the potential of permissible mismatches. Studies published by Morishima et al [19] on behalf of the International Histocompatibility Working Group, evaluated specific HLA-A2 allele mismatched pairs from the JMDP. Morishima's data suggested that certain A2 allele-mismatches (*0201 versus *0206) had a higher chance for mortality when compared to *0201 versus *0205 or *0207. Clearly, more research is needed to determine if permissive mismatches exist and how they may be utilized in donor selection.

In summary, although HLA matching for HLA-A, -B, -C, and -DRB1 at high resolution is preferred, the inability to identify a well-matched donor (ie,

HLA matched or a single HLA-A, -B, -C, or -DRB1 mismatch) is not a contraindication for transplantation. For such patients, the physician should consider the success rate associated with the use of a mismatched unrelated donor versus the use of other donor sources (eg, mismatched related donors or unrelated umbilical cord blood donors) or nontransplant therapies.

SHOULD I BE CONSIDERING PATIENT SENSITIZATION TO HLA ANTIGENS WHEN SELECTING A HLA MISMATCHED DONOR?

For patients with antigen or high-resolution mismatched donors, an evaluation of presence and specificity of antibodies directed to HLA antigens may be important. As a result of blood component support, many patients will be sensitized to HLA antigens as demonstrated by the presence of circulating antibodies. Current solid-phase assays make it very easy to assess the level of presensitization in transplant recipients. Recent studies in both animals and humans [20,21] have shown the association of preformed HLA-directed antibodies on failed engraftment. In a recent NMDP study [22], approximately one-third of patients possessed antibodies to HLA antigens. Among patients with a failed graft, ~24% possessed donor-specific HLA antibodies, compared to 1% in appropriately matched controls without failed engraftment. Interestingly, antibodies against HLA-DP were quite prominent (60% of antibody positive failures). This suggests that even though matching for HLA-DP may not be important for OS, if a patient has HLA antibodies directed against the mismatched DP type of the donor, there may be an increased risk for graft failure. Thus, for patients with HLA antibody and a mismatched allograft, careful antibody specificity analysis and/or testing of the patient's sera for reactivity with cells from potential donors (ie, crossmatching) may be needed prior to transplantation.

DOES THE REDUCED INTENSITY OF THE CONDITIONING PROTOCOL INFLUENCE THE LEVEL OF HLA MATCH THAT I SELECT?

In a recent retrospective analysis of NMDP data on outcomes after unrelated donor hematopoietic cell transplantation following reduced-intensity conditioning (RIC), HLA matching was an important prognostic factor for survival, suggesting that greater degrees of mismatch are not more tolerable in the setting of an RIC transplant regimen [23]. The risk of using a mismatched donor must be weighed against the other therapeutic options available to the patient.

IF THE PATIENT HAS A MISMATCHED DONOR, SHOULD I USE T CELL DEPLETION (TCD)?

TCD reduces the incidence and severity of aGVHD and increasing donor mismatch increases risk of GVHD. Despite this, analysis of the NMDP dataset does not indicate a survival advantage for TCD, whether a graft is matched or mismatched. A prospective randomized trial of TCD did not show improved survival associated with the use of TCD in either matched or mismatched unrelated donor transplants [24].

SHOULD WE BE CONSIDERING OTHER GENETIC LOCI IN ADDITION TO HLA FOR DONOR SELECTION?

A recent report suggests that matching for HLA haplotypes may provide an advantage compared to merely matching for an HLA phenotype. That is, matching for 2 HLA haplotypes may be preferred over matching for 10 of 10 HLA alleles. It is believed that there are other important transplant-related immune response genes that are carried on chromosome 6. Thus, by matching for an HLA haplotype, it might be possible to match for these yet to be defined genes. In a study involving 246 10 of 10 allele matched unrelated transplants, Petersdorf et al [25], showed a decreased probability for aGVHD and treatment-related mortality in patients that were 2 haplotype matched compared to individuals that were phenotypically matched. However, the decreased rate of aGVHD was offset by an increase in relapse, resulting in an OS that was not different compared to phenotypically matched individuals. At this time there are insufficient data to advocate consideration of loci other than HLA, but NMDP will continue to monitor new developments in this area.

SHOULD TARGETS OF NATURAL KILLER (NK) CELL ALLOREACTIVITY BE CONSIDERED?

There are currently no data to unequivocally indicate that unrelated donors with mismatches at HLA class I loci, that is, the ligands for Killer Immunoglobulin Receptors (KIR), should be preferred in any clinical circumstance. An early report from Ruggeri et al [26] indicated a strong antileukemic effect and survival advantage with haploidentical-related donor transplants with particular HLA class I mismatches that generate donor killer cell reactivity directed toward patient tissues. This association was observed only for recipients with AML. A number of subsequent studies have analyzed the impact of KIR on outcome with varied conclusions. An analysis of data from the CIBMTR, European Blood and Marrow Transplant (EBMT) Registry and the Dutch Registry on the effect of KIR ligand mismatching on outcomes following 1571 primarily T cell-replete unrelated donor transplantations for myeloid malignancies showed that

KIR ligand incompatibility in either the GVH or HVG direction had no impact on TRM, treatment failure, overall mortality, or leukemia recurrence [27]. In contrast, an analysis of 1770 leukemia patients who received myeloablative T cell-replete hematopoietic stem cell transplantation (HSCT) from HLA matched or mismatched unrelated donors showed that recipient homozygosity for HLA-B or -C epitopes (ie, potentially missing KIR ligands) may be predictive for leukemia recurrence following transplantation from HLA mismatched unrelated donors [28]. A similar effect could not be observed following HLA identical unrelated transplantation. None of the studies cited here evaluated the donors for the presence or absence of specific KIR loci required to mediate the predicted NK reactivity. The influence of donor HLA on the subsequent reactivity of transplanted NK cells [29] was also not considered. Finally, the impact of subsequent immune suppression on NK recovery may also affect NK reactivity [30]. At this time more information is need to understand the role of this complex system in outcome.

WHERE CAN I FIND ADDITIONAL INFORMATION?

NMDP Web sites include: http://www.marrow.org/ and http://bioinformatics.nmdp.org/.

ACKNOWLEDGMENTS

This project has been supported by funding from the National Marrow Donor Program, the Department of the Navy, Office of Naval Research Grant #N00014-06-1-0704, and the Health Resources and Services Administration Contract No. HHSH234200637020C to the National Marrow Donor Program. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the Office of Naval Research or the Health Resources and Services Administration.

Financial Disclosure: Drs. Spellman, Setterholm, and Confer are employees of the NMDP and have a financial relationship with the NMDP, in that capacity as employees. Dr. Hurley is an unpaid consultant for the NMDP. Drs. Bray, Kamani, Woolfrey, and Müller have nothing to disclose.

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