Using HLA Typing to Support Patients With Cancer

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Background: The human leukocyte antigen (HLA) system plays a crucial role in immune function, and HLA testing is often needed in the support of patients with cancer.

Methods: We briefly review the published literature to clarify the nomenclature of the HLA system, currently available methods for HLA testing, and commonly used HLA assays. The uses of HLA testing in pharmacogenomics, disease association, platelet transfusion support, and in the management of both solid organ and hematopoietic stem cell transplantation are also reviewed.

Results: HLA testing is commonly performed for select patient populations, including patients with cancer and in those requiring solid organ and hematopoietic stem cell transplantation.

Conclusion: Newer molecular typing methods have helped improve patient outcomes following hematopoietic stem cell transplantation.

Introduction

The human leukocyte antigen (HLA) region encompasses a crucial set of genes that regulate immune function. It is the most polymorphic region of the human genome. HLA testing is often required in support of patients with cancer; for example, HLA testing is used in both solid organ and hematopoietic stem cell transplantation (HSCT), for selected pharmacogenomics testing for a personalized medical approach, and in support of immune-platelet refractory patients. The HLA nomenclature has been updated to address new information gained with molecular assays. Both serological and molecular HLA assays are available and the use of these tests will be addressed.

Methods of Testing for HLA Antigens, Antibodies, and Genes

A number of methods for determining HLA types were developed over the years as different technologies were discovered and used. Initially, the presence or absence of certain HLA types and the specific HLA type were determined with the use of antibodies via serological methods, including the microcytotoxicity method, whereby T or B lymphocytes from a patient or donor are incubated in vitro with serum containing HLA antibodies of a certain specificity (reactive against a particular HLA type), and, if the antigen is present, an in vitro activation of complement would occur, leading to detectable cell death in this assay.
Thus, an HLA type for an individual would be determined with the use of an array of sera with different HLA specificities on a plastic tray with multiple wells within which the lymphocytes of an individual would be added. The ability to identify different HLA types by this method is limited to the availability of sera containing the various HLA specificities. Therefore, this method is less commonly used as an initial method for HLA typing due to these limitations. However, it does have value in confirming the presence or absence of an antigen in rare instances in which molecular-based methods predict a certain HLA type but fail to recognize that the antigen is not produced due to mutations present in a gene or promoter not routinely tested. In addition, some laboratories continue to use this serological method for determining the presence or absence of certain disease-associated HLA types (e.g., HLA-B27 for ankylosing spondylitis). Advancement in the use of antibodies to determine HLA type for a specific application has been seen in the use of flow cytometry with fluorescent conjugates added to anti-B27 to identify patients positive for HLA-B27. Otherwise, serological or antibody-based typing of HLA antigens is only used in applications in which knowledge of the HLA type at a broader serological grouping level (low-resolution HLA type) is sufficient (e.g., HLA typing of platelet donors, for solid organ transplantation in certain countries where this is still permitted). It is rare to use serological HLA typing methods for patients receiving HSCT except perhaps for identifying HLA-matched siblings. Therefore, health care professionals should routinely confirm that the method used for patients receiving HSCT is via a molecular method, and that the method employed can generate sufficient specificity to identify the patient or donor HLA types to the allelic level where appropriate.

The development of molecular methods for determining an individual’s HLA type was a significant advancement in avoiding the past technical challenges of needing serum with antibodies of all HLA types, including uncommon types present in only small groups of individuals. Although the HLA genes are highly polymorphic at multiple locations, the majority of these DNA sequence variations are contained within exons 2 and 3. With current molecular methods, once the specific nucleotide sequence polymorphisms unique to a particular HLA type are characterized, the necessary DNA probes or primers can be artificially synthesized and readily incorporated into commercial assay kits.

The number of molecular methods that currently exist can be grouped into 3 categories, i.e., sequence-based typing (SBT), sequence-specific primer (SSP) typing, and sequence-specific oligonucleotide (SSO) typing. SBT can be performed via the traditional Sanger nucleotide termination method or via next-generation sequencing methods for which several platforms have been developed for HLA typing. In general, SSP typing is performed through the use of a heat-stable DNA polymerase to generate detectable, specific DNA amplification products that can be produced and detected if HLA-type specific DNA primers properly bind to the individual’s template DNA. SSO typing is accomplished through the ability to detect more broadly generated, exon- and locus-specific DNA amplification products, but which are not HLA type-specific, that bind to SSO probes. By contrast, SSP typing requires multiple wells of reactions to determine the presence or absence of particular DNA polymorphisms, whereas SSO typing allows for the use of a single tube of locus-specific amplified products that must then bind to a specific location on a solid-phase surface or a uniquely identified bead associated with the particular polymorphism. With all 3 molecular methods, an HLA type is determined based on the collection of polymorphisms identified.

With few exceptions, the majority of the molecular HLA typing assays commercially available and in use focus on identifying polymorphisms in exons 2 and 3 of the various HLA genes tested. As mentioned above with serological HLA testing, rare polymorphisms may exist outside of exons 2 and 3 that lead to lack of expression or altered expression of the HLA molecule, which is a specific limitation of the molecular method. Exon 4 testing may be added for HLA-A, HLA-B, and/or HLA-C typing for recipients of HSCT and their donors for more readily achievable high-resolution typing results. Future and ongoing developments in next-generation sequencing will eliminate these limitations when incorporating broader sequencing of the entire coding and noncoding regions.

**Nomenclature**

The nomenclature of the HLA system has significantly changed in recent years. Serological typing had to account for older “parent” and newer “split” antigens (e.g., B12[44], B12[45]). Molecular methods required significant nomenclature changes; the latest major update from 2011 involved the reorganization of alleles so that they were properly aligned to allow similar antigens to be within the same group. Refer to Fig 1 for an example of the new molecular fields and what they represent.²

Molecular typing methods revealed that many serologically defined antigens were actually created by multiple alleles that could be individually defined. Individual alleles linked to the same antigen may behave differently and affect outcomes in areas like HSCT. Novel alleles are constantly being identified and the extensive polymorphism of the HLA system continues to be recognized. Applying the terms
Pharmacogenomics

Pharmacogenomics refers to specific genes in a given individual associated with particular responses, both beneficial and detrimental, to medications and other therapies. The HLA genes are well recognized as influencing select drug responses. For example, by prospectively HLA typing patients with HIV-positive status to identify those with HLA-B*57:01, a significant reduction was seen in the risk of adverse events due to the strong association of hypersensitivity with the use of abacavir in these patients. In European populations, this allele is relatively common with a frequency of 6% to 7%.7 The highest frequency of HLA-B*57:01 has been reported in south-western Asian populations in which up to 20% of the population are carriers.7 The US Food and Drug Administration recommends prescreening patients for B*57:01 prior to starting treatment with this antiretroviral medication.8,9

Refer to Table 1 for selected examples of drug-related adverse events and the identified HLA alleles associated with those events.10-13

Not all pharmacogenomics testing that held promise has been realized. Prescreening of patients before treatment with vitamin K antagonists such as warfarin for single-nucleotide polymorphisms in the genes VKORC1, CYP2C9, or both have not improved outcomes.14,15 With the advent of next-generation sequencing of the whole exome or genome, further research is likely to identify critical and non-HLA genes associated with both the beneficial and detrimental responses to select medications.

### Disease Associations

Given the role of the immune system in many diseases, it is not surprising that certain polymorphisms in the HLA system, with specific HLA types, are associated with an increased risk for disease

#### Table 1. — Examples of Important Adverse Events and Their HLA Associations

<table>
<thead>
<tr>
<th>Drug</th>
<th>HLA Allele</th>
<th>HLA Frequency</th>
<th>Adverse Event</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>B*57:01</td>
<td>6%–8% Caucasian 2.5% African American</td>
<td>Drug hypersensitivity</td>
<td>Shear16</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>B*58:01</td>
<td>9%–11% Han Chinese 1%–6% Caucasian</td>
<td>Drug hypersensitivity</td>
<td>Hung11</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>B*15:02</td>
<td>10%–15% Han Chinese &lt; 0.1% Caucasian</td>
<td>Stevens–Johnson syndrome/toxic epidermal necrolysis</td>
<td>Chung12</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>B*57:01</td>
<td>6%–8% Caucasian</td>
<td>Drug-induced liver injury</td>
<td>Daly13</td>
</tr>
</tbody>
</table>

**Notes:**

- **High-resolution molecular typing**
- **Intermediate-resolution molecular typing**
- **Low-resolution molecular typing**
- **Serological typing**

**HLA**: human leukocyte antigen.
(Table 2). Despite these associations, the mechanism of the association with certain HLA types remains under investigation; the HLA type is one of multiple risk factors. The presence of a disease-associated HLA type alone is not sufficient to trigger disease. For example, HLA-B27 is commonly present in patients with ankylosing spondylitis, but many individuals who have HLA-B27 are without disease because HLA-B27 is a relatively common antigen and ankylosing spondylitis is an uncommon disease. Therefore, the health care professional should keep this in mind when obtaining and reviewing HLA typing results of a patient with cancer.

Associations with HLA types for certain lymphoid malignancies have also been studied, including certain HLA types to chronic lymphocytic leukemia, multiple myeloma, acute lymphoblastic leukemia, and diffuse large B-cell lymphoma. In fact, the earliest association with HLA type and disease was with HLA-B types and Hodgkin disease. Findings have been more limited of associations of certain HLA types with solid organ malignancies and include an increased risk of progression to hepatocellular carcinoma in patients with chronic hepatitis B and long-term survival rates among patients with gastric cancer. Despite the associations of HLA type with certain malignancies, HLA typing of patients with cancer is not routinely performed because these associations are relatively weak to date. However, HLA typing is routinely performed for patients and their potential donors when HSCT is considered.

### Platelet Support

A poor response to platelet transfusion (ie, platelet transfusion refractoriness) can be due to nonimmune causes, immune causes, or both. Immune refractoriness is most often the result of HLA antibodies (either single or multiple specificities) and, much less commonly, antibodies directed against human platelet-specific antigens (HPAs). The risk of HLA alloimmunization can be significantly reduced with the use of leukoreduced red blood cells and platelets. Despite wide adoption of the leukoreduction of red blood cell and platelet components for patients with cancer, HLA alloimmunization remains a challenge. Parous women have been previously exposed to fetal HLA epitopes that may have elicited prior alloimmunization; the risk is greater with an increasing number of pregnancies. Men and nulliparous women may also have been HLA alloimmunized due to a prior blood transfusion that was either nonleukoreduced or was truly leukoreduced (leukoreduction is not 100% protective).

Patients with poor responses to platelet transfusion at 10 minutes or 1 hour following transfusion should be investigated for possible immune causes for refractoriness. By using the correct count increment, one can calculate that the average-sized person receiving an average dose of platelets should increase his or her platelet count about 15,000/µL above the baseline platelet result at 1 hour following the transfusion if the precount was performed in close proximity to the transfusion.

Qualitative screening assays are available to detect antiplatelet antibodies with HLA specificity, HPA specificity, or both. These specificities can also be identified when antigen-negative platelet transfusions are being considered (eg, HLA-A2-negative platelets for a patient with anti-HLA-A2 antibodies). The management of thrombocytopenia with HLA alloimmunization is covered in the article by Dr Fletcher and others in this issue. Care of these patients can often be quite difficult and preventive strategies are crucial.

### Hematopoietic Stem Cell Transplantation

The outcomes of both related and unrelated donor HSCT are impacted by the extent of HLA matching.

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**Table 2. — HLA Alleles and Associated Diseases**

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA Allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>B<em>27:XX alleles (except B</em>27:06 and B*27:09)</td>
</tr>
<tr>
<td>Antiglomerular basement membrane disease</td>
<td>DRB1<em>15:01, DRB1</em>15:02</td>
</tr>
<tr>
<td>Birdshot retinochoroidopathy</td>
<td>A<em>29:01, A</em>29:02</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>DQA1<em>05/DQB1</em>02, DQA1<em>03/DQB1</em>03:02</td>
</tr>
<tr>
<td>Idiopathic myopathy</td>
<td>DQA1<em>04:01, DQA1</em>05:01</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>DQB1*06:02</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>DRB1<em>04:02, DRB1</em>04:03, DRB1<em>04:06, DRB1</em>08:02, DRB1<em>14:04, DRB1</em>14:05, DRB1*14:08</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>C*06:XX</td>
</tr>
<tr>
<td>Reiter syndrome</td>
<td>B*40:01</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>DRB1<em>03:01/02:11, Multiple alleles of DRB1</em>04:XX, including: DRB1<em>04:01/02:03/04/05/06/07/08/09/10/11/17/26, DQA1</em>03:01, DQB1<em>02:01, DQB1</em>03:02</td>
</tr>
</tbody>
</table>

HLA = human leukocyte antigen.
between the transplantation recipient and the donor. Several large studies have demonstrated that a greater degree of HLA match between donor and recipient improves overall survival rates, reduces both the incidence and severity of acute and chronic graft-versus-host disease (GVHD) and improves rates of engraftment. When a suitable, related HLA-matched donor is unavailable, unrelated donor registries, such as the Be the Match Registry run by the National Marrow Donor Program, can often identify a perfect or well-matched unrelated donor. The recipient's racial and ethnic group will affect the likelihood of finding a high-resolution HLA-A, HLA-B, HLA-C, and HLA-DRB1 match, although whites of European descent have the highest probability (75%) and blacks of South or Central American descent have the lowest (16%). When these large, unrelated donor registries also fail to identify a matched unrelated donor, alternative donors such as mismatched adult unrelated donors, haploidentical-related donors, and umbilical cord blood (UCB) stem cell products are often used.

The widespread use of DNA-based tissue typing methodologies has increased the accuracy and specificity of HLA typing, thus allowing for more precise HLA matching between recipients and donors. For most HSCT, a minimum of 4 HLA loci (HLA-A, HLA-B, HLA-C, HLA-DRB1) and, more often, 5 (HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1) are generally matched between recipient and donor pairs. Volunteer unrelated adult donors are selected to be closely matched to recipients at HLA-A, HLA-B, HLA-C, and HLA-DRB1 at the allele level when related HLA-matched donors are not available. High-level donor–recipient HLA matching is crucial for the success of unrelated adult donor HSCT. Additional loci considered by some HSCT programs include DPB1 and KIR.

Although close HLA matching is crucial, it is not always possible and some mismatches fare better than others. Pidala et al. identified certain amino acid substitutions that affected the peptide-binding site of the HLA class I antigen and increased the risk of severe acute GVHD and mortality. Some mismatches appear to have little to no increased risk. These “permissible” HLA mismatches have been perhaps most studied in the Japanese population. In Japan, fewer HLA haplotypes gives greater opportunity for studying isolated mismatches between recipient–donor pairs.

The only potential curative measure for many patients with hematological malignancies is HSCT; however, about 70% of patients will not have an HLA-matched sibling donor considering the number of children per family in the United States and the likelihood of HLA identity being 25% with any 1 sibling. Therefore, the majority of recipients must turn to the unrelated volunteer donor pool. The National Marrow Donor Program has more than 20 million HLA-typed donors in its database and affiliated registries. Many patients, particularly those of diverse racial and ethnic backgrounds, will not have a suitable matched, unrelated donor identified in the time period needed. UCB has helped to fill that gap for these patients, and more than 30,000 UCB transplants have been performed to date.

UCB units are typically selected using low-resolution HLA typing (antigen level) for HLA-A and -B and high resolution (allele level) for HLA-DRB1. HLA-C matching was not generally considered in the past, but further study has shown that HLA-C matching with UCB may minimize mortality risks. While the degree of matching for UCB transplantation is not as extensive as it is for non-UCB sources, greater degrees of matching (eg, high resolution for HLA-A, HLA-B, HLA-C, and HLA-DRB1 vs low resolution for HLA-A and HLA-B) may also improve neutrophil recovery and reduce nonrelapse mortality rates when single cord blood units are transplanted.

In general, for non-UCB HSCT, any single locus mismatch is associated with worse outcomes in overall survival, treatment-related mortality, and acute GVHD (ie, 9/10 worse than 10/10 match) with the exception of a mismatch at the DQB1 locus. There is no statistical difference if a single-locus mismatch occurs at the antigen or allele level, except perhaps for HLA-C with antigen mismatch worse than allele-level mismatch.

Because the HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 loci influence the success of HSCT, investigators have also looked at the DPB1 locus to determine its impact. Early studies suggested that DPB1 matching does not impact overall survival rates, a fact that appeared fortunate because tight DPB1 linkage with other loci are lacking and would create difficulty in finding a DPB1 match. About 20% of 10/10 matched unrelated donor transplantations will be matched for DPB1. More recent work in grouping DPB1 mismatches based on T-cell epitopes has distinguished mismatches that might be tolerated (permissive) from those with increased risks (non-permissive). Retrospective analyses in both 9/10 and 10/10-matched transplantations have shown that non-permissive DPB1 mismatches were associated with a significantly increased risk of overall mortality, nonrelapse mortality, and severe acute GVHD than permissive mismatches.

HLA alloantibodies directed against mismatched antigens are well established as a significant risk factor in solid organ transplantation (particularly for the kidney, heart, and pancreas); therefore, prescreening is required and frequently repeated. Increased risk of graft failure in HLA mismatched pairs with positive cytotoxicity crossmatch tests (39%) compared with those with negative compatible tests (10%) was reported by Anasetti et al.
Approximately 35% of patients receiving unrelated HSCT possess HLA antibodies, and the presence of donor-specific HLA antibodies (DSAs) against HLA-A, HLA-B, and/or DRB1 specificities, as determined by solid-phase immunoassay testing, is associated with graft failure. Therefore, HLA antibody evaluation in the recipient should be part of the routine workup for mismatched HSCTs. Both the National Marrow Donor Program and the Center for International Blood and Marrow Transplant Registry recommend the evaluation of HLA-DSAs in both adult and cord blood HLA mismatched HSCTs.

The concept of considering noninherited maternal antigens (NIMAs) when selecting particular mismatched donors is an interesting one. Humans are exposed to NIMA HLA antigens in utero and the immature fetus appears to develop less reactivity to these non-self-antigens compared with non-NIMA alloantigens. Some treatment-related mortality associated with HLA-mismatched UCB HSCT may be alleviated with the use of NIMA-matched vs mismatched donor units and has been associated with improved rates of overall survival (Fig 3).

The ability to provide NIMA-matched donors may prove difficult as the relative frequency of these donors may be low and searching may delay transplantation. In the Rocha et al and van Rood et al studies cited above, 7% to 10% of transplantations with mismatched HSCTs.

Natural killer cells have killer cell, immunoglobulin-like receptors (KIRs) on their surface that allow them to recognize HLA class I and, primarily, HLA-C surface molecules; they then can distinguish “self” from “non-self” and ultimately provide a benefit with such feats as destruction of virally infected cells or cancer cells. All HLA-C alleles can be classified as either HLA C group 1 (C1) or group 2 (C2) and the KIR haplotypes are either grouped as A or B depending on which genes are present. Different pairings of the HLA and KIR molecules elicit either inhibitory or activating signals. Although early studies showed KIR mismatching could provide a survival advantage in acute myeloid leukemia, subsequent studies have had varied conclusions. Use of KIR data for donor selection should be considered within the framework of a clinical trial alone.

The best approach to using HLA typing results when searching for an unrelated HSCT donor includes the following:

- Look for a 7/8 or optimal 8/8 HLA-A, HLA-B, HLA-C, or DRB1 allele-matched donor.
- Consider DQB1 allele-matched donors when multiple 7/8 or 8/8 matches are present for a preferred 9/10 or 10/10 HLA-A, HLA-B, HLA-C, DRB1, and DQB1 match.
- Consider UCB HSCT when no 7/8 or 8/8 matches are identified.
- Identify UCB units that are a minimum of 4/6 HLA-A, HLA-B, and DRB1 match with adequate cell dose.
- A NIMA-matched donor may benefit the recipient and could be sought if there are multiple, similarly mismatched unrelated donor or UCB units and the HSCT is not delayed.
- HLA antibody screening/matching should be performed when mismatched donors are considered.

The National Marrow Donor Program recommends that high-resolution HLA typing be performed at the time of diagnosis for all adult patients with acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndromes with an intermediate or high International Prognostic Scoring System, some with chronic myeloid leukemia, such as when an inadequate hematological or cytogenetic response occurs after a trial of tyrosine kinase inhibitors, and in certain chronic lymphocytic leukemia cases with, for example, high-risk cytogenetic or molecular features (eg, del[11q] or del[17p], ZAP70 or Cor CD38 positivity, unmutated immunoglobulin variable region heavy chain mutational status, short initial remission, resistant to fludarabine).

The use of blood relatives as blood donors prior to stem cell infusion should be avoided because sensitization of the patient to donor minor histocompatibility antigens can increase the risk of allograft rejection.

### Solid Organ Transplantation

Unlike stem cell transplantation, HLA matching is not initially required for solid organ transplantation (heart, liver, lung, kidney, pancreas, or bowel) if the

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### Table: HLA-A, HLA-B, HLA-DRB1 Match/Mismatch

<table>
<thead>
<tr>
<th></th>
<th>HLA-A</th>
<th>HLA-B</th>
<th>HLA-DRB1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NIMA Match</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient</td>
<td>A*02, 24</td>
<td>B*18, 35</td>
<td>DRB1*01:01, 11:04</td>
</tr>
<tr>
<td>UCB unit/donor</td>
<td>A*02, 32</td>
<td>B*18, 35</td>
<td>DRB1*01:01, 11:04</td>
</tr>
<tr>
<td>UCB donor mother</td>
<td>A*24, 32</td>
<td>B*07, 35</td>
<td>DRB1*01:01, 13:01</td>
</tr>
<tr>
<td><strong>NIMA Mismatch</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient</td>
<td>A*02, 11</td>
<td>B*18, 35</td>
<td>DRB1*01:01, 11:04</td>
</tr>
<tr>
<td>UCB unit/donor</td>
<td>A*02, 32</td>
<td>B*18, 35</td>
<td>DRB1*01:01, 11:04</td>
</tr>
<tr>
<td>UCB donor mother</td>
<td>A*24, 32</td>
<td>B*07, 35</td>
<td>DRB1*01:01, 13:01</td>
</tr>
</tbody>
</table>

Fig 3. — Examples of NIMA-matched and mismatched UCB donors. HLA-A*24 is not carried by the UCB donor but is carried by the mother of the UCB donor and the recipient; thus, this represents a NIMA-matched UCB HSCT. HLA-A*11 is not carried by the UCB donor or the mother of the UCB donor; thus, this represents a NIMA-mismatched UCB HSCT.

*HLA = human leukocyte antigen, HSCT = hematopoietic stem cell transplantation, NIMA = noninherited maternal antigen, UCB = umbilical cord blood.

patient is not alloimmunized; rather, identifying and confirming ABO compatibility to avoid hyperacute rejection is more important. The use of HLA matching is associated with potentially improved allograft survival and reduced alloimmunization rates that might otherwise limit the availability of HLA-compatible organs. Furthermore, the preference for HLA matching does not require complete matching of all loci unless the patient is broadly alloimmunized against the majority of non-self HLA types. Typically, low-resolution HLA typing alone is required. No benefit has been identified with the use of allele-level or high-resolution typing in solid organ transplantations except in instances in which a patient might have allele-specific antibodies. In patients who are waiting for an available cadaveric allograft, those who are highly sensitized (> 90% of panel donors are reactive) will be eligible to receive an HLA-matched kidney from outside of their region.

Whenever organ dysfunction is present in a patient with a history of solid organ transplantation (heart, liver, lung, kidney, pancreas, or bowel), an assessment of the possibility of allograft rejection should be considered. Allograft biopsy and testing for HLA antibody production would help assess for cellular and humoral allograft rejections, respectively. An examination of the biopsed tissue includes looking for evidence of lymphocytic infiltrates and thickening or fibrosis of vessel walls. Staining for the complement component C4d is used in kidney biopsies to look for evidence of humoral rejection. Testing for the presence of HLA antibodies against donor-mismatched antigens may be an initial noninvasive approach to identifying humoral allograft rejection in patients with cancer and solid organ allografts. However, the absence of detectable DSAs does not exclude the possibility of humoral rejection because the allograft may absorb most of the antibodies before any excess antibodies are detectable in the serum or plasma (termed silent alloimmunization). Furthermore, previously transplanted solid organ donor-mismatched HLA types should be avoided whenever possible in the selection of stem cell donors for subsequent stem cell transplantation due to the risk of prior alloimmunization and the increased risk of stem cell engraftment failure if a donor is chosen who expresses the same mismatched HLA type.

In the instance of known humoral rejection, monitoring levels or titers of theDSA is commonly performed when detecting antibodies using a single-antigen bead flow cytometry method (eg, Luminex [Life Technologies, Carlsbad, California]) in addition to measuring fluorescence intensity. However, variation in the fluorescence intensity detected might be sufficiently high so that identification of an increasing or decreasing trend in antibody reactivity might require the use of normalization techniques or the use of paired testing of a prior and current sample concurrently to minimize run-to-run variation and identify a true change in the level of reactivity.

Conclusions
Polymorphisms in the human leukocyte antigen (HLA) system influence the immune system in ways not yet completely understood, but associations are known to increase risk among patients with certain diseases and hypersensitivity to certain drugs. Knowledge of HLA type and whether alloimmunization has occurred may inform treatment and transfusion support plans. Numerous methods for HLA typing exist that include a single, multiple, or all clinically relevant HLA loci. In addition, these different methods may generate different degrees of detail regarding the HLA type depending on the specific treatment needed. HLA matching can be defined with different levels of stringency for different loci, thus balancing the increasing time needed to find the “perfect” allograft donor match and the risk of further disease progression/relapse prior to additional treatment with allogeneic stem cell transplantation versus less-stringent matching and an increased risk of allograft failure or life-threatening graft-vs-host disease. HLA antibody production through allosensitization may lead to more difficult, but not necessarily impossible, platelet transfusion support. However, HLA antibodies can also increase the risk of allograft failure for both stem cell and organ transplantations if patient antibodies are directed against donor HLA types. Therefore, it is critical for health care professionals to understand what HLA information (antigen typing, allele typing, or antibody testing) is needed for patient care and what impacts or risks are associated with that HLA type.

References


