ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Prevention of Graft-Versus-Host Disease

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H&O What is graft-versus-host disease?

RR Graft-versus-host disease (GVHD) is one of the most common complications of allogeneic stem cell transplantation (ASCT). The curative potential of ASCT in diseases such as leukemia, myelodysplastic syndrome, and lymphoma relies in part on the graft-versus-leukemia response (GVL), the unique capability of donor-derived immunocompetent cells to eliminate cancer cells.[1] However, a similar immunologic attack can take place against healthy recipient tissues, resulting in GVHD. Mechanistically, GVHD is mediated mainly by donor-derived T cells that react against recipient antigens. Even in the presence of full human leukocyte antigen (HLA) matching between donor and recipient, GVL and graft-versus-host responses still occur due to mismatches in minor histocompatibility antigens that are polymorphic and immunogenic. Recognizing the critical role of GVL and GVHD in determining the outcomes of ASCT, there is a tremendous research effort in both animal models and humans to develop better strategies that prevent GVHD while preserving GVL.

H&O How frequently does GVHD occur?

RR Without the use of any preventive measures, almost all patients will develop GVHD. With current forms of prophylaxis, GVHD occurs in 30–70% of ASCT recipients. GVHD has different grades of severity; it can manifest as a mild transient rash that responds to topical steroid therapy or it can lead to voluminous diarrhea and severe liver dysfunction, requiring aggressive immunosuppressive therapy and causing significant morbidity and mortality.

Several factors are associated with an increased risk for GVHD. The most important risk factor is the degree of genetic disparity between the donor and the recipient. GVHD will occur in 30–50% of patients transplanted from an HLA-matched sibling donor and in 50–70% of recipients of HLA-matched unrelated donor transplants.[2] The risk for GVHD after HLA-mismatched transplants might be even higher. Other risk factors include older donor age, donor parity, and a sex mismatch between the donor and the recipient. A higher incidence of GVHD is observed when a male recipient is transplanted from a female donor due to minor histocompatibility antigens encoded by the Y chromosome. A parous female donor has been alloimmunized to unshared minor antigens carried by her fetus, and is therefore associated with a higher risk of GVHD. The intensity of the conditioning regimen is another determinant of risk; myeloablative ("full") transplants result in a higher rate of GVHD compared to reduced-intensity ("mini") transplants. There is often a delay in the onset of GVHD after reduced-intensity ASCT. Finally, recent genetic studies have shown that polymorphisms in certain immunomodulatory genes and genes that encode chemokines and chemokine receptors affect the risk for GVHD. These findings serve as a useful guide to the development of new therapies and may inform a better choice of stem-cell donors in the future.

H&O How is acute versus chronic GVHD defined?

RR Traditionally, the definition of acute versus chronic GVHD was based on the length of time that elapsed between the transplant and the development of symptoms. GVHD occurring in the first 100 days after the

transplant was referred to as *acute*, and GVHD occurring beyond the first 100 days was referred to as *chronic*. It was recognized that this definition was arbitrary and did not reflect the differences in pathogenesis, clinical manifestations, and response to therapy between the 2 forms of this disease. A better definition focuses on the type and severity of symptoms and the types of organs affected. Acute GVHD is an acute onset syndrome that affects 3 major organs: the skin, the intestinal tract, and the liver. The clinical symptomatology in the skin is a rash, which can vary in type, severity, and extent. Symptoms in the intestinal tract can vary from nausea and vomiting to life-threatening diarrhea of several liters a day, ileus, and even gut perforation. In the liver, the typical presentation is cholestasis with elevated bilirubin levels.

Chronic GVHD can affect any organ in the body, but the most commonly affected organs are the skin, the eyes, the mouth, and the lungs. Patients typically complain about dry eyes and mouth due to lacrimal and salivary gland dysfunction, a sclerodermatous skin rash that can cause contractures and ulcerations, and a pulmonary syndrome called *obliterative bronchiolitis*. Chronic GVHD often has an indolent course, but is one of the major causes of long-term morbidity and poor quality of life after transplant.

H&O How is GVHD diagnosed?

RR The diagnosis of acute GVHD is clinical and is based on typical symptoms that most often include a skin rash, jaundice, and diarrhea. Involvement of a single organ is not uncommon and is sufficient to make the diagnosis. A biopsy of an involved organ is often helpful but is not required to make the diagnosis. It is recommended, however, that a thorough evaluation be done to exclude alternative diagnoses such as infection, drug toxicity, and disease relapse, which may all present with similar symptoms. Because treatment for GVHD always includes potent immunosuppressive medications, it is critical to rule out infections. Biopsies of involved organs are therefore strongly encouraged prior to the start of therapy. Histologic evaluation can assist in establishing the diagnosis and distinguishing between acute and chronic GVHD, but is rarely useful in grading the severity as there is little correlation between the degree of symptoms and the histologic appearance.

Recent studies suggest that levels of plasma biomarkers can be useful in the diagnosis of GVHD, and may have a role in predicting response to therapy. Some of the candidate biomarkers include elafin, regenerating islet-derived 3-□, and tumor necrosis factor receptor-1. Some of these biomarkers are specific for involvement of certain organs, and combining them together may offer an opportunity for risk assessment or early diagnosis.[3]

H&O How often is GVHD associated with severe morbidity or mortality?

RR The severity of GVHD varies among patients. With acute GVHD, some patients present with a transient rash that often resolves with topical steroids, or with nausea and diarrhea that respond to a brief course of steroid therapy. More severe presentations may include high-volume diarrhea and cholestasis leading to liver failure. In the case of chronic GVHD, severe lung disease can lead to debilitating symptoms, superimposed infections, and death. Of all deaths that occur after allogeneic transplants, approximately 15% are directly attributable to GVHD.[4] This rate is an underestimation of the true burden of morbidity and mortality of GVHD because of the higher risk for infections and poor recovery of the immune system that are typically seen in patients with GVHD.

H&O What are the traditional approaches to the prevention of GVHD?

RR The incidence of GVHD can be decreased by various methods such as T-cell depletion and immunosuppressive medications. GVHD is thought to be mediated mainly by donor T cells; therefore, removal of T cells from the graft is a very effective way to decrease the incidence of GVHD. This can be accomplished either by ex vivo manipulation of the donor graft (CD34+ selection or CD3+ depletion) or in vivo depletion by administering T-cell depleting medications to the recipient (eg, anti-thymocyte globulin, alemtuzumab). Strategies that involve T-cell depletion carry a higher risk for disease relapse due to loss of the GVL response, which is also mediated at least in part by T cells. Therefore, patients should be carefully selected for this strategy, and it is mainly useful for patients with low-risk diseases, patients who are undergoing myeloablative conditioning, or patients with an excessive risk for GVHD, for example, those undergoing transplantation from a haploidentical donor.

Various pharmacologic agents have been used to prevent GVHD. The early transplants used methotrexate, which led to some decrease in the risk of GVHD. In the 1980s, the calcineurin inhibitor cyclosporine was introduced, and was shown to be superior to methotrexate. In 1986, both agents were combined to achieve superior results compared to either agent alone. In the 1990s, a second calcineurin inhibitor, tacrolimus, was introduced as GVHD prophylaxis, mainly due to its greater potency and slightly different toxicity profile. Two phase III studies have shown superiority of tacrolimus over cyclosporine in the prevention of GVHD, but no overall survival benefit has been shown.[5] Currently, the combination of a calcineurin inhibitor and methotrexate is the standard of care for GVHD prevention at most institutions.

Standard prophylaxis is only partially successful, which is why GVHD prevention remains an important focus of research in ASCT. Critical to the success of ASCT is the ability to reduce morbidity from GVHD while maintaining an efficient GVL response and supporting adequate recovery of the immune system.

H&O What are the novel approaches to GVHD prevention?

RR There are many preventive methods currently under investigation, and I will review only a few of them here. One novel approach is the use of lymphocyte-trafficking inhibitors. We recently published the results of a study that examined the use of the CCR5 antagonist maraviroc (Selzentry, ViiV Healthcare).[6] This approach had not been previously attempted in humans, but had a good rationale because immune activation is highly dependent on the ability of immune cells to migrate between blood, lymph nodes, and target organs. This approach also had some early success in animal models. In 35 high-risk ASCT recipients in our trial, the cumulative incidence of grade 2–4 acute GVHD was 14.7% on day 100 and 23.6% on day 180. The cumulative incidence of grade 3–4 (severe) GVHD on day 180 was 5.9%, mainly attributed to a very low incidence of visceral (gut and liver) GVHD. At 1 year, the rate of non-relapse mortality was 11.7%, and rates of relapse or infection were no different than expected. Maraviroc was developed for the treatment of human immunodeficiency virus infection, and its use for the prevention of GVHD is a good example of "drug repurposing," a practical and cost-efficient way to introduce new approaches. A follow-up trial with maraviroc is being planned at the University of Pennsylvania.

Another interesting and novel strategy is the use of the proteasome inhibitor bortezomib (Velcade, Millennium Pharmaceuticals) by investigators at the Dana Farber Cancer Institute. In a prospective phase I/II trial of short-course bortezomib added to standard prophylaxis in 45 patients undergoing HLA-mismatched transplants, the incidence of grade 2–4 acute GVHD was 22% at 180 days. At 1 year, the cumulative incidence of chronic GVHD was 29%.[7] Bortezomib suppresses B- and T-cell activation, inhibits antigen presentation by dendritic cells, and attenuates IL-6–mediated cell growth and proliferation. These pleiotropic effects on the immune system provide a good rationale for using bortezomib in the prevention of both acute and chronic GVHD.

Another approach that showed early success in clinical trials is the administration of post-transplant, high-dose cyclophosphamide. Patients receive a standard T-cell–replete donor graft, and several days after the transplant, cyclophosphamide is administered to eradicate activated T cells. This strategy promotes tolerance and results in adequate protection against GVHD, even with cyclophosphamide used as a single agent.[8]

The 3 novel approaches mentioned above will be tested in a prospective multicenter phase II study from the NIH-sponsored Bone Marrow Transplant Clinical Trials Network. Planning of this study is currently under way, and it is expected to launch in 2013.

H&O Are there any other measures that can minimize the effects of GVHD?

RR Decontamination of the intestinal tract with nonabsorbable antibiotics used to be a common practice in ASCT recipients, and was considered a part of the "sterile" environment that these patients need to avoid complications. This practice gradually fell out of favor, but it is now known that bacterial translocation through damaged epithelial barriers has an important role in the initiation of GVHD through activation of innate cells by Toll-like receptors and other mechanisms. Emerging data about the association between the gut microbiome, innate immunity, and GVHD might put manipulations of intestinal pathogens back on the "menu" of potential interventions in the near future.[9,10]

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