CLINICAL UPDATE

Current Developments in the Management of GVHD

New Treatment Options for the Management of Acute Graft-Versus-Host Disease

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H&O What is the pathophysiology of graft-vs-host disease?

YC Allogeneic hematopoietic transplant is a therapy used mainly for hematologic malignancies. The putative therapeutic mechanism behind allogeneic transplant relies on an immunologic graft-vs-malignancy effect, meaning donor leukocytes form an immune response against the recipient's malignancy, which can hopefully lead to a durable remission. An unintended consequence is that the healthy donor's white blood cells may attack the recipient's healthy tissues. This is the basic pathophysiology behind graft-vs-host disease (GVHD). There are probably multiple redundant pathways in the immune system that lead to GVHD. The disease most likely starts during the sentinel transplant admission. Donor leukocytes encounter foreign host tissues and begin to activate and expand. The host may develop tissue inflammation from conditioning chemotherapy/radiotherapy, and this inflammation might generate an inflammatory milieu that encourages an immunologic response. Then weeks later, upon stimulation of an adaptive immune response, the clinical manifestations of acute GVHD arise.

H&O How is acute GVHD defined?

YC Acute GVHD refers to a degree of disease that requires some action by the treating provider. It complicates allogeneic transplants at an incidence of 20% to 60%, according to large published series. Historically, acute GVHD was defined as that occurring within the first 100 days after transplant. This time line was created in an era when transplant was far more homogeneous, and the definition is no longer applicable. There are now many different conditioning regimens, graft sources, and GVHD prophylaxis regimens, all of which likely influence the kinetics of immune reconstitution and the time line of GVHD. Acute GVHD is therefore not restricted to the first 100 days after transplant. All definitions of GVHD—whether acute or chronic, or even the classification of overlap syndrome, which reflects elements of both—are based purely on clinical manifestations. Therefore, if a patient presents with significant diarrhea and a red skin rash 6 months after transplant, the diagnosis is acute GVHD. The time after transplant is no longer a component of the diagnosis.

H&O What are the risk factors for GVHD?

YC The main risk factor is the degree of human leukocyte antigen (HLA) disparity between the recipient and the donor. Throughout the past 2 decades, the incidence and severity of acute GVHD have gradually decreased as technology has allowed more precise matching between the recipient and the donor. Age is a risk factor, as higher incidences of both acute and chronic GVHD are seen among patients who are older and when older donors are used. Some studies suggest that a disparity in sex between the recipient and the donor leads to more cases of GVHD, particularly with a female donor and male recipient. This association is much stronger for chronic GVHD, but some studies also suggest a higher incidence for acute GVHD.

Studies have consistently shown that higher-intensity conditioning regimens correspond to a higher risk of GVHD. The higher the dose of chemotherapy or total

body radiation administered for conditioning, the higher the risk of GVHD. The use of high doses of total body radiation has the strongest association with the risk of acute GVHD.

H&O What are the symptoms of acute GVHD?

YC The main symptoms are a skin rash and diarrhea. The most common skin rash resembles an erythematous maculopapular rash that is symmetric and usually not pruritic. This rash can develop anywhere on the body, but the classic areas are the nape of the neck, the ears, the palms, and the soles.

The most worrisome gastrointestinal (GI) symptom arises in the lower tract and consists of voluminous amounts of watery diarrhea, which bespeaks of significant damage to the GI epithelium. Upper GI GVHD is much less severe and oftentimes difficult to distinguish from other etiologies, such as medication toxicity or residual chemotherapy effects. The symptoms of upper GI GVHD include persistent nausea and anorexia. The least common organ affected is the liver. Generally, liver involvement leads to no specific symptoms. It is usually diagnosed when laboratory analyses show elevations in liver function tests.

H&O What are the diagnostic criteria for acute GVHD?

YC Acute GVHD is oftentimes difficult to diagnose. As discussed above, the main signs and symptoms are skin rash, diarrhea, and liver test abnormalities, all of which may result from a host of other etiologies. It behooves transplant providers to determine whether signs and symptoms do in fact represent acute GVHD.

It is important to emphasize that acute GVHD remains a clinical diagnosis. Although tissue biopsies of affected organs can help the diagnostic workup, a biopsy by itself is not the gold standard. Skin biopsies are notoriously ambiguous. GI biopsies and liver biopsies are somewhat better, but there are common conditions in our patients that can result in histologic findings that mimic those supportive of acute GVHD.

H&O What are the complications of GVHD?

YC The complications of GVHD depend on which organs are affected, the severity of the disease, and whether patients respond to therapy. For example, say a patient develops a skin rash that quickly responds to topical treatment or even a short course of systemic corticosteroid therapy with prednisone. If the patient is otherwise healthy, complications are unlikely. Complications are more common among patients who do not respond to treatment or who must remain on long-term therapy with corticosteroids. Many of the patients who do not respond have severe lower GI involvement, and the complications can be significant. The patient may be readmitted to the hospital for weeks, if not months, depending on the disease course and severity. The GI mucosa is the major barrier between the body and the healthy bacteria that live in the intestines. If the mucosa is injured, then those bacteria that usually live in symbiosis with the patient can become pathogens, break through the mucosa, and cause infections. Infections caused by bowel flora, be it bacteria or fungus, are a major complication.

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The pathophysiology behind the manifestation of diarrhea is that the entire GI epithelium of the small bowel and large bowel is injured, which interferes with the absorption of nutrients and water. Malnutrition and protein-losing enteropathy can cause serum albumin levels to drop significantly, resulting in profound edema of the lower extremities and abdomen. Catastrophic muscle wasting also occurs owing to malnutrition, inactivity, and long-term use of corticosteroids. In addition to these complications, GI GVHD can cause symptoms such as pain, cramping, and distention, and can ultimately lead to ileus or even a small bowel obstruction.

Severe hepatic GVHD can ultimately cause liver failure. The liver is a resilient organ, but if the disease does not respond to treatment, eventually the damage can be so severe as to result in manifestations of liver failure.

Many of the complications of GVHD are associated with treatments of the disease, which traditionally have been based on systemic immunosuppression. This strategy is intuitive since GVHD is an immune-mediated disease, and the aim should then be to suppress the immune system. High-dose systemic corticosteroids, such as 1 to 2 mg/kg/day of prednisone or its equivalent, are the initial standard therapy for patients who require systemic therapy. Treatment with corticosteroids can take a toll, depending on the patient and the duration of therapy. Corticosteroids have a profound proximal muscle wasting effect and can also cause hyperglycemia or frank diabetes. Corticosteroids can also impact bone health and cause hypertension. These drugs clearly suppress the immune

system, thereby contributing to opportunistic infections. There are also psychologic effects associated with high-dose corticosteroids, including mood swings, depression, and psychosis.

Beyond corticosteroids, the historical model of treatment has been additional systemic immunosuppression. However, by suppressing the immune system even more, we further increase the risk of an opportunistic infection in a patient who is already susceptible. Deaths from acute GVHD are not usually from organ failure, but rather from an opportunistic infection in a very compromised patient.

H&O How effective are the traditional treatment options?

YC Traditional treatments have not been very effective. There is a huge unmet need in this area, and research into better options continues. In large studies evaluating systemic corticosteroids as first-line therapy among patients with acute GVHD, only approximately 40% to 50% did not require another treatment at some point. In addition, even some patients with an adequate response will develop significant morbidity from long-term use of corticosteroids. Therefore, a minority of patients are treated successfully and with minimal morbidity.

Conventionally, therapies used in the second-line setting of acute GVHD have included anti-thymocyte globulins (ATGs), inhibitors of the interleukin-2 pathway, inhibitors of the tumor necrosis factor α pathway, sirolimus, mycophenolate mofetil, pentostatin, mesenchymal stem cells, and extracorporeal photopheresis. Although each of these agents showed compelling activity in single-center series, none have yet to show clear benefit compared with other treatments in larger studies. This lack of demonstrated benefit may indicate that these agents are not effective, or it may reflect the many challenges in conducting clinical trials and accurately assessing efficacy of therapy for acute GVHD.

Historically, more severe clinical manifestations of GVHD were less likely to respond to therapy. However, gaining insight into the biology of the patient's disease has been difficult. Without accurate prognostication, it has not been possible to conduct risk-stratified clinical trials, which has likely hindered progress. With newer methods of risk stratification, such as consensus clinical criteria or emerging noninvasive biomarkers, this may be changing. In addition, patients may be so ill that if therapy does not work quickly—and most agents do not—there may be complications, competing clinical risks, or impatience on the part of treating providers that render it impossible to determine whether the treatment was in fact successful.

H&O What led to the recent approval of ruxolitinib in this setting?

YC Until recently, no agents were approved by the US Food and Drug Administration (FDA) for the treatment of acute GVHD. In May 2019, the FDA approved ruxolitinib (Jakafi, Incyte) for the treatment of corticosteroid-refractory acute GVHD. The approval of ruxolitinib was based on the single-arm, multicenter phase 2 REACH1 trial (A Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease). Before the REACH1 trial, a series of anecdotal publications illustrating successful treatment with ruxolitinib propelled momentum and provided the enthusiasm for clinicians to enroll patients in the trial and advocate for it.

The data from REACH1 were impressive. It was a relatively large trial for corticosteroid-refractory GVHD, enrolling 71 patients from multiple centers. The study used several different criteria to define corticosteroid-refractory: disease that became worse after initial corticosteroids, disease that did not improve after initial corticosteroids, and disease that worsened after a taper of corticosteroids. Ruxolitinib appeared to have compelling efficacy across all definitions of corticosteroid-refractory disease, as well as all organs of involvement. The overall response rate was approximately 55% at day 28, and the complete response rate was approximately 27%.

H&O What is the mechanism of action of ruxolitinib?

YC The mechanism of action of ruxolitinib is uncertain. There are several potential mechanisms. Ruxolitinib inhibits the Janus kinase (JAK) 1 and 2 pathways. These pathways operate at a cellular level and lead to the production of cytokines that skew the immune response, leading to a certain type of inflammation that is thought to be very active in acute GVHD. One theory is that ruxolitinib inhibits or shuts down the T-cell activation that leads to acute GVHD. Another theory is that by shutting down the production of cytokines, ruxolitinib disrupts the cascade that initiates the activity of these pathways. Another possible mechanism is that ruxolitinib encourages reconstitution of regulatory T cells, which are suppressive and help in the recovery from acute GVHD. These mechanisms of action are compelling, in that ruxolitinib may be able to target specific pathways, rather than just exert a global immunosuppressive effect.

H&O Could you please discuss the clinical use of ruxolitinib?

YC A notable advantage of ruxolitinib is that many clinicians in the transplant field have already been using it for several years. Ruxolitinib was approved by the FDA for myelofibrosis in 2011 and for polycythemia vera in 2014. Clinicians are quite familiar with the drug's safety profile and thus have confidence in using it. Published data and our own experience clearly show that ruxolitinib has activity in acute and chronic GVHD. Given the REACH1 data and recent FDA approval, ruxolitinib is now the standard of care for patients with corticosteroid-refractory acute GVHD. There are, however, other treatment options, and there is still an unmet need for patients who do not respond satisfactorily to ruxolitinib. As mentioned previously, in the REACH1 trial, the rate of overall response was 55% at day 28.

There has been some concern about using an oral agent in patients with significant lower GI disease, and the corticosteroid-refractory GVHD population is inherently enriched for these patients. These patients may have trouble swallowing oral agents, and there is always a question of whether patients will absorb the agent effectively given the damage to their GI tract. The correlative studies presented in the REACH1 trial suggest that even patients with GI disease absorb a therapeutic level of ruxolitinib, so concerns can be allayed regarding this issue. There are still some clinicians, however, who will opt for therapies that are more easily given to such patients. At the same time, the FDA approval and the REACH1 data make it very compelling to strongly consider ruxolitinib in this setting.

H&O What are the adverse events?

YC At my institution, we have used ruxolitinib a great deal. We have not observed any significant unexpected adverse events that were attributed to ruxolitinib. The main known adverse events are cytopenias, a reflection of how the drug works. Blocking of signaling through the JAK2 pathway can interfere with the production of red blood cells and platelets, which can lead to anemia and thrombocytopenia, respectively. For most patients who develop cytopenias, the effects can be alleviated by temporarily discontinuing the drug or reducing the dose. We have not needed to stop treatment with ruxolitinib in a GVHD patient owing to adverse events, which are usually easily managed and not significant compared with those of other treatments used in this setting.

H&O Do you have any other recommendations for the management of acute GVHD?

YC There is clearly still more work to be done in the field of therapy for acute GVHD. In some patients, the disease will not respond to corticosteroids or ruxolitinib. We must continue to investigate additional therapeutic options for patients with corticosteroid-refractory acute GVHD, as well as to develop additional first-line treatments and novel strategies for prevention. Essential to this mission is an emphasis on enrolling patients into clinical trials, as well as overall thought and dialogue regarding the appropriate design and conduct of such trials. We should not be satisfied with only one approved agent for corticosteroid-refractory acute GVHD. We need to continue to engage in multicenter, collaborative clinical trials to move this field forward. The approval of ruxolitinib represents a major step, and it was especially encouraging to see investigators come together to conduct a multicenter clinical trial in collaboration with industry.

Finally, I would like to emphasize that caring for patients with severe GVHD is a team sport. Management requires contributions from physicians, nurse practitioners, nurses, physical therapists, nutritionists, social workers, and multiple other collaborating providers. Working in this multidisciplinary environment has been personally rewarding for me, as it has provided the opportunity for collaboration at my own institution as well as with many dedicated colleagues on the national level.

Disclosure

Dr Chen has performed consulting for Takeda, Magenta, Incyte, Kiadis, and AbbVie.

Suggested Readings

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