Allogeneic hematopoietic stem cell transplantation (HSCT) remains the sole curative treatment option for many patients with hematological malignant entities or bone marrow failure states. The population of patients undergoing allogeneic HSCT continues to increase because of expansion in the potential donor population achieved through the increasing use of both less than fully matched allogeneic donors and allogeneic HSCT in older recipients.\(^1\) The Center for International Bone Marrow Transplant Research estimated that the number of allogeneic HSCTs performed in the US increased to 9028 in 2018; it is likely that more than 30 000 allogeneic HSCTs are performed worldwide annually.\(^1\)

Yet, in the midst of a period of such improved patient access to care, major clinical challenges remain. Acute graft-vs-host disease (aGVHD) and chronic graft-vs-host disease (cGVHD) continue to affect patient outcomes and remain substantial causes of post-HSCT morbidity and mortality. aGVHD develops in approximately 30% to 70% of patients after allogeneic HSCT.\(^2\) In addition, cGVHD may develop in 35% to 50% of allogeneic HSCT recipients.\(^3\) The burden of illness associated with cGVHD may be enormous. The National Institutes of Health consensus criteria for cGVHD detail the potentially widespread nature of cGVHD, which may include ocular, cutaneous, oral, lung, gastrointestinal, liver, musculoskeletal, and urogenital tract involvement.\(^4\) Despite advances in transplant immunology, Center for International Bone Marrow Transplant Research data demonstrate that the incidence of cGVHD after allogeneic HSCT is actually increasing.\(^5\)

For patients for whom an adequate trial of systemic corticosteroids fails, a further escalation of systemic immunosuppressive or immunomodulatory treatment is necessary.\(^6\) For patients with steroid-refractory cGVHD, salvage treatment regimens include calcineurin inhibitors, mycophenolate, extracorporeal photopheresis, ibrutinib, imatinib, low-dose interleukin-2, pomalidomide, rituximab, sirolimus, and ruxolitinib.\(^3\) Despite increases in the number of effective treatment options over the past decade, there are still many patients whose care needs are not fully met. Moreover, the care of these patients is made even more complex by the enormous variability in patient presentation and cGVHD biology and a limited clinical ability to predict the optimal salvage regimen for a particular patient.

Over the past 3 years, the US Food and Drug Administration has approved 2 immunomodulatory agents for the salvage treatment of GVHD. This includes the approval of ibrutinib in 2017 for patients with steroid-refractory cGVHD and ruxolitinib in 2019 for salvage therapy of patients with aGVHD. There is particular interest in ruxolitinib for the management of cGVHD. Ruxolitinib is a janus kinase (JAK2) inhibitor, which may inhibit interferon-\(\gamma\) and interleukin-6 receptor signaling. An advantage of this agent is that it may have a clinical effect on GVHD while still preserving the graft-vs-tumor effect. In the REACH1 trial, ruxolitinib demonstrated significant activity in the treatment of steroid-refractory aGVHD. This effect was subsequently confirmed in the randomized, phase 3 REACH2 trial.\(^6\)

There is a growing body of evidence supporting a role for ruxolitinib in the treatment of steroid-refractory cGVHD. Wu and colleagues\(^7\) add materially to this growing body of evidence through their retrospective review of 41 consecutive patients with steroid-refractory cGVHD. Their patient cohort included 14 women and 27 men who had undergone allogeneic HSCT from either 32 human leukocyte antigen (HLA)–haploidentical or 9 HLA-matched donors. Of note, the patients undergoing...
haploidentical transplantation did not receive posttransplant cyclophosphamide as part of their GVHD prophylactic regimen. Instead, they received antithymocyte globulin. cGVHD was diagnosed in this cohort at a median (range) of 9.0 (3.3-27.2) months after HSCT. A median (range) of 3 (1-6) prior second-line regimens had failed for the patients before treatment. The patients received ruxolitinib at a dose of either 5 mg twice daily (for those weighing ≤60 kg) or 10 mg twice daily (for those weighing >60 kg). 

In the study by Wu et al,7 the median (range) time to a clinical response in the cohort was 2 (0.5-6.0) months. At a median (range) of 7.5 (1.0-24.9) months of treatment, the overall response to treatment rate was 70.7%; 15 patients achieved a complete response and 14 achieved a partial response. Among 26 patients with a response and 4 patients with stable disease, reductions in steroid dosing were achieved in 27 patients (90.0%), including discontinuation of steroids in 8 patients. Similarly, among 23 responding patients taking additional immunosuppressive salvage treatment, these agents were discontinued for 6 patients and the dose was reduced for 15 patients. Eighteen patients discontinued treatment because of treatment failure, infection or progression or relapse of the underlying malignant entity.

Wu et al7 found that salvage treatment with ruxolitinib was well-tolerated with a safety profile that included cytomegalovirus viremia in 5 of 34 patients undergoing assessment, Epstein-Barr virus viremia in 19 of 36 patients, hepatitis B virus reactivation in 1 patient, and bacterial infection in 2 patients. Ruxolitinib-related cytopenia was noted in 6 patients, including 1 with grade 4 thrombocytopenia.

Although the study by Wu et al7 is not a randomized clinical trial, in this group of 41 consecutive patients with steroid-refractory cGVHD, ruxolitinib demonstrated evidence of activity in heavily pretreated patients and appeared to be effective in patients receiving either HLA-haploidentical or matched-related donor grafts. Although the patients who received HLA-haploidentical grafts did not receive posttransplant cyclophosphamide as aGVHD prophylaxis, it is important to note the ruxolitinib response rate in this group. Treatment with ruxolitinib was reasonably well tolerated with predictable toxic effects that were manageable through effective preemptive detection and management of infectious complications and dose adjustments for cytopenia.

Before widespread clinical adoption, however, the results from Wu et al7 require further validation. These data may be forthcoming soon in data from the REACH3 phase 3 trial. Exciting preliminary REACH3 were presented at the American Society of Hematology annual meeting in December 2020.8

The advances put forth by Wu et al7 are welcome, but it is important to remember that patients with cGVHD require multidisciplinary care by a team that is experienced in the care of this unique patient population.3 Patients affected by cGVHD represent a unique population for whom a focus on distress management, infection monitoring, wound care, and management of the breadth of their care needs extends well beyond a single pharmacological intervention. By effectively integrating evidence-based advances in the care management of patients with cGVHD, including the use of agents such as ruxolitinib, into a multidisciplinary care delivery model, we can advance progressively toward a more effective, patient-centered set of care solutions for this unique population.
REFERENCES