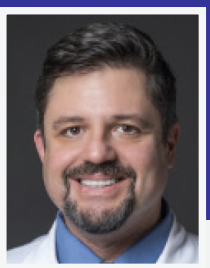

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The Risk of Delayed Diagnosis in Steroid-Refractory Acute GVHD

Up to half of patients undergoing allogeneic hematopoietic stem cell transplantation will develop graft-versus-host disease (GVHD), one of the major causes of transplant-related mortality.[1] The molecular events leading to acute GVHD (aGVHD) are thought to begin with damage incurred during conditioning, setting the stage for the alloimmune reaction that can occur after transplantation of the donor's stem cells.[2] Clinical manifestations of aGVHD generally arise days to weeks later due to activated immune cell migration and tissue damage in the skin, liver, and upper and lower gastrointestinal tract.[2,3]

> "We think everything starts when we see it clinically, but the reality is, it has been happening since we infused the graft."

Although systemic corticosteroid therapy has been the standard first-line treatment for aGVHD, only half of patients achieve durable aGVHD disease control and can have their steroid dose successfully tapered.[4-6] A joint task force of the EBMT, NIH, and CIBMTR has defined steroid-refractory (SR) disease based on the length of steroid treatment and resulting response.[3] Successful clinical trials in SR aGVHD have often employed similar SR definitions, which include patients with progressive disease following 3 days on ≥2 mg/kg/day prednisone or lack of improvement within 7 days of starting systemic corticosteroids.[7]

Failure to respond to steroids is an urgent situation, especially for patients with more severe manifestations. Cumulative steroid burden in patients who fail to respond or cannot taper leads to significant morbidity and mortality compared with patients who respond to steroid treatment.[8] This may help to explain why steroid-refractory and steroid-dependent populations have similarly poor 1-year outcomes.[9]

Few studies have examined progression of SR aGVHD in a modern setting. In an Incyte-sponsored retrospective chart review of 168 patients with SR aGVHD who reached a maximum GVHD grade of II to IV, disease progression was a frequent occurrence (Figure).[10]

Median time from diagnosis to maximum grade: 6 days

Among Patients Having Steroid-Refractory aGVHD at Diagnosis With:

SKIN ONLY	GRADES II OR III	ANY GRADE OR ORGAN
36% (n = 66)	**40%** (n = 134)	**54%** (n = 168)
Developed symptoms in a new organ	Advanced to a higher maximum grade	Developed new organ involvement or an increase in grade

High mortality was also observed in this population; 70% of the total population died at a median of 118 days.[10] This is similar to the mortality previously reported for the SR population.[8]

It is critical to closely monitor transplant patients for initial signs and symptoms of aGVHD and to frequently assess aGVHD response to steroids in order to optimize outcomes in this potentially life-threatening condition.

> "Identify [aGVHD], rule out other causes, and start treatment—I don't wait for biopsies. Acute GVHD is a time-sensitive disease.
>
> You need to intervene fast. The longer you wait, the greater the potential for organ damage."

CIBMTR, Center for International Blood and Marrow Transplant Research; EBMT, European Society for Blood and Marrow Transplantation; NIH, National Institutes of Health

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