FDA NEWS PERSPECTIVE

FDA approves Imbruvica as first therapy for chronic graft-versus-host disease

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The FDA approved ibrutinib for the treatment of adults with chronic graft-versus-host disease who failed prior systemic therapy.

Ibrutinib (Imbruvica; Pharmacyclics, Janssen) — a Bruton's tyrosine kinase inhibitor already indicated for treatment of certain patients with leukemia, lymphoma and Waldenstrom's macroglobulinemia — is the first therapy specifically approved to treat chronic GVHD.

"Patients with chronic GVHD who do not respond to other forms of therapy — typically corticosteroids to suppress their immune system — now have a treatment option specifically indicated to treat their condition," **Richard Pazdur, MD,** director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research, said in a press release. "This approval highlights how a known treatment for cancer is finding a new use in treating a serious and life-threatening condition that may occur in patients with blood cancer who receive a stem cell transplant."

The FDA based the approval in part on results from the open-label, multicenter, single-arm PCYC-1129-CA trial, designed to evaluate the efficacy and safety of 420 mg ibrutinib once daily for 42 patients with chronic GVHD who failed first-line corticosteroid therapy and required additional therapy.

Most patients (88%) had at least two organs involved at baseline, the most common of which were the mouth (86%), skin (81%) and gastrointestinal tract (33%).

Twenty-eight patients (67%; 95% CI, 51-80) achieved a response, with median time to response of 12.3 weeks. Researchers observed responses in all organs involved.

Twenty patients (48%) experienced symptom improvement for 5 months or longer.

The most common adverse reactions included fatigue, bruising, diarrhea, thrombocytopenia, stomatitis, muscle spasms, nausea, hemorrhage, anemia and pneumonia.

One patient experienced atrial fibrillation.

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Chronic GVHD is a major toxicity of bone marrow transplant, which is one of the most effective therapies we have for high-risk malignancies. Both patients and physicians are reluctant to undertake transplantation, not only because of its initial intensity, but because of some of the long-term toxicities. Even if patients are cured of their leukemia or lymphoma, they can end up with this immune-mediated disease that can affect their skin, liver, lungs, gastrointestinal tract and joints. When it is severe, it can be fatal. It is the dark side of the therapy.

Despite dozens of trials, nothing has ever worked, in part because we have not had good drugs, and in part because the trials are difficult to perform. Patients go home, and chronic GVHD may devlop insidiously; it is often initially treated by local physicians who do not have experience with chronic GVHD. By the time the patients make their way back to the transplant center, chronic GVHD can sometimes be very advanced and may not easily respond to therapy. This is one of the most challenging scenarios, not only in transplant medicine, but in all of medicine.

We have tried for a long time without making any headway. Steroids, the primary treatment, only work in less than half of patients. Further, chronic steroid treatment can cause diabetes, bone disease, joint problems and muscle wasting. Other drugs that have been investigated have produced responses in approximately one-third of patients, usually with inconsistent results.

Studies have now shown that B-lymphocytes that produce antibodies are involved in chronic GVHD pathology. Ibrutinib blocks a key signaling pathway primarily for B cells, including malignant B cells. It has already been FDA approved in diseases such as mantle cell lymphoma, lymphocytic lymphoma and chronic lymphocytic leukemia. Once we found out these cells were involved in chronic GVHD and the pathophysiology, we tried repurposing ibrutinib in this setting.

The results have been remarkable, with two-thirds of patients responding — almost one-quarter having complete response and about half having a partial response, many lasting for more than 6 months.

The FDA approval is based on a small, single-arm trial. But, nothing else has worked, and these patients with chronic GVHD who do not respond to steroid treatment are often desperate. This is great news for patients.

Because we now have strong evidence that ibrutinib works in chronic GVHD, we may be able to move this approach forward to primary treatment. Ibrutinib may be one way to catch the disease early, improve response rates and avoid some of the serious toxicities of steroid treatment.

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Disclosures: Ferrara reports he has no relevant financial disclosures.