FDA Approvals Expand Initial Treatment Options for Multiple Myeloma

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Two recent approvals by the Food and Drug Administration (FDA) broaden the initial treatment options for people who have a new diagnosis of multiple myeloma.

On July 30, FDA approved an injectable form of the drug daratumumab that includes hyaluronidase (Darzalex Faspro) given with bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone for patients who are eligible for an autologous stem cell transplant. On September 20, FDA approved isatuximab (Sarclisa) given with the same three drugs for patients who are not eligible for a stem cell transplant.

Both drugs target a protein called CD38, which is often found at high levels on myeloma cells.

For people newly diagnosed with multiple myeloma, stem cell transplants are a standard treatment and can lead to long-term remission. However, because of the intense chemotherapy-based conditioning regimen required to receive a stem cell transplant, some people—including those with other health conditions or pre-existing heart or lung issues—are not physically able to get a transplant.

The new approvals are a continuation of researchers' efforts to find combinations of different therapies that can lead to longer remissions in patients, regardless of whether they qualify for stem cell transplants.

Both approvals involve adding a drug—either daratumumab or isatuximab—to the standard initial three-drug regimen for newly diagnosed multiple myeloma, a combination of bortezomib, lenalidomide, and dexamethasone, commonly called VRd.

The approvals were based on findings from clinical trials showing that the four-drug regimens substantially increased the time patients lived without evidence of their cancer coming back or getting worse.

Patients treated with the four-drug regimens also were more likely to be minimal residual disease (MRD) negative, meaning that a highly sensitive test could not find any myeloma cells in bone marrow samples. Patients' MRD status is an indicator of how well a treatment is working beyond what can be detected with imaging scans and standard blood tests.

"These FDA approvals are good news for patients with multiple myeloma, who may now benefit from these more effective initial treatments," said Elizabeth Hill, M.D., a multiple myeloma specialist in NCI's Center for Cancer Research, who was not involved in either trial.

However, Dr. Hill cautioned that there are still unanswered questions about the best way to use these new combinations as initial treatments, including whether some patients might benefit from reserving the CD38-targeted therapies for when the cancer comes back, which happens in nearly all cases.

Daratumumab approval for transplant-eligible patients

FDA based its new approval of daratumumab for transplant-eligible patients on the results of a large clinical trial called PERSEUS, which was funded by the European Myeloma Network and Janssen, the manufacturer of daratumumab.

VRd has been the preferred treatment for people with newly diagnosed disease who are eligible for a transplant. But after a small clinical trial testing daratumumab combined with VRd produced promising results, PERSEUS was launched to confirm that the four-drug regimen was indeed better than VRd alone in these patients.

In the trial, 709 patients were randomly assigned to receive VRd alone or VRd with the injectable form of daratumumab. Lenalidomide and dexamethasone are taken as pills and bortezomib is infused into a vein (intravenous).

Because patients in the trial were eligible for a stem cell transplant, they underwent initial treatment with the three- or four-drug regimens, called induction therapy, followed by the transplant. They then received consolidation therapy with the same three- or four-drug regimen.

Following consolidation therapy, all patients received ongoing treatment, called maintenance therapy, with lenalidomide; those assigned to the daratumumab group also received daratumumab maintenance.

After a median follow-up of nearly 4 years, 84% of people in the daratumumab group were still alive without their cancer getting worse, compared with 68% of those who only received the standard treatment.

A greater number of people who received daratumumab had a complete response, meaning they showed no signs of cancer on standard tests. Additionally, 75% of people who received daratumumab reached MRD negativity and 65% remained MRD negative for more than a year. For

people receiving standard therapy, 48% reached MRD-negative status and only 30% remained MRD negative after one year.

Almost all people in the trial experienced side effects, regardless of which treatment they received, with most side effects ranging from moderate to severe (grade 3 or 4). The most common side effects were low blood levels of neutrophils, a type of white blood cell (neutropenia), and platelets (thrombocytopenia).

About 9% of patients in the daratumumab and VRd group stopped treatment because of side effects, compared with 21% in the VRd-alone group.

Isatuximab for transplant-ineligible patients

Isatuximab's approval was based on results from a large clinical trial called IMROZ, funded by Sanofi, the drug's maker. In this trial, 443 patients were randomly assigned to treatment with VRd alone or to VRd with the addition of isatuximab, given intravenously.

Patients underwent four cycles of induction therapy, followed by maintenance therapy with either isatuximab and lenalidomide or lenalidomide alone until there was evidence that the cancer was getting worse or that patients could no longer tolerate the side effects of treatment.

After nearly 5 years of follow-up, 63% of people in the isatuximab group were alive without their cancer getting worse, compared with 45% in the standard treatment group.

About 75% of people who received isatuximab had a complete response, compared with 64% of those treated with standard therapy. And more than 55% of isatuximab-treated patients had a complete response and were MRD negative. For those receiving standard treatment only, fewer than 41% had MRD negative responses. MRD negativity was maintained for more than a year in almost 47% of people receiving isatuximab versus about 24% in the VRd-alone group.

Side effects were similar between treatment groups and occurred in almost all patients. More than half of people in both groups had low levels of white blood cells called lymphocytes (lymphopenia), but neutropenia occurred more often in patients in the isatuximab group (54%) than in those receiving VRd alone (37%).

More people in the isatuximab group (11%) than the VRd-alone group (5.5%) died from causes other than multiple myeloma during treatment. Treatment-related deaths in both groups were most often related to infection (including COVID-19).

The importance of MRD negativity

Although multiple myeloma is considered incurable, advances in treatment have led to longer remissions and longer overall survival.

Assessing a patient's MRD status has emerged as a sensitive means of evaluating a patient's response to treatment, beyond traditional assessments such as bone marrow scans and blood tests for myeloma-specific proteins.

"We know that MRD is important for prognosis. If a patient's disease becomes MRD negative and that response is sustained, then progression-free survival is improved and overall survival is improved," said Dr. Hill.

In both trials, MRD was assessed using a highly sensitive test that can detect a single myeloma cell among 100,000 normal bone marrow cells. Dr. Hill said it's very encouraging that, in both studies, so many people treated with the four-drug regimens had complete responses and achieved MRD negativity.

"As recently as 5 or 10 years ago, we were not seeing MRD-negative outcomes, but now we are," Dr. Hill said.

Questions about four-drug therapy

One of the big questions patients and their oncologists will face when using these newly approved regimens involves the duration of maintenance therapy, Dr. Hill said.

The current standard treatment is for patients to stay on maintenance therapy until their cancer starts to progress again—which means continually having to deal with side effects, visits to receive treatment, and the costs of treatment.

However, with more effective therapies that are helping more people reach MRD negativity, is indefinite maintenance therapy still necessary? Dr. Hill suggested the example of a patient who has no evidence of disease and is MRD negative for several years. Can maintenance therapy be stopped in that patient?

"We still don't know the answer to this question but it's an exciting area of active research," she said.

There are also questions about whether including CD38-targeted therapy as part of the initial treatment is the best use of these drugs, wrote Edward Stadtmauer, M.D., of the University of Pennsylvania's Abramson Cancer Center, in an editorial that accompanied the results of the PERSEUS trial.

For example, daratumumab is often used, and is quite effective, as part of second-line treatment—that is, in people whose cancer has returned after their initial treatment.

But, Dr. Stadtmauer wrote, will using daratumumab as part of up-front maintenance therapy "compromise the efficacy of second-line daratumumab-based therapies that have become staples of modern treatment" for multiple myeloma?

NCI is sponsoring several trials to help answer some of these questions. In one trial, researchers are investigating whether people who are MRD negative after 2 years can stop maintenance therapy. Another trial is comparing maintenance therapy with daratumumab and lenalidomide versus lenalidomide alone.

Finally, investigators with both the PERSEUS and IMROZ trials continue to follow study participants to determine how these regimens affect overall long-term survival and other outcomes.

“This is a golden age of treatments for patients with myeloma,” wrote Dr. Stadtmauer. He concluded that most patients with newly diagnosed disease can expect rapid and lasting responses to therapies with tolerable side effects.

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