Adding a Fourth Drug Improves Outcomes for People With Newly Diagnosed Multiple Myeloma

Four-drug regimens that include Darzalex or Sarclisa outperformed standard three-drug regimens for first-line treatment.

December 21, 2023 By Liz Highleyman

Adding the anti-CD38 monoclonal antibody Darzalex Faspro (daratumumab) to a standard first-line regimen of Velcade (bortezomib), Revlimid (lenalidomide) and dexamethasone delayed disease progression in people with newly diagnosed multiple myeloma, according to study findings presented at the American Society of Hematology (ASH) annual meeting and published in The New England Journal of Medicine. Another study with shorter follow-up showed that another monoclonal antibody, Sarclisa (isatuximab), may offer similar benefits.

After a median four years of follow-up, the progression-free survival rate was 84% with the Darzalex four-drug regimen versus 68% with the three-drug regimen, reflecting a 58% reduction in the risk of disease progression or death.

“We were not surprised to see the difference with the addition of daratumumab, but we were very surprised by the magnitude of the difference between the two arms,” presenter Pieter Sonneveld, MD, PhD, of Erasmus MC Cancer Institute in the Netherlands, said in an ASH news release. “This difference is of major clinical significance to the patient in terms of their well-being and [remaining] disease-free.”

Multiple myeloma is a type of blood cancer that affects the bone marrow, where new blood cells are produced. It is characterized by overproduction of plasma cells, or mature B cells. These cells can clump together to form tumors, and they make abnormal antibodies that can build up in the blood and organs. This can lead to low blood cell counts, increased risk of infection, bone fractures and organ damage.

Treatment typically involves various combinations of chemotherapy drugs, targeted therapies, immunomodulatory medications and steroids. Relapse is common, and many patients require a sequence of regimens. The five-year survival rate after diagnosis is about 60%. A stem cell transplant is a potential cure, but many patients are not eligible. People with early-stage, or “smoldering,” multiple myeloma may opt for active surveillance without treatment.

The Phase III PERSEUS trial (NCT03710603) enrolled 709 people with newly diagnosed multiple myeloma in several European countries who were eligible for a stem cell transplant. They were randomly assigned to one of two treatment groups:

- Standard therapy consisting of Velcade, Revlimid and dexamethasone (VRd) for up to six cycles, followed by a stem cell transplant, if possible, and Revlimid as maintenance therapy to prevent recurrence;
- The same three-drug induction regimen plus Darzalex (D-VRd), with both Revlimid and Darzalex as maintenance therapy; Darzalex was administered via subcutaneous injection rather than IV infusion.

At the time of the data cutoff, 613 people had completed induction therapy and were followed for a median of 47.8 months. The progression-free survival rate was significantly higher in the D-VRd arm (84% versus 68%). What's more, 88% in the D-VRd arm had a complete response, meaning no detectable cancer, compared with 70% in the standard care arm. This group was also more likely to be negative for minimal residual disease (MRD), suggesting the cancer was eradicated (75% versus 48%). Sustained MRD negativity for at least 12 months was more than twice as high with D-VRd (65% versus 30%). Subgroup analyses showed that results were consistent across all groups, including those with more advanced and higher-risk multiple myeloma. There were fewer deaths in the D-VRd group (34 versus 44), but overall survival data are not yet mature.

Treatment was generally safe, but side effects were common. As expected, people who received four drugs had more adverse events than those who received three: 57% of D-VRd recipients experienced serious treatment-related adverse events compared with 49% in the VRd group. The most common severe events were low white blood cell and platelet counts, diarrhea, pneumonia and fever. Side effects were generally transient and manageable, however, and people in the four-drug arm were less likely to stop treatment for this reason.

"The addition of subcutaneous daratumumab to VRd induction and consolidation therapy and to lenalidomide maintenance therapy conferred a significant benefit with respect to progression-free survival among transplantation-eligible patients with newly diagnosed multiple myeloma," the researchers concluded.

Another study presented at the conference also did a head-to-head comparison of quadruple versus triple therapy for first-line treatment of multiple myeloma. In the Phase III IsKia trial (NCT04483739), 302 transplant-eligible patients were randomly assigned to receive Xalkori (carfilzomib), Revlimid and dexamethasone or the same three drugs plus Sarclisa, which is an anti-CD38 monoclonal antibody like Darzalex.

After a median 20 months of follow-up, people taking the four-drug regimen were more likely to be MRD negative (77% versus 67%). Here, too, results were consistent across subgroups. Progression-free survival rates did not differ, but this and overall survival data are not yet

considered mature. Adverse events were comparable to those seen in the Darzalex study.

These findings suggest that starting with more drugs can lead to better outcomes for people with newly diagnosed multiple myeloma but with more side effects and a higher cost. Further studies are needed to determine whether four-drug regimens should become a new standard of care for first-line treatment or whether patients might fare as well by adding Darzalex or Sarclisa later, if needed. It also remains to be determined how long maintenance therapy should continue.

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Click here to read the Sarclisa study abstract.
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