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Is There a Universal Standard of Care for Frontline Therapy in Multiple Myeloma?

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H&O What is the most common regimen for frontline treatment in multiple myeloma?

SL The standard regimen in the United States for fit patients with multiple myeloma consists of a monoclonal antibody that targets CD38 plus an immunomodulatory drug, a proteasome inhibitor, and a corticosteroid. In practice, that usually refers to the monoclonal antibody daratumumab (Darzalex, Janssen Biotech) plus lenalidomide, bortezomib, and dexamethasone—a regimen known as Dara-VRd. This may be followed by autologous stem cell transplant, consolidation therapy with Dara-VRd, and maintenance therapy, typically with lenalidomide. The Dara-VRd regimen became widespread on the basis of results of the phase 3 PERSEUS trial, which showed that the addition of daratumumab to triplet therapy increased the 4-year estimated progression-free survival rate from 67.7% to 84.3% among transplant-eligible patients with newly diagnosed multiple myeloma.[1]

H&O What other regimens are used as frontline treatment in multiple myeloma?

SL An easy switch that we often see is the replacement of daratumumab with a different CD38-targeting antibody, isatuximab (Sarclisa, Sanofi Genzyme), in a regimen known as Isa-VRd. This regimen was examined in the phase 3 IMROZ trial, which found that the addition of isatuximab to VRd during initial therapy improved the estimated progression-free survival rate at 60 months from 45.2% to 63.2% in adults with newly diagnosed multiple myeloma who were ineligible to undergo transplant.[2]

Another option is to change the proteasome inhibitor from bortezomib to carfilzomib (Kyprolis, Amgen), creating the regimens Dara-KRd and Isa-KRd. Several studies have looked at the use of Dara-KRd, including the MASTER study, which demonstrated high rates of MRD negativity and attempted to make use of short-term sustained MRD negativity to de-escalate therapy.[3] Isa-KRd was studied in the IsKia, GMMG-CONCEPT, and MIDAS trials. The phase 3 IsKia trial found that the addition of isatuximab to KRd therapy improved the rate of MRD negativity (10^{-5} cutoff) after consolidation from 67% to 77% among transplant-eligible patients with newly diagnosed multiple myeloma.[4,5] The phase 2 GMMG-CONCEPT trial found that Isa-KRd induced high rates of sustainable MRD negativity in patients with high-risk, newly diagnosed multiple myeloma, regardless of transplant status.[6] The phase 3 MIDAS trial supported the use of Isa-KRd in transplant-eligible patients with newly diagnosed multiple myeloma, in which 91% of patients achieved a very good partial response or better after induction.[7] This is an exciting time for patients because we have so many treatment options.

H&O What are the most common adverse events with Dara-VRd, Isa-VRd, Dara-KRd, and Isa-KRd? How do you choose among these regimens?

SL The most common adverse events associated with

CD38 antibodies are related to an elevated incidence of infections. This risk can be addressed with the early use of antibiotics and, in the setting of recurrent infections, by administering prophylaxis with intravenous immunoglobulin. Some patients experience more neutropenia when an immunomodulatory drug is combined with an anti-CD38 antibody, but otherwise, side effects are not appreciably higher than those seen with VRd or KRd alone. VRd has been the backbone of therapy for some time at our center, so that adding subcutaneous daratumumab has been our go-to approach for patients who are fit. For those who are frail, Dara-Rd is our go-to regimen.

> My advice is to find a regimen you are comfortable with and stick with it so you can anticipate the adverse event profile and know how to tailor the regimen according to what the patient is telling you during the course of treatment.

H&O Should patient age, performance status, or transplant eligibility drive different frontline approaches to multiple myeloma, or is there a one-size-fits-all regimen?

SL A lot of trials have looked at the use of a 4-drug regimen in transplant-eligible and transplant-ineligible patients. The divide between eligible and ineligible patients is a bit artificial because in the United States we do not typically use age as a discriminator between those who can and cannot receive a transplant. Among transplant-eligible patients, receiving all 4 drugs is the standard, but among those deemed to be ineligible, the dose and schedule of the drugs may be changed a little. The challenge with many of the trials performed in an "ineligible" population is that they were done in Europe, where transplant eligibility ends at 65 years, whereas it is not uncommon for 74-, 75-, and 76-year-olds to undergo transplant in the United States. I prefer to categorize patients as either fit or frail. If you have a fit patient, a 4-drug regimen makes sense, whether that means Dara-VRd, Isa-VRd, Dara-KRd, or Isa-KRd—whatever flavor of treatment you want. If you have a frail patient, I am not convinced that the use of 4 drugs is the answer. In that case, I would often use daratumumab in combination with lenalidomide and dexamethasone, or Dara-Rd, because I am not sure what the value of bortezomib is as the fourth drug in a frail patient.

H&O Are we seeing too much variation in practice patterns, or does the variation reflect appropriate personalization of care?

SL We see variation in determining which patients are transplant-eligible vs which are not, but that is something that can evolve over time. Decision making about transplant eligibility can be challenging on the first day you meet a patient because the patient's functional status may improve with treatment. Some patients who are not transplant-eligible at first may become transplant-eligible over the course of their first few cycles of therapy.

To maximize long-term outcomes, it is important to lay out a solid long-term plan when you first meet the patient, even if you need to adjust the plan later according to the response and side effects. At the same time, we do not want to be switching from one CD38-targeting agent to a different one because they all work the same—there is very little biological rationale for making that change.

H&O What role should access play when multiple effective frontline options exist?

SL We can learn a lot by looking at statistics regarding transplant. We know that of the patients with multiple myeloma in the United States who are considered transplant-eligible, only 30% are referred for a transplant, which tells me that access is a big issue. Another example is that when we look at outcomes by race, the survival curves are not as good for Black patients as they are for other patients with multiple myeloma because fewer Black patients are offered quad induction or transplant as part of their initial therapy.

H&O Where do you see the field heading—toward more standardization or the continued diversification of frontline approaches?

SL I think there is going to be more standardization. The idea of genomic personalization does not really exist in multiple myeloma the way it does in many solid tumors; mutation-driven therapy does not last very long in multiple myeloma. For now, we are focusing on the backbone

agents that make up Dara-VRd and related regimens, and we are looking forward to the introduction of B-cell maturation antigen–targeted therapeutics such as antibody-drug conjugates, chimeric antigen receptor T-cell therapy, and bispecific antibodies.

H&O How do you reconcile the gap between clinical trial populations and real-world patients who may not qualify for these studies?

SL It is always a bit of a challenge to reconcile the gap between clinical trial populations and real-world patients because the patients in clinical trials tend to be fitter and younger, with fewer comorbidities. That is where the art of managing patients becomes more challenging—something that exists in every disease we treat as oncologists. My advice is to find a regimen you are comfortable with and stick with it so you can anticipate the adverse event profile and know how to tailor the regimen according to what the patient is telling you during the course of treatment.

H&O What advice do you have for community oncologists who treat patients with multiple myeloma?

SL The field of multiple myeloma treatment is moving fast, so it can be difficult to stay in touch with what is going on. My advice to community oncologists is to partner with a major myeloma center—there are approximately 10 of them around the country—to make sure that your treatment paradigm aligns with theirs. This partnership means that the community oncologist is aware of state-of-the-art approaches to treatment while patients can still be treated relatively close to home. Allowing patients to receive treatment closer to home is an important goal, but we do not want to compromise care because not every oncologist can be aware of exactly what was presented at a meeting a month earlier. Approaches to treatment are changing almost every 3 to 6 months in multiple myeloma, which is so fast that the guidelines often cannot keep up.

Furthermore, guidelines can be vague—they may not provide all the subtleties and nuances that come from having a connection with an oncologist who sees many patients with multiple myeloma. Here at Emory, we see approximately 300 patients with myeloma weekly. We also receive a fair number of phone calls, texts, and emails from physicians in our region who are trying to understand what we are doing as our standard of care. A common question is how to find appropriate ways to make dose modifications. These are quick communications, rather than someone trying to get through via our call center. This allows our institution to share our experience and have a broader impact. For instance, with bortezomib, we find that providers often want to know whether they should adjust the dose of bortezomib according to adverse events during the cycle as opposed to waiting until the end of the cycle and seeing if the week off therapy makes a difference. It is important that infusion nurses be empowered to help guide dose holds or reductions in response to the development of symptoms, even in the middle of a given cycle. The same can be said for dexamethasone dose reductions. This is a relatively easy decision if patients have had a good response to the first 2 to 4 cycles of therapy; reduction in dosing is much easier if the patient's disease is responding to therapy. These are subtleties that we have been able to pick up on because we treat a lot of people.

Disclosures

Dr Lonial has served on the scientific advisory board of Takeda, Amgen, Novartis, BMS, GSK, AbbVie, Genentech, Pfizer, Regeneron, and Janssen; has received research support for clinical trials from Novartis, BMS, Janssen, and Takeda; and serves on the board of directors with stock from TG Therapeutics (neurology and autoimmune indications only).

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