Managing Myeloma

Multiple Myeloma Safety, Tolerability, and AE Considerations

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Overview

Welcome to this issue on safety, tolerability, and adverse event (AE) considerations in newly diagnosed multiple myeloma (NDMM). This edition will focus on treatment toxicities and the importance of providing patients with the best outcomes without adding additional toxicity and side effects when adding more drugs. We will discuss the clinical data that support the use of triplet and quadruplet regimens in patients with NDMM and consider the benefit-risk profile of current treatment regimens.

The SWOG777 trial showed the benefits of RVd (lenalidomide + bortezomib + dexamethasone), but the median age was only 63 years.[1] The RVd-lite regimen was tested in older patients with a median age of 73 years but showed that two thirds of patients develop peripheral neuropathy.[2] Does this cause safety concerns for the RVd regimen in older patients?

The SWOG777 study was one of the most important trials of its time, revealing that a combination of three medications was superior to two, regarding progression free survival (PFS) and overall survival (OS). We now know that a minimum of three drugs is important in all patients, but as with all regimens, it's important to watch for toxicities. SWOG777 was an older group but it was designed for those who do not intend to go to transplant; SWOG777 did include some younger patients.

RVD-lite offers an option for older patients who are frail or are not going to transplant and allows for dose adjustments of these three medications. Patients still get the benefit of three medications but with less toxicity. Bortezomib is an excellent drug, but it does require significant monitoring to ensure peripheral neuropathy doesn't develop. All patients need to be monitored for peripheral neuropathy, not just older patients. Certainly, it is applicable to our older patients who may already have underlying peripheral neuropathy, as a complication of diabetes, for example, or frail patients who may be at risk of falls and no additional insults can be allowed that may compromise their balance, or their functional capacity. We must pay attention to our frail patients and not withhold drugs while remaining vigilant about dose adjustments and monitoring for peripheral neuropathy to know when to stop or decrease the dose accordingly.

The MAIA trial tested DRd (daratumumab + lenalidomide + dexamethasone) in patients with a median age of 73 years, while SWOG777's RVd regimen was tested in patients with a median age of only 63 years.[1,3] Does this make the DRd regimen preferable to the RVd regimen in older patients with NDMM?

The MAIA trial did include an older frailer population as opposed to the SWOG777 trial, which included younger patients who opted out of transplant. The MAIA trial offers appropriate therapy for older patients as it is the true cohort. MAIA data was fantastic, showing real benefit and tolerability, and is the preferred regimen in older frailer patients with NDMM.

CEPHEUS compared daratumumab + RVd versus RVd alone as induction therapy.[4] Daratumumab has shown promise in first-line NDMM treatment.[4] Do you have any safety, tolerability or AE concerns with the use of daratumumab on its own or in combination NDMM treatment?

As we previously learned that three drugs are better than two, now we are seeing that four drugs give better outcomes than three. It's important to provide patients with the best outcomes without additional toxicity when adding more drugs. The significant benefit of daratumumab upfront means that we need to figure out how to manage any overlapping toxicity. Daratumumab does not add significant toxicity on its own, but in combination with other medications causes some overlapping toxicity, such as neutropenia or infusion-related reactions, which are very manageable. The aim is to give patients the best treatment that they can safely tolerate.

The IMROZ trial is comparing isatuximab plus RVd versus RVd alone as induction therapy to treat NDMM, but isatuximab caused grade 3-4 AEs in 63% of patients with the most common grade 3-4 AEs being blood and lymphatic system disorders (26%), neutropenia (23%), and lymphopenia (15%), all common effects of the disease itself.[5] Do you see a place for isatuximab in the treatment of NDMM based on these safety concerns?

I see a place for CD38 monoclonal antibodies in the treatment of NDMM, whether that is isatuximab or daratumumab. Trial results are showing the benefit of monoclonal antibodies upfront, and while grade 3 and 4 toxicities are real, they are manageable. With adequate surveillance and oversight to monitor safety concerns, we can justify their use because of the significant response and improvement in outcomes seen. The benefit outweighs the risk with isatuximab and daratumumab.

Anti-B-cell maturation antigen antibodies (BCMA)-directed CAR T-cell therapy, ciltacabtagene autoleucel (cilta-cel), is quite active in late relapse and early relapsed multiple myeloma.[6] However, the CARTITUDE trial showed higher rates of grade 3-4 lymphopenia, neutropenia, leukopenia, anemia, and thrombocytopenia with cilta-cel.[6] Do these safety issues cause concern for cilta-cel use in early and later line NDMM therapy?

CAR T-cell therapies cause cytopenias and potentially prolonged cytopenias as common side effects, not specific to cilta-cel. The benefit we have seen from cilta-cel as late relapse therapy make its use worth any potential cytopenia-related toxicity.

Do these safety concerns affect other BCMA-directed CAR T-cell therapies?

We see hematologic toxicity with any hematologic malignancies receiving CAR T-cell therapies, so with careful surveillance and monitoring, we can justify and mitigate these risks to allow patients to enjoy the successes of CAR T-cells both in late relapse and hopefully in earlier lines of therapy in the future.

As we move towards early versus delayed transplant, instead of transplant-ineligible versus transplant-eligible, we will see more NDMM patients getting stem cell transplants.[7] Do stem cell transplants carry any significant risk of serious complications?

Upfront early transplant remains the standard of care and while the most recent data tells us that patients can delay their transplant, doing so may give them a decreased PFS. Our transplant trends have not changed, and the timing of a transplant does not necessarily alter the risk of serious complications. The transplant-related complications, including cytopenias and infections, remain the same whether the transplant is early or delayed.

The FORTE study showed KRd (carfilzomib + lenalidomide + dexamethasone) to be superior to KCd (carfilzomib + cyclophosphamide + dexamethasone) but 24% of patients in the KRd arm required plerixafor versus only 10% in the KCd arm.[8] What are the implications of the high need for plerixafor in the KCd arm?

The University of California, San Diego investigated plerixafor use and found that using it upfront for stem cell collection decreased overall costs because it decreased stem cell collection time overall. Plerixafor use could decrease medical care costs through shorter therapy duration, with greater success. The University of California, San Diego uses plerixafor upfront for all patients.

The MASTER 2.0 trial incorporates T-cell engagers as part of the consolidation approach in the hopes of being able to stop therapy.[9] Bispecific T-cell engager (BiTE) therapies are one of the most promising therapeutic approaches in multiple myeloma and in cancer in general. Are you concerned about the safety profile of T-cell engager therapy, specifically grade ≥3 cytokine release syndrome (CRS) and neurotoxicity?

With new drugs come new toxicities that we all must learn and understand how to manage. The benefits and successes of bispecific T-cell engager therapies have been positive and have shown that new toxicities we have become comfortable with, including CRS and neurotoxicity, are very relevant. However, fortunately, at least with the one BCMA targeted BiTE that is available and approved by the FDA, the rates of grade 3 or greater CRS and neurotoxicity are relatively low. While we are learning how to manage these and potentially prevent them from happening altogether, the severity of the AEs in patients receiving these drugs are generally grades 1 and 2. With respect to the safety profile, the benefits outweigh the risks to those patients receiving the medication.

Are there mechanisms to reduce the risk of bispecific T-cell engager systemic toxicity such as CRS and neurotoxicity?

To date, we have learned how to manage toxicity of bispecific T-cell engagers such as CRS and neurotoxicity with medicines such as tocilizumab and dexamethasone. We will see however, there's going to be more of a pre-emptive approach to reducing the risk of this happening, potentially using for example tocilizumab upfront, which may also not only reduce the risk of CRS, but potentially allow for the treatments to be administered in the outpatient setting successfully and safely. Institutions are trying to figure out how we can reduce this risk and make it a better experience for patients.

Lenalidomide has been used as maintenance therapy in the PERSEUS trial.[10] Are there any long-term side effects of lenalidomide maintenance therapy use?

We have a wonderful track record on the use of lenalidomide as maintenance in the post-transplant setting and we've learned a lot over the last decade or more about strategies of how to manage potential acute side effects and surveillance for long-term toxicity of lenalidomide maintenance. Many patients with myeloma who have received lenalidomide maintenance can testify to the fatigue and diarrhea that are common with long-term lenalidomide use. The fatigue can sometimes be both a physical and a mental fatigue. With some dose adjustments we could provide patients with a more tolerable side effect profile which will allow them to stay on therapy and benefit from the improvements and OS.

We always discuss cost of therapy. The cost of drugs is real and must be reviewed with patients. In addition, the fact that there is a small increased risk of secondary cancers for patients who undergo transplant and lenalidomide maintenance, requires patients stay up-to-date on age-appropriate cancer screening, including dermatologic skin cancer screening, to monitor for secondary malignancies.

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