Managing Myeloma

## Optimizing Treatment Sequencing and Strategies

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**Overview**
Welcome to this issue on optimizing treatment sequencing and strategies in newly diagnosed multiple myeloma (NDMM). The main topics of this issue will be treatment sequencing and approaches, as well as the significance of giving patients the best results without increasing toxicity and side effects when adding more drugs. The clinical evidence that supports the use of triplet and quadruplet regimens in patients with NDMM will be discussed, and the benefit-risk profile of the available treatment regimens will also be considered.

**The standard of care in transplant-eligible patients with NDMM is induction therapy with RVd (lenalidomide + bortezomib + dexamethasone), followed by transplant, followed by maintenance.[1] Is RVd still the appropriate standard of care induction therapy or are new studies challenging this standard?**

When we think about standard induction for a transplant-eligible patient, two sets of questions come up. The first is, RVd versus KRd (carfilzomib + lenalidomide + dexamethasone), which was addressed in the ECOG (Eastern Clinical Oncology Group) trial for standard-risk myeloma patients and demonstrated equivalency between RVd and KRd in a standard-risk myeloma patient. The second question remains unknown in terms of high risk, but most groups are willing to accept the potential increased toxicity of KRd in a high-risk patient to try and deepen and maintain a response early on.

The second question is about the addition of an anti-CD 38 monoclonal antibody. I think most groups now, at least among the academic centers, have adopted the addition of daratumumab or isatuximab to an RVd backbone to make it so that we no longer use a triplet in newly diagnosed myeloma, but we really talk about a quadruplet in NDMM. The area where there is still some level of disagreement is the potential benefit of an anti-CD 38, particularly in a high-risk patient population. Quadruplet therapy has become the mainstay of treatment with an RVd plus daratumumab approach for induction.

We have not yet adopted daratumumab in the maintenance or consolidation phase. I never think about what I'm going to do in relapse. I want to maximize first remission and duration, and second, if I'm only using four cycles, collecting cells, taking them to transplant, and then putting them on risk-adapted maintenance, I can still use daratumumab in the salvage setting because I've only given it for four cycles with induction. I think that's how most of us think about this right now.

**RVd-lite (modified lenalidomide + bortezomib + dexamethasone) is an option for older frail patients, allowing dose adjustments of the three medications.[2] What are the factors that clinicians consider when choosing RVd-lite over RVd induction therapy?**

It is about frailty, it's not about age. The reason I say that is there are patients aged 50 whom I wouldn't perform a transplant on, and there are patients in their mid to upper 70s whom I would. I think frailty and function are what it comes down to. If you're not sure, challenging them with regular doses of induction therapy and seeing how they tolerate it likely represents one way to answer that question. I think RVd-lite or modified RVd are regimens that do have value. In the frailer patient, I use it in the high-risk group. DRd (daratumumab + lenalidomide + dexamethasone) has almost become the standard, and except for high-risk patients, I'm going to use DRd for most of my frail patients.

**The CEPHEUS trial is looking at daratumumab + RVd quadruplet induction therapy.[3] Do you expect quadruplet therapy to become the standard of care induction for NDMM treatment?**

The adoption of daratumumab plus Rd came to use from the Maia trial where DaraRD was compared with RD and there was a significant improvement in PFS and OS favouring the use of DRD for transplant ineligible patients.[4] While the construct of eligible vs ineligible remains under scrutiny, it is clear that the DRD PFS, OS and depth of response was much higher than anything we have seen in the past. In an effort to further build on that, CEPHEUS randomizes transplant ineligible patients to either VRD or DVRD with the goal of seeing if a quad induction is tolerable, and ultimately better than VRD alone. This is an important study, but I think will be very helpful as we seek to better define optimal therapy for older patients, and in particular the frail older patient.

**The GMMG-HD7 study measured minimal residual disease (MRD) with the addition of an anti-CD38 monoclonal antibody, isatuximab to RVd.[5] At the end of induction therapy, isatuximab plus RVd resulted in significantly more MRD negative patients than the RVd-alone arm.[5] Is MRD a relevant substitute for PFS and overall survival (OS)?**

One of the challenges with MRD assessment is knowing when the right time to check is. It's a surrogate for response to induction because the complete response (CR) rate and the VGPR (very good partial response) rates are so high with either triplets or quadruplet-based induction. In that sense, I don't have an issue using MRD negativity as an endpoint from a regulatory perspective. The mistake is using MRD negativity to make a treatment decision. While from a regulatory perspective, it's a reasonable thing to look for, I don't think it's a treatment decision endpoint, particularly after only four or five cycles of therapy. I think it's far too soon to make a decision on treatment that early.

**The FORTE study showed KRd (carfilzomib + lenalidomide + dexamethasone) to be superior to KCd (carfilzomib + cyclophosphamide + dexamethasone).[6] How do you compare these regimens to RVd and/or DRd?**

The FORTE study demonstrated that the best response in PFS was with KRd plus a transplant with KR maintenance. Unsurprisingly, KCd and VCd (bortezomib + cyclophosphamide + dexamethasone) are inferior. We know that KRd head-to-head with RVd in the ECOG trial was no better for standard risk.

For high-risk KRd may offer benefit. I have doubts about whether the risk-benefit ratio translates into a standard risk patient in general.

DRd is a different story because it has only been tested in an older frail population. Both the IFM trial and the FORTE trial were in younger, fitter patients. I'm not sure that's a fair comparison, but certainly, KRd does have data supporting its use and I believe it's strongest in the high-risk group.

**Early upfront transplant has been the standard of care and studies show that delaying transplant may decrease the patient's PFS. What are the major factors for a patient with NDMM to be classified as transplant-ineligible?**

For the ineligible subset, in my opinion, it's about frailty. It's not about age but more about function. Patients that have significant cardiac or vascular comorbidities or patients who are not very mobile for pre-existing reasons, are patients that I would consider frail or transplant ineligible. It comes down to function more than any individual factor.

**It is widely stated that distinguishing NDMM as transplant eligible or non-eligible will fall away as CAR T-cell therapies and bispecific antibodies become frontline treatment.[7] Is this because CAR T-cell therapies and bispecific antibodies are expected to make early transplants possible in almost all patients with NDMM? Even those previously classified as transplant-ineligible?**

CAR T-cell therapies are certainly easier to take for the average patient than a transplant. I don't think of it as being nearly that intense. If your intent is to replace transplant, meaning high dose melphalan with CAR T-cells, then that might be one way to increase the pool of people who are able to get consolidation with something different than they have had as part of induction. It remains to be seen what the PFS of CAR T-cell therapy after induction therapy is. Will you give those patients maintenance? If so, for how long and what will you use? Those are all questions that we don't have the answer to right now.

Transplant continues to offer benefit, not because of the immunologic maneuver, but because of high dose methylate. It clearly has activity and can take patients to lower levels of MRD negativity and can be safely done in the right patients. For patients for whom I don't think transplant is eligible because of frailty, I'm not 100% sure that I'm going to feel comfortable giving them a CAR T-cell therapy, but certainly, some of them might be eligible for bispecific antibodies. I think those are questions we have to determine over time.

**Daratumumab has few safety or toxicity concerns on its own, while long-term use of lenalidomide commonly causes fatigue and diarrhea. Could daratumumab be used as maintenance therapy in patients that are able to go into clinics for the injections? Are there any studies of its use as maintenance therapy?**

Daratumumab does potentially offer the opportunity to be used as a maintenance backbone due to the issues with lenalidomide and particularly with bortezomib in the chronic administration state. The real question with chronic administration of daratumumab is the infectious complications that may occur by suppressing anti-CD38 for an extended period.

One of the biggest predictors of lack of response to the covid vaccine in myeloma patients is being on either daratumumab or an anti-B-cell maturation antigen (BCMA)-directed therapy. In my

opinion, the question is how long you have to treat to get the clinical benefit without potentially exposing the patient to infectious complications. There are current trials looking at daratumumab or cetuximab as maintenance therapy, and we await that data.

**The FORTE study used KR (carfilzomib + lenalidomide) versus R (carfilzomib) as maintenance.[6] Do you expect dual maintenance therapy to become standard therapy?**

If a patient is at standard risk and they get RVd, single transplant, and lenalidomide maintenance, the median PFS for that group is 80 months. That's a long time. I don't know that I want to give KR maintenance to those patients because they do so well with single-agent lenalidomide.

However, many of them can be salvaged with a long-second remission. On the other hand, in high-risk patients, it's been proven that VR (lenalidomide + bortezomib) is better than R (lenalidomide) alone. I think KR is our current approach for those patients. I don't think KR has become the standard for everybody. I think KR has become a standard for high-risk patients, and either you need to show that you can make the PFS longer than 80 months with KR, which I think is hard to do, or show that you can stop maintenance sooner by giving KR, and that's a set of questions that I don't think we have yet begun to ask.

**For patients that cannot tolerate lenalidomide, what maintenance therapy options are available?**

I try and get my patients to at least a year on lenalidomide if I'm able to, by adjusting the dose or changing the schedule. If I really can't get them to a year, then I'll switch to either carfilzomib or bortezomib as a potential maintenance approach. Cetuximab is something I've used as well. We just know that lenalidomide in general is so much easier to give. Even if I get down to 5mg or 2.5mg every other day, I'll try and do that if I can to try and keep patients on some form of oral maintenance for as long as I can.

**There is data that suggests that pomalidomide-based triplet therapies are effective following the development of lenalidomide-refractory disease in early and later relapses.[8] Are pomalidomide-based triple therapies used regularly following early and later relapses?**

Some of this is a question of style more than anything else. If you've got a patient who is relapsing on lenalidomide, what is your go-to salvage regimen? At our center, it has been pomalidomide + daratumumab for a long time. What we then did was look back and try to understand which patients got the most benefit from that. What we identified was that patients who'd been in remission for at least three years from diagnosis, seemed to gain the greatest benefit from pomalidomide + daratumumab as maintenance therapy.

However, in patients who had a shorter than three-year initial remission, their PFS with pomalidomide + daratumumab was relatively short. In general, pomalidomide + daratumumab or pomalidomide + isatuximab, which has similar data from other studies, represent our go-to regimen for patients who fit the right category.

**Patients who become refractory to immunomodulatory drugs, proteasome inhibitors, and CD38 antibodies have a poor prognosis.[9] What are the options, if any, for these patients?**

These are patients whom I begin to go to BCMA-directed therapy, whether it's a bispecific antibody or a CAR T-cell as an alternative option. Those are certainly options we go to relatively quickly. If

they're t(11;14)-positive, then venetoclax might be something we think about in that situation. Selinexor represents another potential option. I tend to go with BCMA-directed therapy if I can in this patient population because we know the efficacy is very good and the data is strong. It's just a matter of the timing of that treatment and what the patient's tolerance for adverse events is as you make a decision for a bispecific antibody versus a CAR T-cell therapy.

**References:**


1. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet*. 2017;389(10068):519-527. doi:10.1016/S0140-6736(16)31594-X
2. O'Donnell EK, Laubach JP, Yee AJ, et al. A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. *Br J Haematol*. 2018;182(2):222-230. doi:10.1111/bjh.15261
3. Zweegman S, et al. ASCO 2019. Abstract TPS8066. ClinicalTrials.gov Identifier: NCT03652064. Accessed February 24, 2022.
4. Facon T, et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. *N Engl J Med*. 2019;380:2104-2115.
5. Goldschmidt H, Mai EK, Bertsch U, et al. Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplantation-eligible patients with multiple myeloma (GMMG-HD7): part 1 of an open-label, multicentre, randomised, active-controlled, phase 3 trial. *Lancet Haematol*. 2022;9(11):e810-e821. doi:10.1016/S2352-3026(22)00263-0
6. Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. *Lancet Oncol*. 2021;22(12):1705-1720. doi:10.1016/S1470-2045(21)00535-0
7. Richardson PG, Jacobus SJ, Weller EA, et al. Triplet therapy, transplantation, and maintenance until progression in myeloma. *N Engl J Med.* 2022; 387:132-147. DOI: 10.1056/NEJMoa2204925
8. Lovas S, Obajed Al-Ali N, Varga G, et al. Pomalidomide Treatment in Relapsed/Refractory Multiple Myeloma Patients-Real-World Data From Hungary. *Pathol Oncol Res*. 2022;28:1610645. Published 2022 Oct 3. doi:10.3389/pore.2022.1610645
9. van de Donk NWCJ. Sequencing multiple myeloma therapies with and after antibody therapies. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):248-258. doi:10.1182/hematology.2020000109


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