Managing Myeloma

The Advent of Four-drug Combinations in the Frontline Setting: How Will This Change Current Practice?

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Learning Objectives:

- Describe recent clinical trial data evaluating novel four-drug combinations in the frontline setting in the treatment of myeloma
- Discuss the role of MRD testing in trials investigating four-drug regimens and the impact to clinical practice
- Identify treatment-emergent side effects associated with four-drug regimens and optimal management strategies to mitigate these toxicities

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We are hearing an increasing amount about the potential for moving beyond 3-drug combinations to improve the efficacy of multiple myeloma treatment in the frontline. What is the rationale for looking at a quadruplet therapy in that setting?

The current standard of care for newly diagnosed myeloma is to use 3-drug combinations, which also includes dexamethasone. The 2 most commonly used combinations right now are the bortezomib, lenalidomide, and dexamethasone (VRd) combination that's used both in the transplant eligible and non-transplant eligible setting, as well as the daratumumab, lenalidomide, and dexamethasone (DRd) combination that has been studied primarily in the setting of non-transplant eligible patients. Both these regimens have excellent data from phase 3 trials.[1-4]

The VRd combination was studied in the Southwest Oncology Group (SWOG) S0777 trial, in comparison to lenalidomide and dexamethasone, demonstrating an improved progression-free survival (PFS) as well as an overall survival (OS) for the 3-drug combination compared to the 2 drugs.[1,2] The VRD combination was also studied as a pre-transplant induction therapy. Newly diagnosed myeloma patients were eligible to go to a stem cell transplant in the IFM 2009 phase 3 trial where they compared transplant versus no transplant, and it was found to be an excellent induction regimen prior to the stem cell transplant.[5] Based on data from these trials, the VRD combination had become the standard initial treatment for

patients with myeloma. Even in the patients who are older, transplant ineligible, and more frail, adaptations of the VRD regimen like VRD lite[6] have been used as initial therapy for those patients, thus giving them the benefit of using the 3-drug combination in comparison to 2 drugs.

With the introduction of the new classes of drugs, particularly the monoclonal antibodies, the question that came up is, should we replace bortezomib with a monoclonal antibody? Or are we better off adding that newer class of drug to the existing 3-drug combination to create a 4-drug regimen? That led to several clinical trials.

The CASSIOPEIA trial[7] was the first to evaluate a 4-drug combination, particularly in the setting of transplant eligible patient populations. The CASSIOPEIA trial randomized patients to getting bortezomib, thalidomide, and dexamethasone (VTd) triplet versus adding daratumumab to that VTd regimen. That trial also had a second randomization to daratumumab maintenance versus no maintenance. What we know from the results of that trial is that adding daratumumab to VTD clearly improved PFS.[7] We are still waiting for the OS data, as well as data on the impact of the maintenance with daratumumab versus no maintenance.

Given that VTD is not a commonly used regimen in the United States, the GRIFFIN trial, which randomized patients to VRd vs daratumumab plus VRd, is more pertinent to the US practice. In that trial, daratumumab was added to VRd, given for 4 cycles before stem cell transplant, 2 cycles of consolidation, and then daratumumab plus lenalidomide maintenance vs lenalidomide maintenance. The primary results of GRIFFIN demonstrate that daratumumab with VRd induction and consolidation significantly improved the depth of response—a 2- to 3-fold higher proportion of patients were minimal residual disease (MRD) negative compared to the VRd combination.[8] We still don't have data in terms of PFS or OS, as we don't have long-term follow-up on that study yet.

A similar approach has been taken in phase 2 studies, where daratumumab has been added to ixazomib, lenalidomide, and dexamethasone, as well as to bortezomib, cyclophosphamide, and dexamethasone. Both of them have demonstrated a high rate of response, and also deep responses, suggesting that 4-drug combinations are highly effective.[9,10]

In the non-transplant patient population, daratumumab has also been added to bortezomib, melphalan, and prednisone (VMP) regimen, which had been the backbone regimen for older patients until newer drugs came along. The ALCYONE trial randomized patients to receive the daratumumab plus VMP versus VMP, again showing that there was an improved PFS, and with longer-term follow-up, there was also improved OS.[11]

The data we have from these multiple trials suggest that adding a monoclonal antibody to the existing 3-drug combinations seems to really improve patient outcomes, both in terms of depth of response, and the durability of response, though the data on overall survival is still lacking in majority of these studies.

There are other combinations that are being explored as well. There is another anti-CD38 monoclonal antibody, isatuximab, which is being studied in combination with VRd in a phase 3 study called IMROZ.[12] And then we also have elotuzumab, the SLAMF7 antibody, which has been combined with VRd and with carfilzomib, lenalidomide, and dexamethasone (KRd). There was a randomized phase 2 SWOG trial that looked at adding elotuzumab to VRd in a high-risk patient population that did not show any benefit for adding elotuzumab.[13] Similarly, there was a trial that was done in Europe where elotuzumab was added to ixazomib, lenalidomide, and dexamethasone that did not show an improvement in outcome.[14] It's unclear if elotuzumab as a fourth drug has really any role in the upfront setting yet.

There are other ongoing trials that are looking at these 4-drug combinations. One is PERSEUS,[15] a randomized phase 3 trial that is similar to GRIFFIN, but much larger, and instead looking at patients for whom transplant is not planned as initial therapy. Patients are randomized to daratumumab plus VRd or VRd with a primary endpoint of MRD negative status.

How do 4-drug combinations figure into treatment decision making for patients with newly diagnosed myeloma?

Whether we should routinely use 4 drugs or 3 drugs is an important question that will not be fully answered for at least for the next 2 or 3 years when we have more data from clinical trials. However, I think we can use some of the data we have right now to help make that decision for individual patients.

From our own perspective, we have decided to use the 4-drug combination in patients with high-risk disease. We know that patients with high-risk disease have the best outcome if they achieve MRD-negative status. We know we can get deeper responses by using 4-drug combinations, so we believe that might be the best option for these patients, just looking at the MRD data alone.

Now, it's quite possible that the 4-drug regimen will also be much better in standard-risk patients; however, we are not ready to do that yet because we don't have any long-term survival data for 4-drug combinations compared to the 3-drug combinations. Standard-risk patients already have excellent outcomes with the 3-drug combination, especially in the context of transplant, so whether the potential for long-term toxicity with 4 drugs will in any way offset any advantage that the 4 drugs brings along is an important question. I think we feel more comfortable using 4 drugs in high-risk patients because we know that the existing 3-drug combinations only go so far for them.

One other aspect of the 4-drug regimens that is going to be important is their impact on cost of therapy. As we know, none of these drugs are inexpensive, and when we use 4-drug combinations, the cost of therapy significantly goes up. One question is, can we limit the duration of therapy? If these treatments are continued until disease progression, that can be quite expensive. There are trials that are looking at

this question of whether every patient needs 4 drugs, or can we identify the patients who are likely to benefit the most. A currently open phase 3 trial in the Eastern Cooperative Oncology Group (ECOG) called the EQUATE[16] includes newly diagnosed myeloma patients who are either transplant ineligible or are willing to defer the stem cell transplant to first relapse; they are treated with 9 cycles of DRd and then randomized, stratified by MRD status, to adding bortezomib to DRd or to continue on the same DRd regimen for another 9 cycles, and then they go on to maintenance. What we really would like to learn from this trial is whether adding the fourth drug provides a benefit, and if so, is that benefit limited to people who have not responded well to the initial therapy? Or does everyone benefit, irrespective of the depth of response? If everyone benefits, then I think that data, combined with the data we have on the upfront 4-drug combination trials would prove beyond doubt that 4 drugs is better than 3 drugs.

With the EQUATE trial in mind, what is the current role of MRD testing in myeloma, both in terms of prognosis, and in terms of its potential for guiding treatment?

While MRD testing has been fairly common in hematology, particularly in the acute leukemia setting and in chronic myeloid leukemia, it has become mainstream in myeloma only more recently. Data from many of the phase 3 trials that were done over the past decade have demonstrated that there's a clear survival advantage for patients who reached MRD negativity with their treatments. This led to the incorporation of MRD assessment as part of the International Myeloma Working Group response criteria.[17] In multiple myeloma, MRD negativity in the bone marrow is defined as having less than 1 in 100,000 nucleated cells being myeloma cells. There have been two different approaches that have been used in determining MRD status in the bone marrow in myeloma: one is flow cytometry, and the other is next-generation sequencing. They are quite comparable in sensitivity, but each have some advantages and disadvantages, and different institutions and different studies have adopted one or the other methodology.

The prognostic value of MRD status has been demonstrated in two large meta-analyses,[18,19] both of which showed that for patients with MRD negativity in the bone marrow, the outcomes are better, both in terms of PFS and OS. This has been shown in the context of patients within transplant as well as non-transplant, and also for patients with complete response as well as patients who continue to be in a very good partial response. From a response criteria standpoint, a patient is truly considered to be MRD negative when they're immunofixation negative in the serum and urine, and also have a bone marrow assessed by next-generation sequencing or flow cytometry to be having less than 1 in 100,000 plasma cells. Now, with the next-generation flow cytometry and next-generation sequencing, we can achieve a sensitivity of 1 in 1,000,000. We know that if we can go deeper in terms of the response, the outcomes are better, though that hasn't necessarily translated to any change in how we define MRD negativity at this point in time.

So when we think about the role of MRD status in myeloma, there are 3 main uses. The simplest use is as a prognostic factor, based on evidence from those meta-analyses and phase 3 trials. If a patient achieves MRD negativity with a given treatment, they will do better than the patients who aren't MRD negative at the same time point, with the same treatment.

The second use of the MRD status is as a surrogate endpoint for survival in clinical trials. We are looking at a median PFS close to 8 to 10 years for myeloma patients today, which makes it very difficult to do clinical trials if we are looking at PFS and OS as endpoints. There has been a lot of interest in identifying surrogate markers that can be assessed much earlier and that will translate into a much longer-term outcome like PFS or OS. MRD testing appears to fit the bill there, based on the meta-analyses, so there's an ongoing effort to put together the data for the regulatory agencies to allow us to do clinical trials with MRD negativity as an endpoint.

The third potential use of MRD is to guide treatment, and that has been the biggest challenge. If a patient is MRD positive, we don't know whether or not we can improve their outcome by giving a different treatment or intensifying treatment to try to achieve MRD negativity. On the other end of the spectrum, if a patient is MRD negative over a year or 2 years of therapy, we don't know if decreasing or discontinuing therapy would improve their overall quality of life and also decrease the cost of care, without reducing the survival outcomes.

There are no prospective data from the clinical trials to guide us, though there are clinical trials currently ongoing that are specifically asking this question. One is the EQUATE trial that we already discussed, where we are thinking about using MRD status as a potential tool for intensifying therapy. A similar trial is being initiated in ECOG, called the OPTIMUM trial,[20] which will include patients with multiple myeloma after stem cell transplantation. The patients will receive MRD testing after one year of lenalidomide maintenance, and if they still have residual disease, they are randomized to getting ixazomib, lenalidomide, and dexamethasone versus continuing on lenalidomide, dexamethasone. A third is SWOG study S1803, also known as DRAMMATIC, which is a phase 3 study of daratumumab/rHuPH20 plus lenalidomide or lenalidomide as maintenance therapy after autologous stem cell transplant.[21] This study is essentially looking at the role of MRD to direct duration of therapy; after 2 years of maintenance, if patients are MRD negative, they are randomized to discontinuing therapy versus continuing on to maintenance. Between these trials, I think we will be able to get some answers to the question of whether can we use MRD negativity as an actionable tool in the clinic.

How could MRD status also inform the use of 4-drug combinations, as explored in the MASTER trial?

The MASTER trial[22] evaluated the use of daratumumab and KRd as induction prior to autologous transplantation, and also assessed the feasibility of using MRD by next-generation sequencing to inform

the use and duration of post-transplant consolidation with daratumumab and KRd. This was a relatively large phase 2 study with more than 100 patient. If they had 2 consecutive MRD-negative tests, then they would discontinue therapy, versus continuing on to the subsequent phases. A substantial proportion of patients, almost three-fourths, achieved MRD negativity with this approach. It is clearly a very important study in the sense that it shows that an MRD-targeted approach is feasible. It is a single-arm trial, so it could be hard for us to draw conclusions as to what is the right thing to do. Nevertheless, I think it will give us a good sense of where to start when designing future trials. I think it's very important in terms of trying to limit the duration of therapy, especially in patients who are getting really deep responses, because doing so may improve the patient's quality of life while decreasing the cost of therapy. If patients can go for years without treatment, and then their myeloma does come back, it's more than likely that they will continue to get good responses by reusing some of the same drugs.

What about treatment-emergent side effects with 4-drug regimens? Does the efficacy advantage of adding a fourth drug outweigh any additional toxicity burden?

Obviously, one of the biggest concerns that we have with quadruplets is the potential for toxicity. There's no question the efficacy is much better, so if efficacy was the only metric that we went by, then the quadruplets would be preferred over the triplets. However, adding a fourth drug to the mix does increase the risk of toxicity. Whether we look at GRIFFIN, ALCYONE, or CASSIOPEIA, we do see a higher rates of hematological toxicity, including more grade 3 to 4 hematological toxicity, with the use of the 4-drug combinations.[7,8,11]

What are the implications of a higher rate of toxicity? The impact might be limited in younger patients who are proceeding to a stem cell transplant and using a 4-drug combination for a limited period of time, ie, 4 months of induction therapy. However, quadruplet therapy may also affect stem cell yield. In the CASSIOPEIA trial, the median number of CD34+ cells collected was lower for patients receiving daratumumab-VTd compared to those that were induced with the 3-drug combination. Nevertheless, there was no difference between groups in the number of patients who went on to receive autologous stem cell transplantation.[23] Further study is needed in terms of the potential impact of these drug combinations on the ability to collect adequate stem cells, especially for more than one stem cell transplant in patients in whom we are considering a tandem approach.

Now, for the patients who are not candidates for transplant, continuing on these quadruplets for the longer term could also bring out cumulative toxicity, particularly cumulative hematological toxicity that might really limit how long we would be able to give these drugs. So the trade-off here is whether by using 4 drugs, patients may be more likely to end up discontinuing some of these drugs, whereas by giving it as a 3-drug combination, we may be able to sustain the therapy for longer periods of time. That

is an important question, because at least in the triplet setting, we know that the longer duration of therapy certainly seems to be associated with better outcomes in some of the studies.

On the other hand, with the 4-drug combinations, if you are able to limit the total duration of therapy with the 4 drugs and still get the same or better benefit as the 3 drugs used for longer period, there could be a upside to it, because there might be long-term toxicities that we might be able to mitigate.

With some of these newer drugs, including the monoclonal antibodies, we really don't know what the long-term effects will be because we have only more recently started using them in this setting. We know there is some immunosuppression that goes with this class of drugs. Both proteasome inhibitors and monoclonal antibodies increase the risk of viral reactivation of herpes zoster, hepatitis B, hepatitis C, and so forth, so that is something that needs to be kept in mind. We also know that myeloma patients may experience profound hypogammaglobulinemia, especially when they're getting these 4-drug combinations. What would be the impact of these kind of toxicities in the long term?

So while all of these toxicities could be of concern, by limiting the duration of therapy yet still getting the same degree of benefit, the quadruplets might be able to overcome these disadvantages by giving patients a drug-free interval, which will allow patients to reconstitute their immune system in a better manner, now that the disease is under better control.

As we await further results from 4-drug combination studies, what do you see as the most important future goal that could be achieved with this approach?

Treatment of myeloma has significantly improved over time. A lot of that improvement has been as a result of combination therapies that have allowed us to achieve deep responses in the majority of patients. The ability to get the disease down to a very low level is certainly one of the goals that we need to be able to achieve, while at the same time minimizing the toxicity. So I think the goal for the future would be using quadruplet regimens in a fashion that does not significantly enhance the toxicity, but in fact limits the toxicity by limiting the duration of therapy, while still achieving deep responses.

These drug combinations are going to be the way to treat many patients with myeloma in the future, though the type of drugs and regimens will change over time as we get new and effective therapies. In particular, as some of the new immunotherapies come on board, we might see that these drug combinations will change in terms of the particular drugs in the mix.

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. Durie BGM, Hoering A, Sexton R, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: Bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). *Blood Cancer J.* 2020;10(5):1-11. doi:10.1038/s41408-020-0311-8

3. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2016;375(14):1319-1331. doi:10.1056/NEJMoa1607751

4. Kaufman JL, Usmani SZ, San-Miguel J, et al. Four-Year Follow-up of the Phase 3 Pollux Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) Alone in Relapsed or Refractory Multiple Myeloma (RRMM). *Blood.* 2019;134(Supplement_1):1866-1866. doi:10.1182/blood-2019-123483

5. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. *N Engl J Med.* 2017;376(14):1311-1320. doi:10.1056/NEJMoa1611750

6. 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

7. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): A randomised, open-label, phase 3 study. *Lancet.* 2019;394(10192):29-38. doi:10.1016/S0140-6736(19)31240-1

8. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: The GRIFFIN trial. *Blood*. 2020;136(8):936-945. doi:10.1182/blood.2020005288

9. Kapoor P, Gertz MA, Laplant B, et al. Phase 2 Trial of Daratumumab, Ixazomib, Lenalidomide and Modified Dose Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma. *Blood.* 2019;134(Supplement_1):864-864. doi:10.1182/blood-2019-131476

10. Yimer H, Melear J, Faber E, et al. Daratumumab, bortezomib, cyclophosphamide and dexamethasone in newly diagnosed and relapsed multiple myeloma: LYRA study. *Br J Haematol.* 2019;185(3):492-502. doi:10.1111/bjh.15806

11. Mateos M-V, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): A randomised, open-label, phase 3 trial. *Lancet*. 2020;395(10218):132-141. doi:10.1016/S0140-6736(19)32956-3

12. ClinicalTrials.gov. A Phase 3 Randomized, Open-Label, Multicenter Study Assessing the Clinical Benefit of Isatuximab (SAR650984) in Combination With Bortezomib (Velcade®), Lenalidomide (Revlimid®) and Dexamethasone Versus Bortezomib, Lenalidomide and Dexamethasone in Patients With Newly Diagnosed Multiple Myeloma (NDMM) Not Eligible for Transplant. clinicaltrials.gov; 2020. Accessed March 4, 2021. https://clinicaltrials.gov/ct2/show/NCT03319667

13. Usmani SZ, Hoering A, Ailawadhi S, et al. Bortezomib, lenalidomide, and dexamethasone with or without elotuzumab in patients with untreated, high-risk multiple myeloma (SWOG-1211): Primary analysis of a randomised, phase 2 trial. *Lancet Haematol*. 2021;8(1):e45-e54. doi:10.1016/S2352-3026(20)30354-9

14. van de Donk N. 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.

15. ClinicalTrials.gov. A Phase 3 Study Comparing Daratumumab, VELCADE (Bortezomib), Lenalidomide, and Dexamethasone (D-VRd) With VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects With Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant Is Not Planned as Initial Therapy. clinicaltrials.gov; 2021. Accessed March 4, 2021. https://clinicaltrials.gov/ct2/show/NCT03652064

16. ECOG-ACRIN Cancer Research Group. Effective Quadruplet Utilization After Treatment Evaluation (EQUATE): A Randomized Phase 3 Trial for Newly Diagnosed Multiple Myeloma Not Intended for Early Autologous Transplantation. clinicaltrials.gov; 2021. Accessed March 4, 2021. https://clinicaltrials.gov/ct2/show/NCT04566328

17. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016;17(8):e328-e346. doi:10.1016/S1470-2045(16)30206-6

18. Landgren O, Devlin S, Boulad M, Mailankody S. Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: A meta-analysis. *Bone Marrow Transplant.* 2016;51(12):1565-1568. doi:10.1038/bmt.2016.222

19. Munshi NC, Avet-Loiseau H, Rawstron AC, et al. Association of Minimal Residual Disease With Superior Survival Outcomes in Patients With Multiple Myeloma: A Meta-analysis. *JAMA Oncol*. 2017;3(1):28-35. doi:10.1001/jamaoncol.2016.3160

20. ClinicalTrials.gov. Optimizing Prolonged Treatment in Myeloma Using MRD Assessment (OPTIMUM). clinicaltrials.gov; 2020. Accessed March 4, 2021. https://clinicaltrials.gov/ct2/show/NCT03941860

21. ClinicalTrials.gov. S1803, Phase III Study of Daratumumab/RHuPH20 (NSC-810307) + Lenalidomide or Lenalidomide as Post-Autologous Stem Cell Transplant Maintenance Therapy in Patients With Multiple Myeloma (MM) Using Minimal Residual Disease to Direct Therapy Duration (DRAMMATIC Study). clinicaltrials.gov; 2021. Accessed March 4, 2021. https://clinicaltrials.gov/ct2/show/NCT04071457

22. Costa LJ, Chhabra S, Godby KN, et al. Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd) Induction, Autologous Transplantation and Post-Transplant, Response-Adapted, Measurable Residual Disease (MRD)-Based Dara-Krd Consolidation in Patients with Newly Diagnosed Multiple Myeloma (NDMM). *Blood*. 2019;134(Supplement_1):860-860. doi:10.1182/blood-2019-123170

23. Hulin C, Moreau P, Attal M, et al. Stem cell (SC) yield and transplantation results from transplant-eligible newly diagnosed multiple myeloma (TE NDMM) patients (pts) receiving daratumumab (DARA) + bortezomib/thalidomide/dexamethasone (D-VTd) in the phase 3 CASSIOPEIA study. *Haematologica*. 2021 Mar 4. doi: 10.3324/haematol.2020.261842. Online ahead of print.

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