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Fighting Multiple Myeloma With Triplet Therapy

Dr. Turck:
For multiple myeloma patients looking to delay a stem cell transplant, a triple therapy treatment plan may improve outcomes. Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck and here to share a patient case example of triplet therapy in multiple myeloma is Dr. Joshua Richter, an Associate Professor of Medicine, Hematologist, and Oncologist at Mt. Sinai Hospital. Dr. Richter, thanks for joining me today.

Dr. Richter:
Thank you so much for having me.

Dr. Turck:
So, Dr. Richter, let's begin by taking a look at the treatment landscape for multiple myeloma. What treatment options are currently available and what kind of patient would be right for triplet therapy?

Dr. Richter:
So, you know, I think one of the things that's been a push and pull throughout the years in myeloma is do you shove all of your drugs upfront and then have nothing in the back end or do you really space things out and give what we used to call 'sequential doublets'? And we, kind of, sort of, met in the middle and now the general schema is sequential triplets. Triplet up front, triplet at relapse, and triplet at subsequent relapses. So, in general, three drugs seem to be the better. And although there is quite a number of drugs that are approved, what we know in the current day and age is one drug is better than zero, two drugs is better than one, three is better than two, and in a handful of situations, four may be better than three. But for the time being, three drugs is our standard.

Dr. Turck:
And how does triplet therapy compare to doublet therapy alone?

Dr. Richter:
So, we've had quite a number of therapies across the last five to ten years that have compared two versus three-drug regimens. And, you know, starting off at the beginning of up-front therapy, initial treatment for many years in the United States, lenalidomide and dexamethasone, what we call Rd as a doublet has been the standard of care based off of a trial called the FIRST trial. But there've been a few studies in recent years to show that three is even better. There is the SWOG 0777 trial which looked at giving Velcade, Revlimid, and dexamethasone, VRd compared with Rd, and the more recent MAIA study that compared DARZALEX-Rev-dex, so DRd versus Rd. And in both studies, the triplet did far better than the doublet and this has really emerged as our two standards of care in the up-front setting.

Dr. Turck:
Now, let's look at this in the context of a patient case. Dr. Richter, would you give us an example of a patient with multiple myeloma who fit the profile for triplet therapy, and would you give us a sense of how the patient presented?

Dr. Richter:
Absolutely. So I see many, many patients with myeloma and I am a big believer in transplant, but I recognize that it's not appropriate for everyone. And earlier this year I saw a lovely 79-year-old female who had a long-standing history of id a bone marrow biopsy review and we saw that along with, you know, evidence of polycythemia vera, she had about 30 to 40 percent clonal plasma cells in her bone marrow. She had a free light chain, a free kappa light chain of over 1,300 and along with it, her creatinine was rising, and her creatinine was now just a little over 2.0, about 2.1, 2.2, a little bit of anemia. And we did a PET scan, and we found a few small lesions so we, you

know, described her as having symptomatic multiple myeloma.

So, you know, we discussed with her a variety of different induction regimens. We explained that there are a few key triplets up-front VRd and DRd, given the fact that she's a little bit older and has a myeloid malignancy, we are not planning to pursue a stem cell transplant, so we discussed the outcomes of these two major trials, the SWOG 0777 and the MAIA study. And the SWOG 0777 was amazing, it showed that VRd had a median progression-free survival of 43 months, but the MAIA trial, which has been presented recently, the median progression-free survival has not yet been reached but is greater than 60 months. So, with our older, frailer, transplant-ineligible patients, we can now get them more than five years of continued remission without the need for a transplant. So, we decided to proceed with a DARA-Rev-dex regimen. She's about five cycles into it. She has achieved a biochemical complete remission, and her most recent creatinine is down to 1.3. So, she's doing phenomenal, and the overall plan is to continue her on this treatment until intolerability or progression of disease.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck and I'm speaking with Dr. Joshua Richter about triplet therapy for patients with multiple myeloma.

Let's dig a little bit deeper into this patient case. Dr. Richter, after assessing the patient for triplet therapy, how did you then approach treatment?

Dr. Richter:
Absolutely. So, you know, there are a lot of the studies that we've looked across the last few years have been comparing three versus two drugs. There haven't been many three-drug versus three-drug or triplet versus triplet regimens, although there was a study that was presented recently called the ENDURANCE trial, which compared the VRd regimen, which has been a standard triplet for many years with KRd, substituting Kyprolis for Velcade. And what that study found was that in transplant-ineligible patients, there was no difference in outcome between the two regimens. However, those receiving KRd had a higher rate of cardiac, renal, and pulmonary toxicity and specifically people over the age of 70 had a higher rate of cardiac issues. So, although there is some hint that KRd may be more optimal in a transplant-eligible patient, for older patients, it seems like VRd is equivalent in terms of efficacy and a safer regimen. But overall, we decided to go with the DARA-Rev-dex because not only is the efficacy amazing, but logistically, it's quite easy, as once you get six months out on the regimen, the DARZALEX is just a once-a-month subcutaneous shot and the rest is oral medication.

Dr. Turck:
Now, with that in mind, how do you think the use of triplet therapy impacted this patient's outcomes and overall care experience?

Dr. Richter:
So, one of the things that we've recognized is that at every phase in myeloma, the deeper remission you achieve correlates to better outcomes. So, if we get you in a PR, partial remission, you'll do better than if you have stable disease. And if we get to you a VGPR, a very good partial remission, that's 90 percent reduction or more in your M-spike, you'll do even better. And a complete remission is even better and so on. And the fact is we know that you get deeper and more durable remissions with triplets. So, the fact that this patient is able to not only tolerate it, but has so far achieved a biochemical complete remission, means on average, she is not going to relapse until sometime in her mid-80s or beyond, meaning that with this type of triplet approach, we may be approaching her actuarial survival if she did not have myeloma at all.

Dr. Turck:
So, Dr. Richter, what do you think this experience stands to teach us about the use of triplet therapy in patients with multiple myeloma?

Dr. Richter:
Absolutely. We, for years, have been, kind of, thinking 'well, what's a better approach: a dose-adjusted triplet or a full dose doublet?' And, you know, time and time again, we see that the dose-adjusted triplet is better. So, although I could've given this patient 40 mg of dexamethasone and 25 mg of Revlimid, which would've been the full dose doublet, here instead, we dose-adjusted everything. The DARZALEX is a standard dose, 1,800 mg. We brought the dexamethasone from 40 mg down to 20 and the Revlimid from 25 down to 10, accounting for her renal insufficiency. And overall, this has resulted in not only excellent response, but she's tolerated the therapy very well. And that's the key. We know that patients who come off of therapy for reasons such as toxicity, overall do worse because they don't reap the full benefit of the regimen. So, making sure you dose-adjust all of the medicines according to your renal levels, renal function, age, other comorbidities, and really having these long discussions, we're able to kind of walk that perfect balance between efficacy and toxicity.

Dr. Turck:
And before close, Dr. Richter, what would you say are some key takeaways for our clinicians on the use of triplet therapy in multiple

myeloma?

Dr. Richter:
I think the key takeaways are a triplet can be given in essentially all patients. You know, I think in the realm of general oncologists who see a lot of solid tumors like colon cancer, lung cancer, going from a two to a three-drug regimen with classical chemotherapy is quite difficult, especially in older patients. You know, trying to add on cisplatinum or adrimycin to a 90-year-old on top of a doublet of chemo is quite a lot to ask of them in terms of toxicity. But for myeloma in the realm of novel agents, going from two to three drugs is often extremely tolerable, especially if dose-adjusted appropriately. And the reality is that our triplets, both in the up-front and early relapse have predominantly shown the best outcomes by utilizing DARZALEX or daratumumab in combination with drugs like Revlimid, drugs like pomalidomide or drugs like KYPROLIS.

Dr. Turck:
Well, with those considerations in mind, I want to thank my guest, Dr. Joshua Richter for joining me today and sharing his insights on the use of triplet therapy in patients with multiple myeloma. Dr. Richter, it was great having you on the program today.

Dr. Richter:
Thank you so much for having me and I hope to do it again one day.

Dr. Turck:
I'm Dr. Charles Turck, to access this and other episodes in our series, visit ReachMD.com/ProjectOncolgy, where you can be part of the knowledge. Thanks for listening.