Choosing the Best Treatment Regimen in Multiple Myeloma

Podcast Episode 1: Newly diagnosed multiple myeloma

Brought to you by;
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Joshua Richter
Hello, and welcome to this podcast series on multiple myeloma.

My name is Dr. Joshua Richter, I'm an Assistant Professor of Medicine at the Tisch Cancer Institute Icahn School of Medicine at Mount Sinai in New York, New York and the Director of Myeloma at the Blavatnik Family Chelsea Medical Center at Mount Sinai. I'm joined with Dr. Karthik Ramasamy.

Karthik Ramasamy
Thank you, Josh. Exciting to chat about myeloma with you, as always. My name is Karthik Ramasamy, I'm a Consultant Haematologist as well as Associate Professor of Haematology at Oxford University Hospitals UK.

In these two podcast episodes Josh and myself will discuss how we go about choosing treatment regimens in our patients with multiple myeloma. In this episode we will focus on newly diagnosed myeloma patients and in the second episode we will discuss treatment selection in the relapsed/refractory setting.

Let's start to talk about selecting the best approach for treatment in newly diagnosed myeloma patients Josh. So, I guess the first thing to really think about when we see a patient diagnosed with myeloma is… What are the key factors we consider when deciding how we

start treating this particular patient? So, I want to invite your views about this particular issue.

Joshua Richter
Thank you so much, and as always, a pleasure to chat. I think you and I have chatted over the years and we have a lot of agreements, a few disagreements, but I think we see eye to eye on a lot of this.

At least on this side of the pond in 2021 we would still say upfront at initial diagnosis: is somebody transplant eligible or transplant ineligible? Not that there are any firm and hard rules about what you can or cannot do, except kind of the two main things I keep in the back of my head. If we're going to take someone to auto transplant I don't give them melphalan as part of their conditioning upfront therapy. And if we're going to collect stem cells, I try not to give more than four to six cycles of lenalidomide as part of their treatment.

Other than that, deciding: is the patient fit or frail, old or young? And, at least from my standpoint I think many patients benefit from the potential to get stem cell transplant, so I collect stem cells on almost all of my patients. And I still think it's a big question of, do we still need to be planning this way for up front therapy? How do you approach this topic?

Karthik Ramasamy
That's a very good point Josh. I mean, obviously we take a more classical approach. We try and define as much as possible. As you know, there are no hard rules about who would be transplant eligible, but clearly, performance status and organ function make a key clear determination about who we would transplant. Once we would take that approach, clearly, we would take stem cells from all of these patients.

I do have a question for you. Would you have that same view for all patients, irrespective of genetic background you're dealing with, high risk versus standard risk? The exact same approach or different?

Joshua Richter
I think that's a really great one. For transplant eligible, the younger fitter patients, I think transplant really should be considered for everyone. What changes for me if they're high risk upfront is, am I going to consider something like KRD as part of their initial approach? I think, at least in the United States, VRD has been the standard. Then there is the ongoing question whether KRD is better than VRD for some? Or do we need to get to a quadruplet, which we'll talk about shortly? To me, if you are high risk and young, I tend to be very forward with the KRD regimen. How about yourself?

Karthik Ramasamy

That's a very good point. We do feel our hands are tied with the choice that we can make with these treatment regimens. But I'm increasingly concerned that we are playing off the same playbook for both groups of patients, when we know that the outcomes are going to

be significantly different about how long they're going to stay in remission. So, I'll be keen to personalise the approach in the future. But you're quite right, I think we are still tied to a single template of approaching their care at the moment.

Joshua Richter
To me, the one thing that has really impacted my selection of upfront therapy is more for the older transplant ineligible patients. I think for many years, some variation of Velcade, Revlimid, dexamethasone has been given, regardless of age. And we colloquially refer to them as RVD-light or VRd-light if we're giving it once weekly or lower dose. But with the MAYA regimen (daratumumab, lenalidomide and dexamethasone) we are having such impressive response rates and it's being relatively so well tolerated that I really moved towards utilising that regimen in some of the patients who are clearly too old to get high-dose therapy or too many comorbidities. Has that regimen has impacted your approach as well?

Karthik Ramasamy
Clearly, I think you'd be starting to bridge the gap there. Particularly when we used fixed-duration therapy for transplant ineligible folks there were people who were progressing too early. You're quite right, the kind of VRD-light-type combination or dara-len-dex are really bridging the gap here.

And then you have to ask yourself the question: with improved clinical outcomes, both PFS and OS that's been shown, what more are we going to achieve and are we going to just set these guys back for three or four months with heavy duty intensive therapy? You're quite right, all of that kind of things are creeping in. But I live in hope that we start to personalise things based on their genetic background with the improving combinations that we have.

Joshua Richter
Absolutely. I think one of the things that we talk about a lot with cancer care in general is goals of care. When we set out at the beginning, what are we trying to achieve? I'm very interested to hear your thoughts: is it MRD or bust in the upfront setting? Do we have to get everyone down to the zero level and does it matter how we get there? I'm fascinated to hear your thoughts.

Karthik Ramasamy
Clearly, we are both seeing quite a lot of data about MRD negativity being a very deep level of remission state. But you and I know in clinical practice, when we start treating folks, we do end up with quite a lot of adverse events that folks pick up along the way. So, it is a challenge. I think it can be one of those holy grails that you can walk towards. But we know our patients better and it's these constant conversations that we have in our clinics about what we are trying to achieve here, based on what has been achieved, to how a person is feeling. Because important other clinical factors come into play, particularly in our folks. The

vast majority of them are around the age of 70. In some cases, myeloma becomes less of an issue, but their heart becomes a problem, or their kidney becomes a problem or something else becomes a problem. So, I'd quite like to think that I want to get all my folks into a very

good remission state, but I don't think that could be the driver for everybody. We have to personalise care when it comes to that.

Joshua Richter
I think your point is absolutely perfect, I could not agree more. I'm a big believer in the goldilocks phenomenon pretty much everywhere. Yes, MRD negative is great, but we have to balance that by too much toxicity. There are probably some patients we've seen with some of our older therapies, before we had this MRD technology, where we never got rid of all of their paraprotein and stayed in remission for years. So I think you and I see very much eye to eye on this.

Actually, I think this is a wonderful transition to one of the topics I know we wanted to touch on. Which is: what do we need up front? Is the three-drugs standard still the way to go? Is it four drugs? Does everyone need a quadruplet? I know there's some differences between the UK or the US. I would love to know your thoughts on triplets, quads… Is the future five drugs?

Karthik Ramasamy
Very good point, Josh. So clearly, I think we are in some agreement that what we're trying to do early on in these patients is try and get a treatment combination going which gives them deeper remissions.

What I find with the CASSIOPEIA data set is that the addition of daratumumab to VTd clearly drives a significantly high MRD negative rates in this patient population. You've also shown in a US study, Griffin with Dara-VRD, that you can get a quadruplet treatment combination going that achieves MRD negative in a group of patients.

The question that remains in my head is: do you always need four drugs for all patients to get to MRD negativity? That is the question that I have in my head. Because you know that there is a proportion of patients, even with triplet combinations, who get to MRD negativity. So to me it's about not just thinking of adding more drugs as much as you can. It's about understanding who the folks are where we can get away with three drugs. Because often we find the particular three-drug recombination, if it has less adverse effects, then that's preferred over having a four-drug combination.

I'm sorry I'm taking philosophical approach, but we can't just be throwing everything at every patient.

Joshua Richter
I think that the philosophical approach is wonderful. This is a data free zone. There's a lot of interesting data that's coming along. And I think your point is perfect, how do we use all of these big studies to personalise it to the patient in front of us?

The Griffin data has been quite impressive, the MRD negative rates are through the roof. But, to your point, does everybody need four drugs? And when you start adding four drugs, besides just general toxicities… I know from my experience we've been having some more

difficulty collecting stem cells in patients who received daratumumab-based regiment up front. I think we all think of monoclonal antibodies, like rituximab, CD20, but daratumumab which targets CD38… CD38 is on everything. So we've had some difficulty collecting stem cells.

I almost use the Griffin regimen a little bit like I used VRD in the old days. And when I mean the old days, I mean the IV bortezomib days. We were worried about giving IV Velcade because of the high risk of neuropathy. So in some of the patients we'd start off with Rev-dex and if they were suboptimally responding we would then add the IV Velcade. I find myself giving RVD to a number of patients and if they're underresponding I then add the dara as opposed to just doing it up front. I don't know if you've had similar thoughts about staggering this if they're suboptimally responding?

Karthik Ramasamy
My concern is… I like the fact that adding daratumumab has resulted in a deeper response, high MRD negativity. But it does have some additional toxicity attached to it, particularly our folks have higher levels of infections. And that's been a concern.

We've not consistently used Dara combinations prior to stem cell collection, but that's the place that we're going to get to. We are concerned because Niels van der Donk has presented some data which clearly shows that there is a reduction in stem cell collection numbers.

So I'm going to take the view that four-drug combinations do appear to be more beneficial, but I continue to feel that if there are good three-drug combinations which have less adverse events and that can achieve the same that four drugs can achieve, then I would prefer that.

Joshua Richter
I think that's actually a perfect segway into the next topic, which is maintenance therapy.

I think that we've kind of had these arguments back and forth across the years - fixed duration versus continuous therapy. The big trial that comes to mind, the first trial looking at melphalan prednisone thalidomide versus len-dex and showing that continuous therapy was better. Now that we have better tolerated therapies, we can give someone treatment until progression or intolerance. But the question comes up for those that we take either to autograft or patients that we don't take to autograft on the other end of induction, how do we approach maintenance therapy?

We'll start off with the straightforward ones. After transplant, do you do maintenance? And, if so, how do you delineate your options?

Karthik Ramasamy
Yes, absolutely we do do lenalidomide maintenance in the UK and certainly I'm a big believer of maintenance driving improved outcomes. But what I'm not a believer of is that

you need maintenance until progression. And I'm keenly awaiting the American segment of the VRD trial, followed by lenalidomide maintenance.

I do have much persuasion to do to keep people on lenalidomide maintenance forever. And for that particular reason I am keen on seeing augmented maintenance. And the reason why I want to see augmented maintenance is principally the way I'm thinking. If you are going to deepen the MRD negativity and sustain the MRD negativity I'd rather do that with an augmented maintenance for a defined duration of time rather than tell my folks you have to stay on maintenance forever and then keep coming to my practice every month to pick medicines up.

That's my view. I'm interested in your view about continuous maintenance.

Joshua Richter
I think for all the topics that we've ever discussed; this is going to be the one area that we see differently. I'm going to be the typical American by saying: if a little is good, more is better. So I am definitely of the camp of maintenance forever.

I think that my standard approach is Len maintenance for everyone. At least the follow up so far from the STaMINA 0702 trial seems that keeping them on longer is better than fixed duration. However, that big MRD question is out there. If you achieve sustained MRD negativity, do you still need to be on maintenance? I don't know the answer. My guess is that there are probably a subset of patients who achieve sustained MRD negativity, so MRD negative a year apart both being negative. If you have standard risk, my guess is that you could probably stop, but I don't know.

I agree that augmented maintenance is the way of the future. I do like some of the data from the FORTE trial, about Kyprolis and Revlimid maintenance. Although I could tell you, in the US nobody is going to use Kyprolis as maintenance. It's hard to get through.

We're using a lot of daratumumab and lenalidomide in combination for maintenance therapy. But right now I'm still of the camp: I just keep you on as long as possible. But time may tell that I'm being too much of a glutton here and giving too much treatment.

Karthik Ramasamy
Well, let me ask you a different way, to see if you have a different view. You plug and play up front in your induction regimen more and more, better regimens and you get more and more MRD negativity as you keep filtering through. Would you have the same view about continuous maintenance therapy until disease progression? I mean what about MRD negative patients five year out, still maintenance?

Joshua Richter
This is actually a conversation that some of my mentors here at my institution and I have a friendly disagreement about. I've had the privilege of working with people like Bart Barlogie

and Sundar Jagannath. I think Sundar would say yes, MRD negative after five years: you may be cured, we can stop some of this. What I tell people is: I don't know if the therapy I'm keeping you on is exactly what's needed to hold those few cells under control. I am still of the belief that myeloma is a biological construct and that MRD is an arbitrary line in the sand. We're at 10 to the 5th or 6th in this year. Next year, maybe 10 to the 7th. What was MRD negative 100 years ago? Not having a giant tumour sticking out of your head…

At some point, we may know exactly who can stop and who cannot. Until then, my conversations with the patients are: I don't know if you could stop. And I apologise to them. I say: listen if I've kept you on therapy for five years and five years from now, you could have been off I apologise. But I still don't know yet, who is safe to take off.

Karthik Ramasamy
Very good, we will continue to debate this topic over the years Josh, with interest.

Okay, so this is really an amazing discussion we've had so far. It's been a real pleasure discussing with you all these topics Josh.

The key takeaways for us are that we still have that clear distinction between transplant versus no transplant. We collect stem cells. And that's an important approach. That may change in the time to come, but that's an important approach.

The second takeaway is we still can't differentiate who would need triplet and who will need quads. Certainly, four drug regimens are driving outcomes and maybe that is the way that we would go, but if there are good three drug regimens which give the same desired outcome, we prefer that.

We certainly disagree between continuous versus fixed duration maintenance, but it's good that at least you agree with me that augmented maintenance has a role to play, and maybe that can change your views.

Anything you want to add to this?

Joshua Richter
No, I think you covered it beautifully. I think things that we both hinted on is the nature of risk stratification playing into this. I agree with you that we don't have the granularity yet to say which approach is needed for which patient, but I think we're on the precipice of starting to understand who really needs the long-term therapy and who doesn't; who really needs the quad and who doesn't. And a lot of this will probably be driven by cytogenetic risk. So I'm very excited about what's coming down the pipe with some of the tools we have in our toolbox today.

Karthik Ramasamy
Brilliant.

Joshua Richter

Karthik, thank you very much for this lovely discussion.

Before we close, I invite you all to listen to the other episode of this podcast series as well to learn more about treatment selection in the relapsed/refractory setting. The full series is available on lymphomaconnect.info and on your preferred podcast platform.