Choosing the Best Treatment Regimen in Multiple Myeloma

Episode 2: Relapsed/refractory multiple myeloma

Brought to you by;
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Karthik Ramasamy
Hello, and welcome to this podcast series titled multiple myeloma choosing the best treatment regimen every time. I'm Karthik Ramasamy, I'm a Consultant Haematologist and Associate Professor of Haematology at Oxford University, in the UK. I'm joined by my esteemed colleague across the pond Dr. Joshua Richter.

Joshua Richter
Thank you so much Karthik. I always love it when someone with an accent that sounds so elevated refers to me as esteemed, I am honoured to accept it. I'm Josh Richter: Assistant Professor of Medicine at the Tisch Cancer Institute Icon School of Medicine at Mount Sinai, and the Director of Myeloma at the Blavatnik Family - Chelsea Medical Center at Mount Sinai.

So, this is the second episode of our series. In the previous episode Karthik and I discussed treatment decisions in newly diagnosed myeloma patients, but now we're going to transition and focus on the relapsed and refractory setting.

So Karthik, I'll throw it back to you.

Karthik Ramasamy

Thank you, Josh. We're going to start talking about treatment in the relapsed setting. The first question, to somebody who believes in continuous therapy and keeping patients on treatment; when do you actually consider your patient to be relapsing? What is your set threshold?

Joshua Richter
I think there's at least a few sides to this. There is what the textbooks say, and I think you and I could probably sit here and quote The International Myeloma Working Group criteria backwards and forwards: of a biochemical progression of an M-spike, increase of more than 0.5 g/dL and at least 25% from the baseline and an increase in the difference of free light chains of 100, and all of these things. But more granularly, I think it's more important to talk about biochemical versus a clinical relapse.

So yes, I keep people on therapy lifelong. When their blood work starts showing a rise in the paraprotein I say: listen, this is on the horizon, we're going to need to talk about switching. As opposed to the patient who shows up in the emergency room with acute renal failure or hypercalcemia or new lytic bone disease and fractures. To me that's the big difference and that helps guide how aggressive my treatment needs to be.

I don't know what your thoughts are on the subject?

Karthik Ramasamy
Completely agree, I'm a big believer. I do have a provocative way of saying things which is: our mentors didn't have many drugs, so they didn't bother treating at biochemical relapse. For me, we need to stay on top of this incurable illness, unfortunately. So I'm a believer of coming in early. But the problem I have is, how early is early? How early is too early? So I'll tell you what I do and I'm interested in hearing your views about what too early may sound like.

When I see my folks starting to put out paraprotein or increase their paraprotein, I'm often getting a bone marrow, doing genome sequencing and then trying to get a whole-body imaging going. If I actually see all of this to be pretty good and I'm not seeing any high-risk features emerge and my folks are working – you know quality of life is critically important – then I tend to back off a little.

Is that approach similar to what you do, or you do things differently?

Joshua Richter
I could not agree more. I'm glad we see eye to eye on this. I actually saw a patient who is treated by another physician, and another institution who went simply from MRD negative to MRD positive and they threw four new drugs at them.

I completely agree. I have a number of patients, as I'm sure you do, that have a slow glacial rise in the paraprotein. You know we don't cure the disease, we have limited options albeit more of them. If I don't need to intervene with a new therapy for months or even a year or more, that's extra time for the patient. And at the time that we really need to intervene, the

disease is the same biology, it will be sensitive. So I completely agree, I follow a number of patients with rising paraprotein. I love your approach, which is, if they go from a paraprotein of 0 to 0.5 I, just like you, restage them and they have no CRAB – no change on imaging, we observe closely and have an ongoing discussion of risk and benefit. So we see very much eye to eye on that.

Karthik Ramasamy
Thank you, Josh. But there's one point though, in this whole process of restaging we do pick up a high-risk genetic feature that's emerging that clearly concerns you or me. At this point in time I'm well aware that there is no data to say: do things early. But certainly, I'm more of the view at that time, starting to counsel my patients to start treatment early or I'm on the lookout for the next clinical trial that I can put them on to get the patients started on treatment.

Would you concur that view?

Joshua Richter
100%. I think that if we look back, as you talked about our mentors and the therapies they had, not only in the clinic but in the clinical trials they had in front of them. There were a few good ones and many of them were not. Now, not only do we have many approved therapies globally, but the clinical trial space in myeloma is a revolution. It's an immunologic wonderland of different options. So, I completely agree.

In fact, I actually saw a patient not long ago, who has a little bit of a biochemical relapse but does not fit any criteria for any clinical trial. And I literally told her I'm going to wait a few months, because in a few months, you are going to be fine, but you will now be eligible for a CAR-T trial and have a whole bunch of options. Instead of simply throwing treatment at them for treatment's sake. So I completely agree with your approach.

Karthik Ramasamy
Brilliant. We have some agreement.

Joshua Richter
When we talk about relapse and we really separate out, what does that first relapse look like, we'll have a lot of our go-to's. But when we start looking at later relapses, so once you've gotten beyond that upfront therapy and the first relapse when you start getting into the kind of second, third relapse: what are you thinking in terms of choice of different regimens?

Karthik Ramasamy
So clearly our dominant thinking would be about what I gave upfront, what is my particular patient refractory to? That is the dominant part of my thinking. Clearly, all other characteristics are critically important. The disease biology is important that we've already touched upon, particularly in the high risk, patient population. But also, what else has happened to our folks from when they started upfront therapy to now: do they have a new

illness of some other type. Those considerations that we need to think of, are critically important.

But I think simplistically looking at it, I think a key feature is refractoriness to agents. So, if our patient is lenalidomide refractory, then clearly avoiding an IMiD-based combination is what I would prefer. If a patient is PI refractory, then trying to avoid a proteasome inhibitor-based combination is what I would prefer. All of these choices were difficult about three four years back, but now increasingly less so with all the new combinations we have, particularly with all these new targets that we've got. As you rightly say, we are in an immunological wonderland right now. So, we can have a number of options avoiding these two key pillars of therapy that we've had.

I would like to find out If those are your dominant features in your thinking of choice of therapy or are there other things that predominate?

Joshua Richter
I completely agree. The main one that comes to the front is: what are they refractory to? You and I see completely eye to eye.

In the back of my head, I like to imagine that I have some insight into an optimal sequence for patients, even though I know, in practice, I clearly don't. I don't think there's a clear roadmap for everyone. I think that, if I have not utilized daratumumab in the frontline setting, it's part of my first relapse. And if it has not been the first relapse, it's in the second relapse.

I still go back and forth between the role of elotuzumab before or after a CD38. Now there's been this ongoing concern that because elo uses NK cells for cell kill, NK cells are CD38-positive, using elo after a CD38 like isatuximab or daratumumab may be suboptimal, so maybe that should come before a CD38. But then again, it's hard to compare trial to trial, but the CD38 therapy seem to be better. So I wrestled with this in my mind.

And then the question is: I think Kyprolis, which used to be my good first relapse drug, has been taken over a lot by dara. Now I bring Kyprolis a lot into the third line but I struggle with what to mix it with, because if they've already seen dara, what am I giving it with? Am I giving it with cyclophosphamide or do I have to start thinking out of the box and giving it with panobinostat or selinexor?

I'm actually curious, when you get to regimens with Kyprolis in third or fourth line, how are you rounding out that triplet?

Karthik Ramasamy
I think that's a very difficult proposition that we have for this patient population. The point you made around, expanding the CD38 option is an important one. And I mean, although there's dominating data of using daratumumab data in the upfront setting one argument could be made, particularly because of the particular scenario you posed, do we actually reserve it for later line therapy?

But the difficulty is, with the levels of MRD negativity you get the upfront setting and the sustained MRD negativity that is being increasingly reported in this patient population is hard to hold that CD38 back. What I'm hoping is that in a year or two, we will have those BCMA combinations with FcRH5 combinations and so on, and GPRC5D combinations where we don't have to particularly bother about the new MoA that we need to add to these treatment combinations.

But you're right, maybe we are undercooking our patients in those settings, but it is difficult to offer a CD38 in somebody who's just progressed on a CD38. I was interested to hear about your CS1 angle, with the elotuzumab. It's being less used in Europe I have to say. There's just not been that interest with elotuzumab, possibly even lack of understanding about how it may even fit in, in the treatment combination. Do you actually find CD38 refractory patients, when you use an elo combination, you do feel that you've had a potent immunotherapy in that context?

Joshua Richter
I think my utilisation of elo falls into two categories: one is the non-CD38 exposed. The classic patient is: they get something like RVD transplant, Len maintenance and have a slow biochemical relapse. Then I use the data from the ELOQUENT 3 study and give them elotuzumab, pomalidomide and dexamethasone. It's a wonderful regimen, it's extremely well tolerated and goes to monthly dosing rather quickly, so from a patient standpoint it's very convenient.

To your point, what happens after you're CD38 exposed? I worry a little bit about it and, I kind of draw on some phase 1/2 data that was originally published by Andrew Yee at MGH. He combined elotuzumab, pomalidomide, bortezomib and dexamethasone: elo-PVD. And in his paper about a quarter of the patients had prior CD38. So, it's really one of the only good studies that I've seen using elo after CD38, and he had over 50% response rates. So if I'm reaching for elo later on, give it in a quad. But again, I think I've had some mixed experiences with it.

Karthik Ramasamy
Interesting to hear.

Right, we would not be doing justice without talking about CAR-T in relapsed/refractory podcast, would we Josh?

Joshua Richter
Of course.

Karthik Ramasamy
Well, you're the centre which brings out all the CAR-T studies. So tell me, what makes you decide switching gears? When do you think enough is enough, I'm just going to use my CAR-T option now?

Joshua Richter
So, I think when I reach for a CAR-T is for functionally high-risk patients or biologically high-risk. We've talked in this series, in the previous podcast, about cytogenetic high risk. You get your genomic studies, you find a 17P, or 1Q gain or something very concerning. But for me, it's those functionally high risk. And it's interesting if you look in the mSMART guidelines from our Mayo colleagues, if they look at upfront and relapsed definitions of risk, they're identical, except in the relapsed one they include patients…if you relapse within one year of your initial therapy or with one year of transplant as functionally high risk.

So, any regimen that I give someone early on that I expect them to be in remission for three, four or five years. If they relapse in one or two, regardless of their cytogenetics, I say that they're functionally high risk. And instead of just giving them variations on a theme, another proteasome inhibitor, another monoclonal, I like to completely switch gears and get them on to a CAR-T. Again, my experience has been mixed. Some people have had amazing responses, some suboptimal. What has been your experience with CAR-T so far?

Karthik Ramasamy
Well, our experience has been limited to a few clinical trials. We've had a challenge of accessing too many CAR-T trials because obviously products have to be shipped to the US and then got back. Our experience so far has been a bit mixed.

What I am concerned about, and wanted to kind delve into a bit more with you, is how selective are we getting with CAR-T? Certainly, the folks I have put in CAR-T studies are folks who are doing really well. Very little comorbidities, a gradually growing myeloma. Which is why I hear with interest your functionally high-risk patients are, the ones who're going to just go on very soon. Do you think that we're getting more and more of the right patients into these CAR-T studies?

And I'd like to hear about CARTITUDE-2, because that's more in the space that CAR-T is going to play. Do you think those studies are capturing the real functionally high-risk patients? You and I need data, so that we can give it to our patients in the in the next few years.

Joshua Richter
Absolutely, I think that the CAR-Ts are following the pathway that all of our therapies do, which is: a new therapy comes out, and the initial trials give it at the end of everything. Then once the drug is approved, as a global myeloma community we learn the more optimal way to use these strategies earlier on; different toxicity mitigation strategies, different combinations.

I think one of the things that CARTITUDE-2 showed us is, is that…we've had this concern about early on utilization of CAR-T may be too toxic. Although the patients may do better, because their disease is not as refractory, their T cell immunity is so much more intact, they may explode with CRS. CARTITUDE-2 showed us quite the opposite. There was no increase in big toxicities. So, I think CARTITUDE-2 is actually leading us to, exactly as you're talking about, the future of telling us what happens when we give CAR-Ts earlier on.

And I am very happy that there are many studies out there now trying to answer these questions about: what happens when we give it in first relapse even what happens when we give it in front line? What happens to functionally high risk? I think the issue is still difficult for the functionally high risk because right now, we still need four to five weeks for manufacturing for the CAR-Ts. Some of those patients don't like to wait around too long. So, I'm very anxious for the future of potentially off the shelf CAR-T's. But I agree, it's been a difficult space to pin down who exactly is the optimal patient for CAR-T.

Karthik Ramasamy
That's a very important point you make there, particularly around allogeneic CAR-T cells, which is increasingly being explored in the myeloma space.

I have two questions, and I want to hear your views around this. One of the concerns early on, we had about the fitness of the T cells that we collect in this patient population. That's been at least doubted as one of the reasons why we may not be getting optimal outcomes in this patient population. Doing it in 1-3 prior lines means you get better T cells. There's some data from U Pen suggesting that, which is interesting, but allo-CAR completely solves this problem. It's going to take T cells off a very healthy individual, and then put it in.

I'd like to see more data, but do you believe that space is going to fix more and more of our CAR-T issues?

Joshua Richter
You know I think it's a big question. I think T cell redirection therapy is this wide-open landscape and from my standpoint, there are a few key players and it's going to be hard to know who's going to be optimal for which one. So, we have autologous CAR-Ts with drugs like idecabtagene, the allogeneic off the shelf CAR-T which are in clinical trials and the bispecific and trispecific antibodies which are off the shelf. You know, we recognise that T cell redirection therapy is one of the futures of myeloma but I'm going to take the easy way out and throw it back to you.

Let's say it's sometime in the future, where you have your pick of a bispecific or a CAR-T, how do you envision delineating who would benefit from which one?

Karthik Ramasamy
As you know, in Europe logistics is key. So for me logistics-wise I think my off the shelf bispecific will always win. But I do have to say, you can see my attraction to keep my patients off therapy, right? So, I am attracted by the fact that, if I can get away from just one-off CAR-T and then leave my patients off therapy, then I think that is that is important.

But we need data. We need data to say that the durability… particularly in CARTITUDE-2 trial, I mean if we see PFS as well over three years in this patient population, then you know that that is going to be very, very interesting for our patient population.

But outside of that I have to say, the driver will be logistics for this patient population. You know 45% of newly diagnosed folks in the UK are over 75. So your CAR-T it's not going to solve all my problems. So, I would need my bispecific antibodies. Maybe we could agree that there will be profiling going on, and there will be patients in equally distributed between these two T-cell redirected therapies.

Joshua Richter
Absolutely and I think one of the things that's going to enter in some of the CAR-T trials is this concept of maintenance. Because, I agree with you, the treatment holidays are absolutely wonderful things. But when we first started going down the road of CAR-Ts, and I don't know if you had the same feeling, we were looking towards our leukaemia and lymphoma colleagues who were curing people, and then we said: okay CAR-T is the cure pathway for myeloma. And the data to date has not shown that. Now that's not saying that it can't in the future, but if this goal is going to be switched from a cure to a prolonged remission approach, is the future of CAR-T's going to involve some type of maintenance therapy within an IMid, a monoclonal or a CelMoD? I don't know if you have thoughts about that?

Karthik Ramasamy
I can see a few trials already being designed in that fashion and that's probably what would be putting me off the CAR-T, because that doesn't solve my problem. I'd rather go the bispecific route and keep giving them rather than chop and change and do different types of maintenance. I say that flippantly, but to me, one of the big attractions of CAR-T is that it's an exciting therapy, worked in the heavily pre-treated cohort, so I do really hope that if we give it early, that we get good treatment free periods for our patients.

Joshua Richter
Absolutely. Along those lines, as we're talking about CAR-Ts and the future, are there any specific therapies, that in your mind, be it CAR-T, CelMoDs, bispecifics, or anything else that you think is coming down the pipe that's really going to change outcomes for our patients?

Karthik Ramasamy
What I'm most excited about I have to say, Josh, is our ability to keep finding targets. We have found three targets. One has been well validated, two ongoing validation we'll have results in a year or two, where we are already excited about. I think to me that's amazing.

The CelMoDs are exciting. I've been involved in clinical trials with CelMoDs, a lot of data out there and that's pretty good. 92480 is very, very good CelMoD. 220 is also pretty good, very well tolerated drug. So, it's exciting that we are able to use those drugs as well in the future.

So, exciting times for our patients. I mean, the last five years were amazing. I don't know what adjective I can use to describe the next 10 years.

Joshua Richter
No, I think the next 10 years are, as you have said several times as we've talked, is really personalising this. We have this litany of targets, you know CD38, BCMA, GPRC5D, FCRH5.

And what is going to happen, I think, to me, which is very exciting is sitting down when we have these drugs approved and saying: okay, can we use some of our physician scientists to analyse patients at a personalised level, to understand who will benefit from which therapy? Because I think you and I have clearly seen patients have unbelievable responses to one therapy and not to another, and we sit around, at least I sit around not knowing why that actually happened. Maybe the next generation is not just more drugs, but how best to give them.

Karthik Ramasamy
I agree. It was great chatting with you, Josh, talking about relapsed/refractory myeloma patient management. So, thank you for that.

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