Video podcast transcript
Exploring the role of targeted radiopharmaceutical treatment in NETs

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Dr Rohit Gosain

Hello, everyone. Welcome back to the Oncology Brothers podcast. I'm Rohit Gosain, along with my brother and co-host Rahul Gosain, with our goal to keep our Community Oncologists up to date in the world of cancer.

Today we are going to be talking about NETs, neuroendocrine tumours. Briefly, we will touch on the treatment landscape, but the focus of the discussion will be on radioligand therapies available and how to best use them.

Dr Rahul Gosain

To touch on this we're excited to welcome Dr Heloisa Soares, a Medical Oncologist focusing on neuroendocrine tumours, and Dr Ken Herrmann, a Nuclear Medicine Physician from Europe. Ken, Heloisa, welcome.

Prof. Ken Herrmann

Thank you.

Dr Heloisa Soares

Thank you for having us.

Dr Rohit Gosain

Thanks very much for joining us. Before we go any further, let's set the stage for neuroendocrine tumours - where we stand from the treatment landscape. We divide them basically into functional versus nonfunctional, where often the nonfunctional ones are rather asymptomatic.

But the active treatment options that are available for functional NETs are somatostatin analogues, we recently saw approval of cabozantinib, and we also have radioligand therapy such as PRRT, and also, for high-grade tumours we take this treatment from small cell lung cancer, that is a chemo option.

Before we dive into more in the treatment world, let's touch on the imaging modality where octreotide scans used to be our thing but now we have been relying heavily on gallium DOTATATE scan.

Heloisa, I'll start off with you here. Could you start us off where, where do you get this gallium DOTATATE scan? Is it at initial diagnosis or rather progression? And if so, what's exactly the utility of it? And importantly, outside clinical trial, other radiotracers that are available that you rely on your practice?

Dr Heloisa Soares

I think we use the imaging studies in combination with their cross-sectional studies. Typically I will have my patient have a, assuming a GI GEP-NET, I'll have my patient having the MRI of abdomen and pelvis with contrast or a CT of abdomen and pelvis with the arterial phase, of this portion of the liver to really be able to identify the tumours.

In addition to that, at diagnosis, I will definitely try to get a somatostatin receptor functional imaging, to help and complement the workup and plan for my patients. And yes, we have the gallium-68 DOTATATE PET/CTs.

We can also use copper 64 that's also available in the US. So, we have these two radioisotopes that we can use. I'll typically use at the time of diagnosis. Typically, if

the patient is going for surgery, I certainly try to have also a DOTATATE PET/CT, given that the sensitivity of the DOTATATE is much higher, it tends to be up to 90%, so it's excellent, to try to identify what we call “occult disease”.

Dr Rahul Gosain

Thanks for getting us started. You brought up DOTATATE, be it gallium or copper. In the community settings, if I don't have one or the other available, am I missing out on some critical information? Is one more sensitive than the other?

Dr Heloisa Soares

No, absolutely not. I think, there is a slight difference in sensitivity and background noise depending on which radioisotope you use. But in general, the concept is you can use one or the other, and you are not missing in quality or information choosing one over the other.

Dr Rahul Gosain

Perfect. And Ken, if the disease is progressing on somatostatin analogues, Rohit brought up a few treatment options, everolimus, cabozantinib and PRRT. For PRRT we often get Nuclear Medicine or a Radiation Oncologist on board. In a patient that has DOTATATE positive disease and you're seeing this patient to consider PRRT, what do we have to support this practice? And in real life what does that conversation look like for that patient in front of you?

Prof. Ken Herrmann

First off I want to say that what Heloisa alluded to is indeed, there's a lot of very, very good data to underline that somatostatin tools have their imaging with PET, it’s better than anything else. Nevertheless, I think it's very important that we actually perform this imaging technology, always in addition of the contrast-enhanced CT. I think it's very important.

Why I actually don't answer your question is because this is actually leading me to my answer. We need to know that the lesions which are disease dominating, are somatostatin 2 receptor positive. And for this we need the additional information from the CT plus the PET information. And in these patients, actually, we really discuss depending on the previous treatment, if the patients are candidates for PRRT. Now, we know that there are different grades. Obviously for well-differentiated tumours, less than Ki-67 of 20%, we have I think, quite solid data. We can also discuss a bit later about patients who have a more aggressive pattern. But overall, right now in daily routine, we really focus on the patients who have a Ki-67 less than 20% who have progressed, to call somatostatin receptor analogues and, where we are discussing and the next line of treatment.

And we actually usually perform this in MDT where we bring all together the different levels of information and also something that we also have to discuss, how quickly is the disease evolving, because PRRT is not a therapy which you treat one time and

you will see response within 1 or 2 days. It's a treatment which needs time to be efficient.

Dr Rohit Gosain

Thanks so much for touching on that Ken. And we will be diving into the world of MDT, multidisciplinary approach, because again, oncology in general is a team sport, but there are some cancers where this team sport applies more than others and neuroendocrine tumours is certainly part of that.

Heloisa, with regards to the available treatment options, now where do you use PRRT? Is it upfront or relapsed/refractory in your setting? And also if you could touch on any role of this in high-grade as well.

Dr Heloisa Soares

We do have data from the NETTER-2 that shows that in patients with more aggressive disease, we think the well-differentiated GEP-NET one, there's a role for 1st line treatment with PRRT. Having said that, the majority of the patients that we will use PRRT on tends to be 2nd line and beyond. And, when we put in context all the treatments that we have, I think especially for the midgut tumours, PRRT is definitely the winner when it comes to 2nd line treatments. You know, we had the NETTER-1 study that showed the use of lutetium-177 versus 60mg of octreotide and then of course, showed that PRRT was, better, was superior in terms of progression-free survival. And just this year, in March, we had a presentation during the European Neuroendocrine Tumour Society meeting that showed via the COMPETE study that lutetium-177 DOTATOC was superior to everolimus. And they used the active compared to everolimus. That really, to me consolidated the role of PRRT particularly in 2nd line.

I think the decision of 1st line, is a little bit more complex, even though the data was positive. Do you miss too much in still using somatostatin analogue? We have data in progression-free survival benefit, but we don't have overall survival. I think definitely for the higher grade tumours, is a little bit more of a discussion. And in terms of well-differentiated G3 tumours, because we do have this population of patients we potentially see the benefit, as well, it's just a question of how fast the tumour is progressing and do we have to start with something else sooner, because sometimes, depending where you are, it might take time to set up PRRT. And there's lots of nuances that, Ken and I can discuss as well about the decision for the higher grade tumours.

Dr Rahul Gosain

One thing important here is the logistics. It's not just saying, all right, this patient is going to get PRRT, off you go. That coordination takes a while. Ken, coming back to you, setting that right expectation with the patients as well, saying you're not going to see a response within that day or two. It's not one and done. So these are the things that we have to keep in mind.

Ken, is your practice any different in Europe in terms of sequencing? Are you relying on this upfront? Are you saving PRRT for refractory/relapsed disease?

Prof. Ken Herrmann

I had the pleasure to work, actually, on both sides of the continent. So, I have to say that, overall it's not that different. The difference is rather subtle to be honest. So, regarding the clinical set-up, the data is the same in Europe as in the US, right? Pretty much what Heloisa said, we have very, very compelling data for 2nd line in midgut.

I think also now with COMPETE, also with P-NETs in well-differentiated ones. NETTER-2 is very interesting data. Right? I'm very curious to see what COMPOSE is going to give us, but we also have to be very honest that bringing it really into 1st line probably needs a little bit more than just what we have seen so far in the higher grade tumours.

Now, regarding the practice, one of the big differences, I think, is that in the US, it's an outpatient treatment. So, you really get the treatment and the patient is sent home the same day. Whereas for example, in Germany we like to keep the patients two days with us.

Dr Rahul Gosain

Ken, keeping that patient in mind that's getting PRRT under your care, what are some of the side effects that we see with this modality? Any clinical pearls to manage this? And is it safe for renal dysfunction? What are some of the contraindications?

Prof. Ken Herrmann

The most important toxicity depends on the angle. You know, if you talk to the patient, actually for them, for us, the most important is that they really do not like nausea, which is actually not associated directly into the treatment itself, but rather to the kidney protection, it's amino acids which are infused. These are usually the thing that patients complain the most about.

When you talk to the regulators, they actually worry the most about the kidney dose and the potential kidney toxicity. Even so, we know now that we have very long term, actually very long term data showing that this is actually very, very tolerated, even, regarding the kidney toxicity.

And the third one is from the clinical angle. And the clinical angle is something that long-term we are the most concerned about is actually the bone marrow function. So, bone marrow function and potentially secondary maintenance is not very frequent but still something you need to worry about. So, in summary, three different toxicities from three different angles - nausea for the patient, kidney toxicity for the regulator, and for me in the clinic it's the bone marrow.

Dr Rohit Gosain

And with regards to tying in with the bone marrow aspect. Heloisa, I'll go to you for this one, where bone marrow suppression is certainly a concern any risk of, when you were talking about secondary malignancies Ken, Heloisa, have you seen any MDS or AML it being transformed? Any role of bone marrow biopsies and how do you go about that?

Dr Heloisa Soares

Absolutely, and that's the big conversation that I have with my patients in clinic is about this risk of MDS and acute leukemia that might develop, which typically, on the phase 3 studies has been between 2 to 3%. And then I think, there is more emerging evidence showing that if you were at some point also have in your treatment journey, the patient have in their treatment journey an alkylating agent, chemotherapy, that risk of acute leukemia or MDS may increase.

The percentage that it may increase, we don't have prospective data, but there are some retrospective studies and one of the highest that I've seen has been from the Moffitt Group with Jonathan Strosberg. But then when you look at the patients that he had in clinic that received temozolomide at some point and PRRT at some point it was up to like 10%. Right? So, that's a big conversation with the patients, particularly those that are going to be using chemotherapy. The clear example here is the patients with pancreatic neuroendocrine tumours with capecitabine and temozolomide is very used. So, that's the big conversation. The timing of when the leukemia MDS will happen is a little bit all over the place right now. So, it can be right away or in right away after finishing treatment. Or it might take some years.

To answer your question about bone marrow biopsies, I typically would expect that the bone marrow will recover because we see some decrease in time in the counts for a while. But typically if they don't fully recover by a year, that's when I start discussing bone marrow biopsy. Obviously, if before that there is some concern, we see blasts in the CBC in the periphery smear, that's a different story. But if it's just that the counts are not recovering, I'll wait up to a year before I refer to my colleagues in hematology for additional workup and potentially a bone marrow biopsy.

Prof. Ken Herrmann

I really want to emphasise what Heloisa just said. I mean, literature gives you MDS rates between 1 to 10%. And I think there's one very nice data set that I want to mention, the long-term follow-up of NETTER-1, really a 5-year follow-up and there, to be honest, as Heloisa correctly mentioned the MDS was more on the lower end of the spectrum, so more like in the 2% rate. That's why I think it's very important to mention, of course, also the additional use of chemotherapy would of course increase that.

Dr Rahul Gosain

So, again coming back to that patient education, setting that right expectation on our end as practicing physicians, we have to get comfortable in what to look out for. Heloisa, coming back to that patient who is getting PRRT and setting that expectation with your patients, keeping the data in mind. What are you expecting with your repeat scans? How frequently are you getting that repeat scan? Which modality? Is it CT scan? Is it PET CT? What is that conversation? And is there any role of chromogranin monitoring here?

Dr Heloisa Soares

I'll start with the easy one. There's no role for chromogranin. We should not be checking that, period, on the patients for monitoring. That's not appropriate, it's a very non-sensitive, insensitive test. So, let's forget about chromogranin.
And then in terms of which scans to do, all these studies have been with cross-sectional imaging. We should monitor patients with CTs or MRIs. And then these studies typically did that every three months. I, in my practice, for most of my patients, if they truly have very indolent disease, I will do CT or MRI, just before starting treatment to have my baseline and the first CT/ MRI that I'm going to do is about three months after completing four cycles. If I have a patient that's a little bit more aggressive in terms of the disease that they have, or the burden of disease is a little bit more than I would do, between cycle two and cycle three, I will do the scan. And I think many of my colleagues will do scans in between. Ken I'd love to see how you do it.

But, for the very indolent tumours, I tend to wait until the end of the four cycles. And I don't do the DOTATATE PET/CTs during or just after treatment. I don't think, that's yet an established role for that.

Prof. Ken Herrmann

We actually perform DOTATATE scans right after end of treatment because we can, and we don't have the same cost as in the US to be honest. Interim, we do the same as you, if there's no clinical reason to suspect progression or we have a patient who maybe from the beginning think that this is a borderline great candidate for PRRT. We don't do interim imaging anymore. We have done this for many, many years. We performed PRRT actually for more than ten years already. And we have stopped this. With the high numbers of patients now being treated we just cannot do this logistically.

Dr Rohit Gosain

Before we close this conversation, it is important to stress the importance of what you started off with initially Ken, that is the multidisciplinary approach. It is an extremely important part of the patient care management here, especially when you're tying in surgery, liver directed therapy, systemic therapy and also radioligand therapy. And this is all to make sure patients have the best outcome. Ken, any final thoughts or rather clinical takeaways from today's discussion?

Prof. Ken Herrmann

MDT is key. There are certain standards we follow, but the truth is that many of the patients, at least in these very specialised centres like ours, and probably also Heloisa's, they are not the ones who follow standard of care. And for this, we need to have these MDT discussions. Where do we add, for example, chemo on top? Where do we add a targeted therapy? Where do we actually go directly to radioablation? So MDT is key.

Dr Rohit Gosain

Couldn't agree more. And again, this is part of the disease where the treatment does not fit everyone. So, you have to again maneuver through this complicated course. We have to tailor things accordingly for our patients. Heloisa, any final thoughts or clinical takeaways from your end?

Dr Heloisa Soares

Yes, thank you. I would definitely agree that, you know, MDT is absolutely essential even from the beginning with the pathology. Having an over read in the pathology. Make sure that the pathology is correct. And then really, explaining to patients and to everybody that's caring for the patient that this is really, for most of the patients, a journey. And then it's just about deciding how to sequence in the treatments in a way that makes sense clinically or medically, but also takes into account the patient's priorities and goals as well, right? Because thankfully, because these patients live for so long, we really need to see what makes sense at what time of the patient's life and so forth. So really, having a good team partnership with the patients and the rest of the groups.

And I think it's an exciting time to be a doctor taking care of neuroendocrine tumours. We have so many new treatments coming. And I think PRRT is here to stay. And then I think very soon we will be talking even about retreatment with PRRT because we now have trials that are even assessing the goal of rechallenging patients with PRRT if they had an initial response to that. Very exciting times for the treatment of neuroendocrine tumours.

Dr Rahul Gosain

Heloisa, I would just echo what you're saying. Patient shared and informed decision is critical. And the other thing to reiterate is neuroendocrine is not as rare as it was once thought to be. This is something that we're seeing day in, day out in our clinics. Ken, Heloisa, thank you so much for walking us through the current role of targeted radioligand treatment options in neuroendocrine tumours. It is important for us to appreciate available options, how to sequence these options, and importantly, how to manage the side effects that come along with these options.

For our listeners, let's go over a quick recap from today's discussion.

In today's discussion with Dr Heloisa Soares, a Medical Oncologist, and Dr Ken Herrmann, a nuclear medicine specialist, we had a chance to focus on PRRT, radioligands, as treatment options in neuroendocrine tumours.

There are multiple different molecules that will soon be available to us, and this field is moving fast.

Now we also have positive data from COMPETE study for 1st and 2nd line PRRT in well-differentiated grade 1 or grade 2 tumours, but selecting the right patient and pairing them with the right treatment option is the key.

Dr Rohit Gosain

Yes, Rahul. Multi D is critical in referring and partnering up with tertiary or quaternary centres early for us in the community is extremely important. As we heard, the data for lutetium-177 DOTATOC, when compared to everolimus has now consolidated the role of PRRT as a 2nd line therapy for neuroendocrine tumours but it is also showing promising results in 1st line as well. And then we also touched on the importance of managing the side effects that come along with our available treatment options.

Thanks for joining us. We are the Oncology Brothers.