Regional differences in NET: Treatment and future developments

Brought to you by
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Tonke de Jong
Welcome back to the second episode of this two-part podcast series, in which the experts, Prof. Martyn Caplin from the UK and Prof. Rachel Riechelmann from Brazil, discuss how to optimize treatment for people living with NETs and future developments in the field. This podcast is an initiative of COR2ED and is supported through an independent educational grant from Ipsen.

Prof. Martyn Caplin
Going back then to the blood screening, you would do the biomarkers and then if you suspect a syndromic patient, if it's pancreatic, you'll send off their insulin levels or gastrin levels, depending on what it is. And then for the 24-hour urine, you say you do on all your midgut patients, even if they're asymptomatic. So that's quite interesting. And you're probably right because as you say, there's a proportion of those patients who are asymptomatic that do have 5-HIAA. So I think it's totally reasonable to do that. And it's a marker, again, not such a great marker of following therapy, but it's helpful. And also, I guess, if you're going to theatre as well, if you know that the patient's got a 5-HIAA level that's elevated, that has an impact on your use of octreotide and covering carcinoid syndrome.

Prof. Rachel Riechelmann
Yes, it helps to get access to the drugs. But also, I've seen, of course, this is rare, but I've seen patients with carcinoid heart disease, elevation of 5-HIAA without carcinoid symptoms. Of course, this is not common, but I've seen it. So I tend to order. In our database, in my centre, we have 14% of patients have elevation of 5-HIAA without any carcinoid symptoms.

Prof. Martyn Caplin
So on this question of the biomarkers, then, and thinking of carcinoid, heart disease, do you use NT-proBNP as a marker for, we use it and we published on it, and we reduced our amount of echo that we did by following NT-proBNP. Do you use that biomarker?

Prof. Rachel Riechelmann
Yes we do. But we do the echocardiogram as well, once a year.

Prof. Martyn Caplin
Yes, okay. And the other, do you want to touch very briefly on the other biomarkers, I suppose, related to considering familial conditions, which we should just mention, which I'll hand over to you to mention the familial conditions briefly and the biomarkers you might do to consider that.

Prof. Rachel Riechelmann
Yes, so about 10% of patients with neuroendocrine tumours have a genetic syndrome. The most common one is the multiple neoplasia type 1, but you can also have von Hippel-Lindau, multiple neoplasia type 2 and others. And for the most common one, the MEN1, we tend to do a whole screening of hormones that includes hormones that may be secreted by the hypophysis, the pituitary, or even sometimes asymptomatic gastrinomas of the duodenum. So we tend to have these patients managed together with the endocrinologist because they do a better job than the medical oncologist evaluating all the hormones. And then if the patient has any specific, other specific syndromes, of course, then we do it directly to that type of syndrome. But overall, I would say this is what we do. And having the endocrinology together, it's so helpful, isn't it?

Prof. Martyn Caplin
And that's the importance of the multidisciplinary sort of team approach. I guess in our basic purpose, because it's so easy, we'd run off a parathyroid hormone, blood test and calcium, which we give in all our pancreatic NET patients, just to give an indicator of whether or not they could have MEN1.

Prof. Rachel Riechelmann
Regardless of age? I do that too, but only for the like less than 50 years.

Prof. Martyn Caplin
Yes, so it tends to be for the younger patients. And you actually, you raise a point in terms of what age do patients present to you. What's the average age of presentation in Sao Paulo, Brazil?

Prof. Rachel Riechelmann
You know, Martyn, I've seen more and more young patients in the last years. So many patients come, let's say, between 40 and 55. In the past, I used to see more patients around 60. But this has been changing. I see a lot of people in their 40s. Do you have that?

Prof. Martyn Caplin
I think that's right. You know, the data shows that the highest prevalence, I suppose, in the 50 to 60 year old age. But we are seeing younger patients and they often have more aggressive disease as well. They do, they do. Yes, so we're seeing that as well. So it's interesting that we're seeing that across both sides of the Atlantic. And then in terms of, we've covered the sort of the diagnostic aspects of it. I suppose the other is that in workup for surgery, we'll probably do small bowel enterographies for those patients being considered for resection of their primary small bowel tumours. EUS of the pancreas, we don't always do an EUS biopsy prior to surgery. If they've got a gallium PET and features compatible. I don't know, do you tend to do EUS on all your patients going to surgery?

Prof. Rachel Riechelmann
We tend to because once we have the pathology diagnosis, it makes things easier and faster for patients to get, you know, surgery or whatever treatment because then we have a diagnosis of a cancer. Yes, that's why we do it.

Prof. Martyn Caplin
And I suppose, whilst my mind is in that set of EUS, for the rectal neuroendocrine tumours, I think EUS is very important because that will tell you, often patients have had an incomplete polypectomy and you're left knowing what's what and you want to do a sigmoidoscopy to look. But also EUS is very sensitive at looking at the local lymph nodes and involvement within the pelvis. We should

probably move on a little bit then in terms of we've talked about, I suppose, the staging with the PET scans and availability of that. Are there any other modalities or in terms of working up then in terms of the management of how you're going to treat the patient? Is there anything else that you do?

Prof. Rachel Riechelmann
No, no.

Prof. Martyn Caplin
I think we've covered that sort of all. What about then briefly stratifying how you treat patients in the different types of neuroendocrine tumours? What's your plan? How do you work it out?

Prof. Rachel Riechelmann
For patients who have a more indolent disease, I think the more rational strategy would be to start with a somatostatin analogue and then move on to lutetium 177 for some patients if I have access to it. But what I tend to do more and more is a management of oligometastatic disease with local regional therapies. So if I can keep the patient on a somatostatin analogue and potentially gradual blade or liver embolize the growing lesion, that's what I do. And then I wait a little bit more to change the whole systemic therapy. But then, of course, targeted therapy and then depends if it's pancreas or small bowel and whatever. CAPTEM is a chemotherapy that we mostly use in patients with that. I tend to reserve that for more aggressive tumours or pancreatic NETs or lung NETs. And very, very rarely, I use it for patients with small bowel NETs because, you know, these tumours tend to be more refractory in overall. And for neuroendocrine carcinomas, of course, then platin-based chemotherapy or for FOLFIRINOX, that's what I tend to use.

Prof. Martyn Caplin
Similar. I think that whole concept of for the oligometastatic diseases is interesting. And I think you're right, actually. So for Grade 1, Grade 2 neuroendocrine tumour, certainly low Grade 2, whether it's small intestinal or pancreatic would probably go for somatostatin analogues first line. The only caveat is if one had a rapidly deteriorating patient with weight loss and sort of that cancer type of patient where they're deteriorating, you would go for a more aggressive treatment in that scenario. But usually somatostatin analogues for intestinal. But you're right, I think if you've got localised oligometastatic disease, then doing targeted therapy is a good way forward, I agree. And we've become more aggressive, I think, even with bone metastasis. You know, we never used to operate on patients. But if there was a single bone metastasis, then we're sending surgeons off, sorry, send patients to the surgeons in that situation. And then, of course, you've got all those different options of ablation and SBRT and so on, even for bony mets, which I think is quite interesting as well. How early on in the algorithm do you use PRRT versus CAPTEM then for a pancreatic neuroendocrine tumour? That's always the big debate. I think it's pretty clear that for intestinal neuroendocrine tumours, there's not really a role for chemotherapy for Grade 1, Grade 2 neuroendocrine tumours. If you progressed on the somatostatin analogues, you'd go to PRRT. I think everyone would probably say that that's the way to go. There is the question of everolimus. Let's go to that question of everolimus. Do you use everolimus much for small intestinal neuroendocrine tumours?

Prof. Rachel Riechelmann
I do. I don't like it that much, but I do. We see a lot of toxicity. It's very common to dose-reduce to five milligrams per day. But yes, we use it. I think that we have the evidence and the drug is approved.

Prof. Martyn Caplin
Yes, I try not to use it. I'd much rather use PRRT for intestinal neuroendocrine tumours up front. And

then if we're struggling, we might consider everolimus. But going to the pancreatic ones, which is always the big debate, once they've progressed on their somatostatin analogue, how do you decide whether to go for PRRT or CAPTEM?

Prof. Rachel Riechelmann
I tend to decide based on the aggressiveness. So if I see that most metastatic lesions are fastly growing, I go for chemo. If the tumour is more on the indolent one, then I go for PRRT. But I confess that using both therapies makes me a little bit nervous in the long run, because patients may develop myelodysplastic syndrome and this is something that we're going to see more and more with the two therapies added. And also I see these hyper progressive tumours with hypermutation that we still don't know exactly how to treat them.

Prof. Martyn Caplin
And so, I suppose, yes we traditionally - similar to you actually, if there's fast progressive disease we'll go for CAPTEM, slow, more slowly progressive disease we would probably go, particularly actually even for now, even for NETTER-2 study coming out for the Grade 2, Grade 3 well differentiated, which is quite interesting. Do you think you'll use more PRRT now in the Grade 3 neuroendocrine tumours?

Prof. Rachel Riechelmann
Yes, in the NETTER-2, I think, you know, although they could have G3 pancreatic NETs, they were very selected because they probably had a high uptake on the gallium PET and a low uptake on the FDG. So although they were G3, they probably were the more easy, I would say, less aggressive G3.

Prof. Martyn Caplin
That's an interesting point you make. And that's where the FDG PET scan comes in, because that really helps. And if you've got a strong FDG PET scan, you think, well, actually, that's a more aggressive tumour and probably go for chemotherapy in that situation, perhaps ahead of PRRT. I think that's a very good point that you allude to in terms of the biology. And where do you use the molecular targeted agents, everolimus and sunitinib in pancreatic neuroendocrine tumours?

Prof. Rachel Riechelmann
I use in third, fourth line after I use PRRT and CAPTEM which I leave it for later lines. But again, it really depends. If I have a very slow growing tumour after progression on PRRT, I may start with sunitinib or everolimus. And something that I don't know, I would like to hear from you. I see more toxicity with everolimus among women. They develop more stomatitis. I don't know why, or maybe it's something that's common here, but I see this.

Prof. Martyn Caplin
Yes, I don't know is the honest answer. I suppose because it's more my oncology colleagues who will be giving everolimus rather than me. Now that you've said it, I will certainly look out for it and see if it's more common in women. That's an interesting point. There was, and it's an important aspect, is they looked at different ethnicities in the RADIANT studies and showed no difference, for example, between Asian and Caucasian groups, which I thought was actually important that they looked at that and published on that, which is quite interesting. I suppose I see the role for everolimus and sunitinib in the more smaller volume disease, slowly progressive volume disease. I think it's probably where I see it, the role, yes, I agree. And then otherwise, I think the data for PRRT is good, CAPTEM. And then the question is when you're going down the line and you're exhausted, because now it's wonderful for our patients that they can go from one treatment to another. The question is then what happens after that when they've progressed through PRRT and particularly the pancreatic ones, and then they've progressed through their chemotherapy, certainly CAPTEM, is that when you

go to platinum after that? Or what, how does it work?

Prof. Rachel Riechelmann
No, usually, well, I go for platinum only if the patient has very aggressive disease. Yes, otherwise, I try to use all the TKIs. So, for example, lenvatinib and now cabozantinib. These drugs are approved in Brazil. They are not on label for NETs. So, it's not that easy to get, but we can get for some patients. So, that's what I try to do. If I can't, then CAPOX or FOLFOX is a very good regimen and really effective.

Prof. Martyn Caplin
Yes, we've been using more FOLFOX as well, actually, as well in both intestinal and in some of the pancreatic. Even in lung, there's some data as well. So, that's interesting. I think the most exciting area then in that group that seems to be progressing looks potentially to be the alpha PRRT, the alpha therapy. Yes, it's coming. Yes. The sooner the better. I think it'll be interesting to see what the toxicities are like, which you alluded to taking a long-term view of alpha PRRT. It's not yet here in the UK. It is in certain parts of Europe and in the States. I don't know, has it arrived in Brazil yet?

Prof. Rachel Riechelmann
Yes, well, we have the trial. The trial is going to open now in June and I'll have it in my centre.

Prof. Martyn Caplin
Very good. Is that with actinium or lead?

Prof. Rachel Riechelmann
Yes, with actinium.

Prof. Martyn Caplin
With actinium. Yes. I think it's a very exciting opportunity there. And finally, I suppose, advances for the future. Where do you see the advances?

Prof. Rachel Riechelmann
Well, I think radiopharmaceuticals are really promising because they are very gentle therapies compared to all the agents like everolimus, for example. And they tend to be effective and it's very good for patients because they take one injection every two months. So it really makes them far away from the hospital. The further, the better. So I think there's a very promising way with these agents. And there's also the oral somatostatin analogue, paltusotine, which is something that we may see because a lot of these patients take these monthly injections for years and years. And this is not very convenient. So having an oral somatostatin analogue would be very convenient for them.

Prof. Martyn Caplin
Yes, it'll be interesting to see if that takes off. The question is, do you want to take a tablet every day or an injection once a month?

Prof. Rachel Riechelmann
I would prefer the tablet for sure.

Prof. Rachel Riechelmann
Very good. And then say, what about molecular profiling and the future? Well, molecular profiling, you know, so far, you know, we try to do it for neuroendocrine carcinomas for sure, because some of them are hyper-mutated, have microsatellite instability. They tend to have the molecular profiling similar to the same organ where the carcinoma, the adenocarcinoma would arise. But for the well-

differentiated NETs, so far, molecular profiling has not been very useful. What I tend to do is at least the immunohistochemistry expression of the MMR enzymes to see if the tumour is deficient or proficient so I could introduce immunotherapy and then NTRK immunohistochemistry. But I have to confess, I've never seen anyone so far with a fusion, NTRK fusion. So, molecular profiling is not very useful, I would say, for most.

Prof. Martyn Caplin
I think that's right. It's limited for the well-differentiated. Maybe it's for the poorly-differentiated, it's a different case. I think we've gone over our time and I think it's been a great discussion. It's been lovely to chat with you. It's good just to see the experiences across the world, but actually not necessarily so different either in the same sort of problems. So, I want to thank you very much.

Prof. Rachel Riechelmann
Thank you, Martyn. It's a pleasure.

Prof. Martyn Caplin
We look forward to meeting at a forthcoming meeting and also to thank all the audience too for watching and listening.

Prof. Rachel Riechelmann
We hope it was useful. Thank you all.

Prof. Martyn Caplin
Yes, on that note, bye-bye.

Prof. Rachel Riechelmann
Bye-bye.

Tonke de Jong
Thank you both for this lively and provocative discussion. There is a lot of information on treatment and future developments in the field of NETs which can help to maximize patient outcomes. If you have enjoyed this episode of this podcast series, then don't forget that episode 1 is also available, in which the experts discuss epidemiology, diagnosis, and referral strategies for NET, and how regional differences can impact them. In addition, look out for another podcast, in which a Consultant in Gastroenterology & Neuroendocrine Tumours and a person living with NET discuss Decoding decisions: navigating shared decision-making in NET treatment including self-injection scenarios. If you enjoyed this and want to find out more about NETs and how to manage people living with NETs, then please look for the other resources from NET CONNECT under the account of COR2ED medical education. Also don't forget to rate this video podcast and share it with your colleagues. Thank you for watching and see you next time. This video podcast is an initiative of COR2ED and developed by NET CONNECT, a group of international experts working in the field of neuroendocrine tumours. The views expressed are the personal opinions of the experts. They do not necessarily represent the views of the experts' organizations, or the rest of the NET CONNECT group. For expert disclosures on any conflict of interest please visit the COR2ED website.