Medical Management of NETs

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So hi. Welcome to today's webinar. So we are going to be speaking over the next 15 minutes on the first-line treatment of metastatic well-differentiated neuroendocrine tumours. I'm Dr. Rachel Goodwin. I will be moderating this session. And this session is meant to be a discussion between myself and Dr. Simron Singh to give some clinical pearls regarding the treatment of neuroendocrine tumour.

So just a point of introduction, I'm Dr. Rachel Goodwin. I treat gastrointestinal cancers, including neuroendocrine at the Ottawa Hospital. And I'll let Dr. Singh introduce himself as well. Hello, Simron.

Hi, Rachel. I'm Simron Singh. I'm a medical oncologist at the Odette Cancer Centre in Toronto, Ontario. I co-founded the Susan Leslie Clinic for Neuroendocrine Cancers-- a dedicated clinic for neuroendocrine cancers here in Canada. And I'm very happy to be here today.

Great. Thanks. So as I mentioned, we're going to be focusing on first-line treatment of neuroendocrine tumours. And I guess we could just take it back right to the beginning of our key trials that put somatostatin analogues on the map in terms of treating neuroendocrine tumours that are well-differentiated. And we do have a slide outlining the PROMID and the CLARINET data. So why don't you give us the key highlights about patients that were included on these trials, their characteristics, and to bring all the readers up to date?

Sure. So I think maybe where to start even before that would be, it isn't that long ago that we didn't really know how to treat these neuroendocrine cancers. And certainly, I think we've seen through epidemiological data watching them grow in incidence and in prevalence has actually been quite remarkable. In many areas such as the UK and Australia, which measure neuroendocrine tumours independently, we find that they are on the top 10 types of cancers in terms of incidence.

And here in Ontario, for example, we've done studies that have shown more than doubling in the last 15 years of the rates of neuroendocrine cancers that also applies to the United States. So I think one of the first things that we want to mention is how these are not rare cancers. They may be uncommon, but they certainly are not rare.

And then as you said, Rachel, approximately what, 15 years ago now, people were using somatostatin analogues to treat carcinoid syndrome. And I think we can talk about that in a second. But there was an unclear role for somatostatin analogues in the role of trying to control the cancer as an antineoplastic therapy.

And both the PROMID and CLARINET studies have really established these as standards of care, particularly the CLARINET, which was published in The New England Journal of Medicine. The PROMID trial was a smaller trial looking at midgut metastatic small bowel neuroendocrine tumours. They were randomized to receive octreotide 30 milligrams versus placebo, about 80 patients in this trial done over in Germany over about 8 years.

The endpoint was time to tumour progression. And one of the unfortunate points we don't know is how were people progressing before they came on the trial? We do know that the majority had a Ki-67 of less than 2%, so grade 1, which would be typical of small bowel neuroendocrine tumours. And we do know that most of them picked up at that time, what was [INAUDIBLE] scan.

And as you've shown here, Rachel, the time to tumour progression certainly was quite profound in terms of difference, 14.3 months versus 6.0 months in placebo. And that was the first indication that somatostatin analogues would therefore be considered use for anti-proliferative therapy.
The CLARINET trial was a much larger trial looking at over 200 patients who had slow-growing disease, but had G1 and G2, what we call GEP-NETs. So that GI or pancreas neuroendocrine tumours. So any neuroendocrine tumours in the pancreatic origin. As you can see here, slightly different patient population that was with a slower progression, the placebo arm had a median PFS in this situation versus time to progression in PROMID. PFS of 18 months. And the lanreotide arm wasn't reached.
Again, with a very significant hazard ratio. So I think that really established somatostatin analogues certainly as the bedrock of care in almost all GI neuroendocrine cancers from that point on. And that's still reflected in clinical practise today. Specifically, I'd say the G1 and the low G2, the CLARINET study included patients with a Ki-67 of less than 10%. And so basically, that's the early portion of the G2 patients.
Yes. Exactly. And I guess before these trials were published, we were using SSAs more for symptom control. But after these trials, then it became known for tumour control as well. And do you expect for the tumour to shrink on these treatments, and what starting dose do you tend to use?
So it's a really great question. So I think when we talk to our patients about these, we have to be realistic. There wasn't any complete responses or even really truly partial responses seen on either of these trials. What we see here is stable disease. So when we talk about treating these patients, we talk about ensuring that we keep the disease stable, it does not grow. That in fact, we want to make sure that we treat this like a chronic disease.
Some patients do ask about watch and wait. It is possible. But for me, I see a slightly more aggressive population in the PROMID trial, I see a slightly less aggressive population in the CLARINET trial. And I see that starting patients on lanreotide seem to benefit either one or an SSA, pardon me. So I'm generally in favour of starting treatment early. But individual patients watch and wait may be an approach to consider.
Yeah. Exactly. Especially if you know you've caught the patient very early in their trajectory and low burden of disease, but you're right. Some patients, and think you publish this data-- it can take up to two years before you diagnose these patients. So you are a bit more worried, heavy bulkier disease. And I agree. Probably starting treatment earlier than later once they're in your practise is good. And you tend to start with the doses of-- drug doses that were used in these trials?
Absolutely. So think a starting dose really effectively for all patients should be 30 milligrams of octreotide or 120 milligrams of lanreotide, either/or. Certainly, there is role for dose escalation, but we can talk about that separately. But I think the initial dose should be as per the trials. Yeah.
Great. Perfect. Yeah. So actually, you brought up dose escalation. So I'm going to move to the next slide. And here we have the CLARINET FORTE study. And we know that sometimes patients when they're on their SSAs, they're not overly symptomatic. We have mild progression. And they want to keep treatment more simple, I guess, per se, and on the treatment that they know. They do ask about increasing the dose of SSAs. Sometimes they want that as a strategy. So why don't you put that in the context of the CLARINET FORTE study?
Sure. So we do know that approximately, around 1/3 of patients in Canada are on dose-escalated SSAs. And I think there's certainly good rationale for that. The first would be for treatment of carcinoid syndrome.

So if we're dealing it for symptom control, carcinoid syndrome, thinking of things like flushing, diarrhea, bronchospasm, cardiac carcinoid disease, hopefully, we've caught it before then, but even elevated serotonin in urine and the serum.

If we're trying to treat that aggressively to normalize that, we'd want to dose escalate. So dose escalation certainly has a role to play there. In terms of anti-proliferative control, this is probably the best data we have. We have some retrospective data that has shown some efficacy. The NETTER-1 clinical trial compared dose escalation from 30 milligrams of octreotide to 60 milligrams of octreotide versus. PRT PRT was clearly better, but what was interesting is that on the NETTER-1 clinical trial, milligrams of octreotide dose escalation in a previously progressing population induced nine months of stability.

And in the NETTER-2 trial, recently presented, we saw a very similar arm about nine months in terms of dose escalation. So that gives us some indication that there's probably some role for dose escalation. The CLARINET FORTE trial was a prospective single-arm open-label exploratory study that followed CLARINET.

These were patients who had progressed on standard dose lanreotide and were then simply divided into a pancreas and a midgut cohort not randomized, but were prospectively followed. And to look at their PFS on dose escalation of lanreotide, which generally is 120 milligrams every 2 weeks instead of every 4 weeks.

And on the right-hand side here, what you could see from Dr. Pavel's paper is that there was some potential signal there in the low Ki-67, and that is in the pNETs and the midguts. And if you actually look at the data in some detail, you'll find that at a one-year mark, about a quarter of the pNETs and about a third of the midguts with low Ki-67 still had stable disease. So these are people who had previously progressed on a standard dose and then per dose escalated, and then for about a year, had stable disease.

So I think it's a worthwhile thinking for your patients. This could be a bridge to therapy, if you're waiting for the next step therapy, whether it be PRT or embolization. Maybe for patients who've had very slow growing disease and grow just a little bit, and you don't want to subject them to the next level of therapy, you can buy some more time with dose escalation.

Maybe for people who are tolerating this treatment well and you're worried, the next step maybe they may not tolerate as well, or have contraindications. It may be an option. But again, certainly in select patient populations, that might make sense.

And in the CLARINET FORTE, trial they did look at safety. And was there any increase in safety issues? Really good point. No. No safety signals found. So that made us reassured as well that dose escalation is a reasonable option from a safety perspective and potentially an efficacy perspective as well.

Yeah. Yeah. Exactly. And I think you brought up a good point. Is sometimes patients want a bridge before they have to go to that next more intensive treatment and personal issues in their life or whatnot. And this is a good strategy to use for those patients. So that's great. So we know that you've been busy and you were recently at ASCO GI presenting this data. We establish SSAs as a solid treatment, a treatment choice for patients. So how do you put that into perspective with the NETTER-2 results, which were also in the first-line setting?

Great. Thank you. So yeah. This was an exciting study. As I mentioned, the CLARINET study included patients with G1 and G2 GEP-NETs up to 10%. There's this new entity that's been described in recent

years of a well-differentiated G3 neuroendocrine tumour. Now, that has to be very-- we have to be very clear that it's different than a poorly differentiated G3, which most likely is going to require chemotherapy. These well-differentiated G3 with the Ki-67 or somewhere between 20 to 55 and the G2s that are greater than 10%. So based on Ki-67, potentially more aggressive population, this was the first trial that looked at first-line RLT or radioligand therapy with 177 Lu-DOTATATE with 30 milligrams of octreotide, which is how the label is, or as opposed to a high dose octreotide arm.

And as you can see here, certainly, there is benefit to first-line lutetium dotatate, hazard ratio of 0.28, and clearly 72% reduction in the risk of disease progression or death in these results. So what, I guess, this shows us is that in first-line therapy for the higher G2s, but especially for the well-differentiated G3s, I think we want to consider PRT with somatostatin analogues as first-line therapy.

And I'm not sure it really matters what somatostatin analogue you use. To me, they're all a class effect. But certainly, we there's a benefit there. Interestingly, the control arm, which was high-dose octreotide, much like the natatorium, again, showed somewhere close to nine months of PFS. So again, making it, at least to me, clear that there's probably some role for high-dose SSAs in some patients in some circumstances.

Exactly. And symptomatic patients were allowed on this trial as well? Like functional patients?

Yeah. Yeah. Symptomatic patients were allowed, although this trial wasn't designed to specifically look at that. Certainly, we want to ensure that patients may need higher doses of SSAs to manage their symptoms. But from a disease progression point of view, certainly it shows that PRT for some of the more aggressive neuroendocrine tumours up into first-line.

Yeah. And do we expect to see an overall survival with this data? Was there crossover allowed? So NETTER-1 has had a ratio of 0.21. And its updated analysis did not show overall survival benefit. And there's probably-- the biggest reason for that is multiple lines of subsequent therapy. I mean, as we know, fortunately, neuroendocrine patients have a longer survival time than most patients of the GI malignancies.

This trial, specifically, was a 2 to 1 randomization with crossover allowed, as well as when you think about subsequent therapy. So although it's too early to say, we'll have to wait for the overall survival data, but I generally think in neuroendocrine tumours, we shouldn't be looking for overall survival benefit as a sole indicator, because when we're seeing hazard ratios of 0.21, 0.28 not translating into a overall survival benefit, it probably means more that not that the drugs aren't effective, but rather, that's just not the right marker based on the natural course of the disease in the real world. And that's what happens, right?

Yeah. And think you point out a very good issue. And I was just looking at the recent CABINET data, and that's cabozantinib, after a number of prior lines, and patients on that study, neuroendocrine tumours, two cohorts as well-- GI and pancreas. And they had up to six lines of therapy.

Yeah.

So it does go to show, right? It's going to be hard to see overall survival. OK. Perfect. OK. So along the theme that we made mention to is the issue around carcinoid. And we know that certainly our small bowel patients are probably more likely to have carcinoid syndrome. And you mentioned some of the issues with flushing, diarrhea, bronchospasm. And titrating up your long-acting SSA was one strategy that you had mentioned.

And in our Canadian consensus document, from 2016, we did give some estimates of-- it was expert's opinion of where you could dose escalate to. And certainly, now, we do have data with lanreotide that you

just summarized. What are some other treatment options that we want to make sure that at least the treating physician thinks of to help with carcinoid that's refractory?
Yeah. So I think one of the important points we should mention here is your third bullet point on the left there is that we want to ensure we have the right diagnosis, because patients who have neuroendocrine cancers can have diarrhea for many other reasons. Bile salt impairment, pancreas impairment, intestinal hypermobility, but also short bowel syndrome, especially after a debulking surgery or mesenteric surgery. So it is important that we ensure that this is, in fact, caused by, and that usually can be confirmed with a urine 5-HIAA, and increasingly we're doing serum serotonin now. We want to titrate up the SSAs. I usually go up to 60 milligrams every two weeks as a max and 120 every 2 weeks of lanreotide. We can supplement that with short-acting, depending on the frequency, if there's precipitating events. That that's the case. I don't use interferon. I find that although it is effective, it has a lot of side effects.
I agree.
So that is a difficult. But it's an option for sure. I think after this, we start to think about getting to the source, which would be liver-directed therapy. And that could be take a number of forms now. It could be cytoreduction, it could be transarterial embolization, transarterial chemoembolization, as well as we're now using more and more sabre and external beam radiation to try to reduce some of the bulk of the disease.
So those are all options. Telotristat or Xermelo is another option. It works really well in patients where you've confirmed that this is really truly carcinoid diarrhea. It does reduce the bowel frequency quite dramatically. And that is certainly very important. Access can be an issue for this drug. So we have to work around that.
And then the other promising therapy that's coming around is [INAUDIBLE], which is an oral SSA, which just recently reported on their phase I and phase II data that show some efficacy in carcinoid syndrome with an oral SSA as well. So we'll see where that story develops.
Great. Great. Wow. So it's really exciting times for neuroendocrine treaters and neuroendocrine patients. And I'd like to thank you today. So you brought us all the way from the beginning of SSAs to modifying the dose, using it for symptom control, and also tumour control. Some new exciting data in the first-line with higher grade Ki-67 well-differentiated disease and looking at radioligand therapy, and remembering that we have many treatments in our toolbox to deal with carcinoid syndrome.
So it's important to always revisit that as well. And certainly, if your patient is having carcinoid symptoms, to make sure you have an updated scan, because it could be an indication of progression that you want to make sure you're not missing. OK. So on behalf of OncologyEducation, Simron, thank you so much.
Thank you.
And we appreciate all your hard work moving the science forward.
Thank you.
[AUDIO LOGO]