INTERVIEW

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Gastroenteropancreatic neuroendocrine tumors and the NETTER-1 trial

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Martyn Caplin* speaks to Senior Editor: Oncology, Roshaine Wijayatunga:

Martyn is a professor of gastroenterology and GI neuroendocrinology at the Neuroendocrine Tumour Unit at the Royal Free London and University College London. He is immediate past-Chairman of the European Neuroendocrine Tumor Society. He is founder and past-Chairman of the UK and Ireland Neuroendocrine Tumor Society as well as NCRI Neuroendocrine Tumor Group. He received a lifetime achievement award in recognition of his clinical leadership and research in the field of NETs. Former clinical lead for 'NHS Evidence' for gastroenterology and liver diseases. He has published over 200 peer review papers, written multiple book chapters and co-authored two books. He regularly lectures both nationally and internationally.

Q What led to your interest in specializing in gastroenterology & GI neuroendocrinology?

My interest in the field was established fairly early in my career, when I was a middle grade doctor (Registrar) at the Royal Free Hospital. I was involved in the care of a number of patients who came into the hospital with neuroendocrine tumors (NETs) and, at the time, there was a lack of specialist knowledge in this area, as well as very little in the way of clinical trials. One patient in particular, a 24-year-old female, particularly sticks in my mind – she was referred to the hospital with large volume liver metastases. She had experienced problems for years, but her symptoms had not been taken seriously and not been properly investigated. As a result, by the time she presented she had very advanced disease. Ultimately, she received a number of therapies over the ensuing years including surgery, somatostatin analog, liver embolization and eventually she underwent a liver transplant. It was clear that NET understanding had a significant unmet need and that I could apply some of my own previous research and patient experience.

My boss at the time, Professor A Burroughs, encouraged me to set up a NET clinic in the Royal Free, and I started a multidisciplinary clinic in 1997, where we saw around 30 patients with NETs. We now have around 2000 patients under our care today. It is a particularly exciting area, which has seen lots of advances in a short period of time. Another nice thing about working with the NET community is the multidisciplinary approach, and both nationally and internationally it is almost like a family that gets on well and that has a lot of advantages – people are more collaborative. It has been an enjoyable area to work in.

Q Can you please tell our readers about any specific research projects you are working on currently?

We have a wide range of research projects ongoing currently, from pathology to imaging and clinical trials. We have a team, led by Professor T Meyer looking at how the immune cells affect NETs – this may help predict the best patients for immune therapies, which is a very new advancement in cancer that is relevant in NETs. We are also looking at

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*Neuroendocrine Tumour Unit, Royal Free London & University College London, London, NW3 2QG, UK;
m.caplin@ucl.ac.uk

biomarkers from the blood, such as liquid biopsies. By counting circulating tumor cells, we can predict outcomes in patients, which is another relatively new advancement with Professor Meyer. In regard of genomics and epigenomics, Dr C Thirlwell leads a team making very promising advances. On a broader scale, Dr C Toumpanakis leads on clinical prognostic markers and we have worked with colleagues to look at new imaging targets for identifying NETs with new radioisotopes as well as new targeted therapies. It is very multidisciplinary, and the nice thing is that we can look at all aspects of NET biology and conduct translational research that changes outcomes for patients. We are very active in clinical trials for new drug therapies.

Q You have accomplished a huge amount in your career to date, including being the Chairman of the European Neuroendocrine Tumor Society, being the founder of the UK and Ireland Neuroendocrine Tumor Society and receiving a lifetime achievement award in recognition of your clinical leadership and research in the field of NETs. How have you seen this field of research develop through the years and what would you class as your greatest achievement?

If you look back to the 1990s–2000, the biggest change has been developing specialist centers and networks for patients with NETs and having guidelines for management. Patients now also have better support through patient support groups, such as the NET Patient Foundation. From a practical aspect, the disease should be seen in specialist centers, which makes a big difference to clinical outcomes. We have looked at survival rates from when we first started in the 1990s and it has probably doubled in terms of advanced disease and survival. It is only because of this organization of centers that clinical trials have been possible on an international basis. I like to think that my biggest achievement has been in setting up the NET society in the UK, which has enabled us to build these centers throughout the UK. At the Royal Free, we have this multidisciplinary team and we have built up specialist nurses for NET. Our specialist nurses have really been role models throughout the UK and Europe, so there is now a specialist nurse group within the European Neuroendocrine Tumor Society. It is knowing that patients can get to appropriate centers and get the right treatment options, that has been the most rewarding.

We are hoping to expand the centers of excellence and the EU now recognizes NETs in what is called the European Reference Network – this network looks at care across borders for patients with rare diseases, so that patients have access to the right expertise, and can get the right diagnosis and appropriate treatments, regardless of their home country [1]. The potential impact of Brexit on this initiative and on research in the UK is not clear and of some concern, so this is a topical subject at the moment.

Q What are the main challenges associated with the treatment of adult gastroenteropancreatic neuroendocrine tumors?

The main challenge is still the time to proper diagnosis for patients. We can still see that patients have years of symptoms before they are referred appropriately for the tests to accurately diagnose NETs. This is something that really has to improve. The other challenge is that you have to interpret the biopsy correctly, and we are still seeing inconclusive and inappropriate reporting of biopsies, which then leads to the patient going down the wrong pathway before they get to a specialist NET center – this is not just in the UK, it is a challenge that is shared internationally.

We know now that, through randomized trials, there are drugs that work, but then we still need to understand what order the drugs should be given, and also what combinations of drugs are best. It has been fantastic that the pharmaceutical industry has been involved in the area and clinical trials are being run, but sometimes you want to combine drugs from different companies, and the practicalities of doing so complicates matters.

Q What was the aim of the NETTER-1 trial & what were the main end points?

The NETTER-1 trial was conducted to evaluate efficacy and safety of lutetium (^{177}Lu) oxodotreotide in comparison to a double dose of the standard of care at the time (Octreotide LAR 60 mg). The primary end point of the trial was to compare the progression-free survival (PFS) after treatment with each agent. Secondary trial end points included comparing objective response rate, overall survival and time to tumor progression between the two study arms. The safety and tolerability of lutetium (^{177}Lu) oxodotreotide were also

evaluated along with health-related quality of life assessments.

Q Can you please briefly outline the results of the NETTER-1 trial & the safety profile of lutetium oxodotreotide for our readers?

The NETTER-1 study met its primary end point by demonstrating a statistically significant improvement in estimated PFS [2].

The median PFS was not reached for lutetium (^{177}Lu) oxodotreotide, and was 8.4 months with 60 mg Octreotide LAR [2].

Treatment with lutetium (^{177}Lu) oxodotreotide was associated with a statistically significant and clinically meaningful reduction of 79% in the risk of disease progression or death versus treatment with Octreotide LAR 60 mg [2].

A preplanned interim overall survival analysis determined that compared with the Octreotide LAR 60 mg arm, lutetium (^{177}Lu) oxodotreotide treatment led to a 60% reduction in the estimated risk of death [2].

Lutetium (^{177}Lu) oxodotreotide, when administered concomitantly with a renal protective agent, had low rates of grade 3 or 4 hematological toxicity, and no evidence of nephrotoxicity observed over the study time-frame (median follow-up time 14 months) [2].

Q What are the next steps/next stages for this clinical trial?

Two hundred and thirty-one randomized patients were enrolled in the study, which continued until July 2017. The follow-up phase is anticipated for Q1 2021, however data collection has been sufficient to proceed with submission for marketing authorization, and the Committee for Medicinal Products for Human Use has provided positive opinion, with the European Commission approving the marketing authorization of Lutetium (^{177}Lu) oxodotreotide in September 2017.

Financial & competing interests disclosure

In the last 5 years, M Caplin has been on the advisory board and/or received research honoraria from AAA, Ipsen, Lexicon, Novartis and Pfizer. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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