Neuroendocrine tumours emerge from the shadows

The so-called zebras of cancer are rapidly becoming better understood and managed, thanks to efforts of patients, clinicians, and researchers worldwide. Judith A Gilbert reports.

The diagnosis and treatment of neuroendocrine tumours (NETs) are uniquely challenging. NETs are relatively rare, diverse in origin, usually slow growing, and frequently associated with clinical syndromes caused by hypersecreted hormones—earning this malignancy the name zebra cancer. Lately, however, there has been a sense of excitement in the NET community, as the efforts of patient groups, medical professionals, and research investigators are rapidly improving the understanding and care of NETs.

NETs have often been misdiagnosed and suboptimally managed. A recent international survey documented the experiences of 1928 patients with NETs from more than 12 countries in the Americas, Europe, Asia, and Oceania. Results showed that the average time between the onset of the first symptom and diagnosis of the NET was 4·3 years. Patients averaged 11·8 doctor visits and 6·2 consultations with health-care professionals before obtaining a correct diagnosis, and 58% had metastatic disease at initial diagnosis. Author Edward Wolin (Montefiore Einstein Center for Cancer Care, New York, NY, USA) said, "I'm hoping this survey will prompt physician awareness. The most common site for these cancers to develop is the small intestine. Upper and lower endoscopy studies frequently miss these tumours…someone has to think of small intestine tumours to make the physician order a small intestinal evaluation."

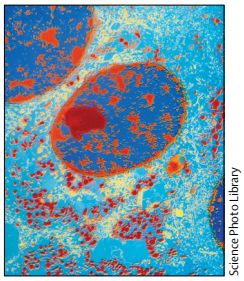
Support groups and advocacy organisations for patients with NETs have been increasing in number worldwide, and building a global coalition. Ron Hollander of the Neuroendocrine Tumor Research Foundation (Boston, MA, USA) serves as president of the International Neuroendocrine Cancer Alliance (INCA), a coalition of NET patient groups and advocacy organisations from around the world. "5 years ago, INCA was formed by a handful of organisations with a commitment to raising awareness of NETs. Today, INCA has 20 members from 17 countries and four continents, and its mission as the global voice of NET patients spans awareness to advocacy", he told *The Lancet Diabetes & Endocrinology*. INCA has been instrumental in drawing attention to the need for improved diagnosis and management of these complex tumours. "The global survey of patients was transformational", notes Hollander. "We are now together in dialogue with NET medical leaders to make progress in addressing unmet needs in standards of care, patient access, and research."

Medical professionals formed interdisciplinary organisations to focus on NETs in the mid-2000s in Europe and North America. These associations developed treatment guidelines based on the recommendation of the 2007 US National Cancer Institute (NCI) NET-carcinoid summit, which stated that multidisciplinary expertise was needed for optimal clinical management. Numerous multidisciplinary treatment centres specialising in NETs have since been established, which work to individualise treatment for patients. The European Neuroendocrine Tumor Society (formed in 2004) has accredited 37 NET treatment centres of excellence throughout Europe since 2008, and the North American Neuroendocrine Tumor Society (established in 2006) developed guidelines in 2010 for standardising care in North America, where currently there are 26 multidisciplinary NET treatment centres.

Following recommendations from the 2010 NCI international planning meeting for NET clinical trials, researchers have rapidly undertaken several multinational phase 3 clinical studies assessing new treatments for NETs. Lanreotide (CLARINET trial) and everolimus (RADIANT-4) each significantly delayed progression of metastatic, non-functioning gastrointestinal (carcinoid) NETs. More promising was ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (NETTER-1), widely available in Europe and currently under review by the US Food and Drug Administration (FDA), which was shown to be significantly superior to octreotide long-acting release in delaying the progression of advanced, somatostatin receptor-positive gastrointestinal NETs. "Traditional chemotherapy doesn't work well in non-pancreatic NETs", explained Wolin. "Until lately, there were no FDA-approved treatments for carcinoid—we now have several excellent options." Ongoing studies include the long-term TELEPATH trial of the oral drug telotristat etiprate and the REMINET trial of lanreotide as maintenance therapy following initial treatment.

Summarising the reasons for the current excitement among patients, clinicians, and researchers in the NET community, Timothy Asmis (Ottawa Hospital Cancer Centre, Ottawa, ON, Canada) said: "There's a lot going on. There've been new treatments recently—the CLARINET, RADIANT-4, and NETTER-1 clinical trials all showed improvement in progression-free survival in patients with NETs. Also, there's been an increase in multidisciplinary care centres and research."

Judith A Gilbert



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For the **international survey** see *J Glob Oncol* 2016; published online June 8. http://dx.doi.org/10.1200/JGO.2015.002980

For the **National Cancer Institute recommendations** see *J Natl Cancer Inst* 2008; **100:** 1282–89

For the **clinical trial recommendations** see *J Clin Oncol* 2011; **29:** 934–43

For more on **clinical trials for NET treatments** see *Cancer Treat Rev* 2016; **47:** 32–45