On the 8th-11th March, the NET Patient Foundation attended the European NET Society (ENETs) Conference in Barcelona, and Catherine (our CEO and co-founder) attended and spoke at the 1st ENETs/INCA Patient Advocacy Meeting. We also had our information stand.

ENETs founding members sought to unify neuroendocrine tumor disease research among European medical professionals. The primary aim was to integrate basic and clinical research with teaching and to establish guidelines for the diagnosis and therapy of gastroenteropancreatic neuroendocrine tumors (GEP NETs). The first guidelines were published in 2005, revised 2006 and 2007, updated in 2012 – with the latest version being published 2016. ENETs attendees now come, not just from Europe, but from Japan, Australia, India, Russia, America, Canada . . . all over the world – to share research and knowledge about NETs with the common aim of improving diagnosis, awareness and care of those living with NET.

This year I was struck by how many of the talks incorporated the theme of quality of life, of tailoring treatments and care to the individual, of listening to the patient experience and involving NET patients in, not just care decisions, but also service and research design.

Cathy will feedback on the Patient Advocacy Summit – so please see below for conference overview (it is a not a verbatim transcript and there are one or two topics I am looking into, that I will put forward for future newsletter inclusion, so forgive any omissions, Nikie)

**A take home message from Professor Caplin's introduction:**

**Often over a period of years patients often go from one therapy to another. It is important that centres treating NETS utilise treatments appropriately (tailored to the individual patient and their disease) and hence the need for referral to specialist Centres.**

Over the next few pages I have summarised some of the talks by topic:

- Diagnostics
- Treatments
- Other news and topics

. . . and linked them with expert advice and information.
Diagnosis and baseline for treatment decision-making:

**Histology** is the gold standard: what the tumour cell looks like, where it's from and how it behaves. Primary site, grading, tumour burden (how much disease not just where it is) and how is it changing – effect on the individual.

Latest World Health Organisation grading:
Grade 1 = NET (well differentiated) < 3%, Grade 2 = NET (well differentiated) 3-20%, Grade 3 = NET (well-differentiated) >20% and NEC (poorly differentiated) >20%

There are genetic differences between NET and NEC – therefore treatment planning needs to take this into consideration when deciding on treatment and monitoring.
By understanding the grading and genetic profile of the tumour – treatments can be used to more accurately target each individual's NET.

**Blood tests – biomarkers:**
Chromogranin A and B were identified as clinically relevant circulating biomarkers for the management of NETs in the late 1980’s – but they, alongside urinary 5HiAA do have their limitations
Chromogranin A can be elevated in ~90% GI NETs, correlates with tumour burden and recurrence – but other factors (see diagram) can alter levels.

Chromogranin B can be a useful marker for phaeochromocytomas, paragangliomas and duodenal NETs – but may also be influenced by other factors.

Urinary 5HiAA – is a more specific marker for metastatic midgut NETs, may also be raised in some Lung and Ovarian NETs (if evidence of carcinoid syndrome)
False positives: foods such as bananas, avocados, aubergines, pineapple, plums, walnuts, . . . and medications such as paracetamol, 5-fluorouacil, naproxen, caffeine . . .
False negatives can be seen if taking levodopa, phenothiazines, . . .

Random urinary 5HiAA or serum 5HiAA/serotonin are measurements used in some centres – and may not require dietary restrictions for the test, but always ask your NET team for advice – and inform them of medications, dietary and supplement intake.

New emerging NET biomarkers include circulating tumour cells, circulating tumour DNA and circulating miRNAs.

Many NET teams are involved in these new developments – if interested in participating, ask your NET team about new biomarkers, bio-banking and how you can get involved.

**Scans and endoscopy:**
A reason we often recommend dual phase CTs rather than plain venous phase – as you can see from the above picture – more can be seen.

Functional scans – such as Octreotide, Gallium68 Dotatate, MiBG, FDG-PET – can all help to assess site and size of disease – but can also help tell the difference in behaviour (grading) and therefore be as, if not more, useful in treatment planning.
Well-differentiated NETs (Grade 1,2 and 3) : often have positive Octreotide sensitive receptors and so will show up on Octreotide and Gallium scans (Gallium being proven to be more sensitive).
Poorly differentiated NECs (primarily Grade 3) may be negative of these scans but positive on FDG-PET scans. Insulinomas, phaeochromocytomas and medullary thyroid carcinomas may also require more specific scans such as GLP1, MiBG, 18FDOPA-PET and 11C-5-HTP, etc.

Some tumours have a combination of cells and activity (called heterogeneity) – and therefore may require both types of scan, that is both Octreotide/Gallium AND FDG-PET.

Such a combination not only allows for greater accuracy in baseline assessment – but can also be used to assess response to treatments.

Endoscopy news:
Endoscopic ultrasound (EUS) has been reported to be highly accurate for the preoperative
localization of PNETs, mainly primary insulinomas which frequently are negative on functional imaging and was established as an alternative to more invasive methods such as angiography. PNETs are identifiable by EUS in 79-95% of suspected cases. Advances mean that now more reliable and timely* cell capture (histology) and imaging is possible (this has implications for treatment too).

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*timely – live review of sample rather than obtain sample and send to lab.

Apologies for poor quality photo – but the 1st circled picture is normal pancreas, the 2nd is a
pancreatic NET, the 3\textsuperscript{rd} is pancreatic cancer.

**Treatments:**
Clinical presentation (performance status, comorbidities, tumor-derived symptoms and hormone syndrome in functioning tumors), histological features [tumor differentiation, proliferation rate (Ki-67), and expression of somatostatin receptors], disease localization and extent, and resectability of primary and metastatic disease, are all key issues that shall be taken into consideration to appropriately tailor therapeutic strategies and surveillance of NET patients. Surgery is the only potentially curative therapeutic strategy in localized disease and may also play a role in advanced stages. Therapeutic options for patients with advanced disease include liver-directed ablative strategies, PRRT and systemic drug therapy.

**Somatostatin analogues (SSAs)** remain the mainstay of treatment in most NETs: as they can help reduce symptoms (antisecretory effect) and tumour growth (antiproliferation).
However, SSAs may not adequately control carcinoid symptoms for all patients experiencing them. **Telotristat** is a new medication (in tablet form) that helps block tryptophan, and therefore reduces excess serotonin release – which then helps reduce diarrhoea. Its use is in combination with analogues.

 Trials : TELESTAR, a placebo-controlled phase 3 clinical trial and TELECAST, the phase 3 companion study to TELESTAR.
 Results : reduction in the average number of daily bowel movements over the first 12-week study period in both treatment arms (250 mg tid and 500 mg tid) compared with placebo, . . . Also a reduction in urinary 5HiAA (the main metabolite of serotonin) was observed at week 12 compared with placebo in both treatment arms.
 The most common adverse reactions associated with the use of telotristat etiprate were nausea, abdominal pain, fatigue.
 It has received FDA approval and is under review by the European Medicines Agency.

 A debate about the use of **Interferon in NETs** concluded that whilst there may be benefit in individual cases, generalised use was not supported – therefore is included in treatment options for consideration.

 Targeted therapies such as **Everolimus** and **Sunitinib** – evidence from trials previously discussed, as was deciding which agent (and when)

 Everolimus is also licensed for use in Lung and GEP (GI) NETs.

 In the UK both treatments are undergoing evaluation by NICE : decision due July 2017 – however a recent communication indicates they may have their decision by April.

 Nb The Scottish Medicines Consortium have recently approved Everolimus for use.

 **Surgery and endoscopic treatments :**

 Curative and debulking surgery is pivotal for NETs and should always be considered (and reconsidered and reconsidered). Minimally invasive surgery (MIC or laparoscopic) can play a role in localised small pNETs, gastric and rectal disease. But given disease pattern – especially in small
bowl and pancreatic/duodenal NETs – an open approach is favoured to allow for mesenteric or pancreatic/duodenal examination and lymph node removal

Advances in endoscopic probe design mean EUS-guided RFA and other novel ablative, approaches, including nanoknife, may now be considered for selected cases.

RADIONET – a trial, awaiting funding, due to start this year – looking at the use of EUS ablation in pNETs
PRRT: In UK – Lutetium is under evaluation by NICE: formal decision due July 2017 - awaiting information from The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP)

Jonathon Strosberg – NETTER1 trial (Lutetium): Quality of life assessment
Carcinoid heart disease:

Historically 50-70% of those with carcinoid syndrome develop CHD, more recently, with "modern therapy" (analogues – hormone control), that figure has dropped to ~20%. NT pro-BNP in patients with carcinoid syndrome is a cost-effective method to select patients for echocardiography.

- MDT approach to these complex patients is required.
- If CHD found - should be monitored at 6 monthly intervals with Echocardiography investigation.
- Aggressive treatment in order to keep the level of Urinary 5-HIAA < 300 µmol/24 hours is necessary to help (hopefully) retard CHD progression.
- Cardiac surgery in selected cases and performed by skilled operators in centres with experience of dealing with carcinoid patients improves symptoms, and probably survival.

**Malnutrition**

Clinical diagnosis:

a. Medical history
b. BMI, body weight and recent changes
c. Clinical examination Composite scores: a. e.g. Nutritional risk index (NRI)

Bioelectrical impedance analysis (BIA) can determine  - Whole body water (WBW, ICW, ECW)  - Fat  - Lean body mass (LBM)  - Body cell mass (BCM)
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