Emerging strategies and future outlook for NeuroEndocrine Tumors

Prof Eric Van Cutsem, MD, PhD
Leuven, Belgium
Why has progress been so slow?

• Limited understanding of cellular and molecular biology of neuroendocrine cells and mechanisms of tumorigenesis
• Paucity of specific targets of new therapies
• Shortage of in vitro and animal models
• No uniform pathologic classification and staging system
• Lack of molecular prognostic factors and lack of natural history
• Few centers offer the multidisciplinary expertise required for the diagnosis, staging and management
• Lack of understanding of disease complications
• Paucity of investigators in NET

Modified from Modlin I et al, JNCI 2008
Some requirements for improved therapeutic outcome in NET

• Optimal classification and grading
• Elucidation of molecular genetics and cell biology
• Identification of serum markers for early diagnosis and follow-up
• Improved molecular imaging
• Identification of molecular therapeutic targets
• Establishment of Centres of Excellence with multidisciplinary specialized clinical teams for NET
Rhetorical Question:

Do genomic technologies and their impact on cancer classification represent a “disruptive” technology or a “revolutionary” technology?

Disruptive: Digital Photography

Revolutionary: Air Travel

Modified from P Febbo, USA
Neuroendocrine cells ~ from hormone producing cells, derived from multipotent GI stem cells

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Localisation</th>
<th>Products</th>
<th>Factors that regulate secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>Gastrointestinal tract</td>
<td>Somatostatin</td>
<td>Hormones, neural factors, and acid</td>
</tr>
<tr>
<td>Enterochromaffin</td>
<td>Gastrointestinal tract</td>
<td>Serotonin, substance P, guanylin, and melatonin</td>
<td>Luminal factors, hormones, and neural factors</td>
</tr>
<tr>
<td>Enterochromaffin-like</td>
<td>Stomach</td>
<td>Histamine</td>
<td>Hormones, gastrin, and neural factors</td>
</tr>
<tr>
<td>G</td>
<td>Stomach and duodenum</td>
<td>Gastrin</td>
<td>Amino acids, neural factors, and acid</td>
</tr>
<tr>
<td>Gr</td>
<td>Gastrointestinal tract</td>
<td>Ghrelin</td>
<td>Luminal factors and hormones</td>
</tr>
<tr>
<td>I</td>
<td>Duodenum</td>
<td>Cholecystokinin, gastrin, etc</td>
<td>Lipids and neural factors</td>
</tr>
<tr>
<td>K</td>
<td>Duodenum and jejunum</td>
<td>Gastric inhibitory polypeptide</td>
<td>Nutrients and hormones</td>
</tr>
<tr>
<td>L</td>
<td>Small intestine</td>
<td>Glucagon-like peptide, peptide YY, and neuropeptideY</td>
<td>Glucose and hormones</td>
</tr>
<tr>
<td>Motilin</td>
<td>Duodenum</td>
<td>Motilin</td>
<td>Neural factors and luminal factors</td>
</tr>
<tr>
<td>N</td>
<td>Small intestine</td>
<td>Neurotensin</td>
<td>Lipids</td>
</tr>
<tr>
<td>S</td>
<td>Duodenum</td>
<td>Secretin</td>
<td>Acid</td>
</tr>
<tr>
<td>VIP</td>
<td>Gastrointestinal tract</td>
<td>Vasoactive intestinal peptide</td>
<td>Neural</td>
</tr>
<tr>
<td>X</td>
<td>Stomach</td>
<td>Amylin</td>
<td>Not defined</td>
</tr>
</tbody>
</table>

*Table 1: Types of gastrointestinal neuroendocrine cells and luminal, paracrine, neural, and hormonal factors that regulate secretion of their bioactive products*

Modlin I et al, Lancet Oncology 2008
Inherited genetic neuroendocrine syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene location (product)</th>
<th>NET frequency (tumor type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN1</td>
<td>11q13 (610-amino acid protein, Menin)</td>
<td>80–100% pancreas + duodenum (NF &gt; gastrinoma &gt; insulinoma)</td>
</tr>
<tr>
<td>von Hippel–Lindau disease</td>
<td>3p25.5 (213-amino acid protein, VHL)</td>
<td>gastric carcinoids</td>
</tr>
<tr>
<td>von Recklinghausen’s disease (NF-1)</td>
<td>17q11.2(2485-amino acid protein, neurofibromin)</td>
<td>12–17% pancreas (all nonfunctioning)</td>
</tr>
<tr>
<td>TSC</td>
<td>9q34, (TSC1) 16p 13.3 (TSC2) (hamartin, tuberin)</td>
<td>6% pancreatic (somatostatinoma)</td>
</tr>
<tr>
<td>MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumor; NF-1, neurofibromatosis type 1; TSC, tuberous sclerosis; VHL, von Hippel-Lindau</td>
<td>&lt;5% pancreas</td>
<td></td>
</tr>
</tbody>
</table>
Genetic changes in NET

- Sporadic pancreatic NET: losses of chromosome 1 & 11q and gain of 9q
- Gastrointestinal (carcinoid) tumors: genetic alterations on chromosome 18

Oberg K. Curr Opinion Endocrinology 2009
Some requirements for improved therapeutic outcome in NET

- Optimal classification and grading
- Elucidation of molecular genetics and cell biology
- Identification of serum markers for early diagnosis and follow-up
- Improved diagnosis and molecular imaging
- Identification of molecular therapeutic targets
- Establishment of Centres of Excellence with multidisciplinary specialized clinical teams for NET
(A) Spiral CT–axial image obtained during the **arterial phase** (25 s delay): liver metastases are not detectable.

(B) Spiral CT–axial image obtained during the **portal phase**, at the same level of the arterial phase (60 s delay): multiple metastatic lesions are clearly depicted.
PET/CT with $^{68}$Ga-DOTA-octreotide
Liver metastases from midgut carcinoid

Oberg K et al, J Clin Onc 2005
Post-treatment imaging

Postsurgical evaluation – persistent increase of chromogranine

Absent intralesional signal on DW-MRI → high negative predictive value

Images Vincent Vandecaveye, MD - Leuven
Future Outlook - NET

Diagnosis and Evaluation:

- Deep genome sequencing
- Transcriptome analysis
- Micro RNA
- Molecular Imaging
  - Diagnosis
  - Follow-up
New markers for molecular imaging
Some requirements for improved therapeutic outcome in NET

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Future Outlook - NET

Treatment:

✓ New combinations of cytotoxic agents with targeted agents (TKI:s HDAC, etc)
✓ Combinations of PRRT with inhibition of DNA repair (Lu$^{177}$ DOTATATE + PPAR inhibitions)
✓ New radio enhancers + PRRT
✓ Oncolytic viruses
✓ Nano particles targeting somatostatin receptors
Molecular switches of growth in GEP NET

New somatostatin-analogues

SSTR-1
SSTR-2
SSTR-3
SSTR-5

GPCR

GTP GDP

TGFB

TGFβR

IFNR

VEGFR

VEGF

VEGF

VEGF

IGFR

IGF-1

IGF-1

IGF-1

PDGFR

p16

Smad4

CgA

VMAT

mTOR

Menin

c-kit

Molecular-targeted therapies

Molecular switches of growth in GEP NET
Binding of somatostatin & its analogues to the five known receptor subtypes
Angiogenesis

- Well differentiated GEP-NETs are highly vascularised and express both vascular endothelial growth factor (VEGF) & VEGF receptors

- Increased VEGF expression is associated with metastasis and shortened PFS

Terris et al. Histopathology 1998; 32 (2); 133-138
Zhang et al, Cancer  2007; 109: 1478-86
RAD001 (everolimus)
Inhibition of tumour cells and angiogenesis

- Inhibition of cell growth and proliferation
- Downregulation of VEGF production
- Blockage of PTEN and PI3-K/Akt/PKB signaling pathways
- Inhibition of mTOR
- Reduction in energy and nutrient availability

Growth factors: VEGF, VEGFR
Integrins: ILK, TSC1/TSC2
Oxygen, nutrients, amino acids
Bevacizumab + temozolomide
Radiological response (RECIST)

<table>
<thead>
<tr>
<th></th>
<th>Intestine, n (%) (n = 12)</th>
<th>Pancreas, n (%) (n = 17)</th>
<th>Overall, n (%) (N = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>0 (0)</td>
<td>4 (24)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11 (92)</td>
<td>12 (70)</td>
<td>23 (79)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>1 (8)</td>
<td>1 (6)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

Table 2.

(A) Patient characteristics and treatment response

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>Radiologic response, n (%)</th>
<th>Biochemical response (baseline elevated), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic neuroendocrine</td>
<td>53</td>
<td>18/53 (34)</td>
<td>16/32 (50)</td>
</tr>
<tr>
<td>Carcinoid tumors</td>
<td>44</td>
<td>1/44 (2)</td>
<td>6/27 (22)</td>
</tr>
<tr>
<td>Lung</td>
<td>8</td>
<td>1/8 (13)</td>
<td>3/8 (11)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>19</td>
<td>0</td>
<td>1/19 (4)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Paraganglioma/pheochromocytoma</td>
<td>4</td>
<td>1/4 (25)</td>
<td>2/2 (100)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51</td>
<td>10/51 (20)</td>
<td>9/31 (30)</td>
</tr>
<tr>
<td>Female</td>
<td>50</td>
<td>10/50 (20)</td>
<td>15/30 (50)</td>
</tr>
<tr>
<td><strong>Median age</strong></td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment regimen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temozolomide/thalidomide</td>
<td></td>
<td></td>
<td>14/25 (56)</td>
</tr>
<tr>
<td>Temozolomide/bevacizumab</td>
<td></td>
<td></td>
<td>9/33 (27)</td>
</tr>
<tr>
<td>Temozolomide/xeloda</td>
<td>1</td>
<td>1/1 (100)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Temozolomide alone</td>
<td>4</td>
<td>0/4 (0)</td>
<td>0/4 (0)</td>
</tr>
<tr>
<td><strong>Treatment status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase II study</td>
<td>63</td>
<td>12/63 (19)</td>
<td>11/37 (30)</td>
</tr>
<tr>
<td>Off-study</td>
<td>38</td>
<td>8/38 (21)</td>
<td>13/24 (54)</td>
</tr>
<tr>
<td><strong>Median time from diagnosis (mo)</strong></td>
<td>19.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. prior systemic antitumoral treatments*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>44</td>
<td>12/44 (27)</td>
<td>11/30 (37)</td>
</tr>
<tr>
<td>1</td>
<td>35</td>
<td>3/35 (8)</td>
<td>10/19 (53)</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>2/6 (33)</td>
<td>2/5 (40)</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>2/6 (33)</td>
<td>1/5 (20)</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1/1 (100)</td>
<td>NA</td>
</tr>
</tbody>
</table>

(B) MGMT status and treatment response

<table>
<thead>
<tr>
<th>MGMT status</th>
<th>n</th>
<th>Radiologic response, n (%)</th>
<th>Biochemical response (baseline elevated), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGMT intact †</td>
<td>16</td>
<td>0/16 (0)</td>
<td>0/10 (0)</td>
</tr>
<tr>
<td>MGMT deficient ‡</td>
<td>5</td>
<td>4/5 (80)</td>
<td>4/5 (80)</td>
</tr>
</tbody>
</table>

* Prior treatment data not available for 9 patients.
† Thirteen of 16 tumors with intact MGMT expression were carcinoids; 3 of 16 were pancreatic neuroendocrine tumors.
‡ All 5 MGMT-deficient tumors were pancreatic neuroendocrine tumors.
Nanoparticles that communicate in vivo to amplify tumour targeting

Geoffrey von Maltzahn\textsuperscript{1,2}, Ji-Ho Park\textsuperscript{3}, Kevin Y. Lin\textsuperscript{4}, Neetu Singh\textsuperscript{1}, Christian Schwöppe\textsuperscript{5}, Rolf Mesters\textsuperscript{5}, Wolfgang E. Berdel\textsuperscript{5}, Erkki Ruoslahti\textsuperscript{6,7}, Michael J. Sailor\textsuperscript{8,9}

and Sangeeta N. Bhatia\textsuperscript{10,11,12*}
Radionuclide Targeted Radiotherapy

Mechanism of Action:

The $\beta^-$-emitter labelled somatostatin analogue delivers a lethal radiation dose to the tumour cell.

- $^{111}$Indium Octreotide - Ultra-short-range
- $^{90}$Ytrium Octreotide - Long-Range Beta
- $^{177}$Lutetium Octreotate - Short-range Beta
Radiolabelled Somatostatin Analogue **LU-177-DOTA,Tyr3 Octreotate** in patients with endocrine gastroenteropancreatic tumours

131 pts¹  CR 2%; PR 26%; MR 19%; SD 35%; PD 18%
321 pts²  CR 2%; PR 28%; MR 17%; SD 35%; PD 20%

¹Kwekkeboom et al, JCO 2005; ²Kwekkeboom et al ASCO 2007 and JCO 2008

Computed tomography scans in a patient with a metastasized nonfunctioning endocrine pancreatic tumor before treatment (left) and 3 months after the last treatment (right)
PRRT is an important new tool for Stage IV

However, there is a need for validation, standardisation, both in methods as well as in reporting and follow-up.

Randomised trials are essential to compare efficacy, but...

- Relatively high tumor response rate
- Limited side-effects
- Good quality of life
- Long progression free period

Compared to historical controls: survival benefit 3.5-6 yrs

$[^{177}\text{Lu-DOTA}^0,\text{Tyr}^3]\text{Octreotate Therapy}$

GEP NET
PRRT
Open questions

✓ Efficiency in comparison to established therapies
✓ Optimal length of therapy cycle and dose cycle
✓ Long-term safety
  ✓ renal and bone marrow toxicity
✓ Efficiency in combination with chemotherapy and with targeted agents
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- Optimal classification and grading
- Elucidation of molecular genetics and cell biology
- Identification of serum markers for early diagnosis and follow-up
- Improved molecular imaging (PET)
- Identification of molecular therapeutic targets
- Establishment of Centres of Excellence with multidisciplinary specialized clinical teams for NET
Collaboration for optimal patient management

- Multidisciplinary patient management
- Clinical research team
- Basic research team
- Expertise/network

ENETS Centers of Excellence
University hospitals Leuven
SAVE THE DATE

15th World Congress on Gastrointestinal Cancer

3–6 July 2013
Barcelona, Spain

Chairs:

Mario Dicato, MD
Luxembourg Medical Center
Luxembourg, Luxembourg

Eric Van Cutsem, MD, PhD
University Hospital Gasthuisberg
Leuven, Belgium