Neuroendocrine Tumors

THE A, B, C’s

Carcinoid tumours: origin

<table>
<thead>
<tr>
<th>Carcinoid site</th>
<th>%</th>
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<tbody>
<tr>
<td>Digestive system</td>
<td>64%</td>
</tr>
<tr>
<td>Other</td>
<td>28%</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>8%</td>
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</tbody>
</table>
| Other                           | 28.5%

- Colon, except appendix: 9
- Appendix: 5
- Rectum: 4
- Duodenum: 2
- Jejunum: 2
- Ileum: 15
- NAS: 6
- Other: 5.5

Definitions

• Neuroendocrine: High Grade or Low grade
• Carcinoid is low grade: WDNT
• In Pancreas: Islet cell carcinoma
• In Lung: Further divided
  • Typical – few mitoses, no necrosis
  • Atypical – 2 mitoses per 10 HPF
**Definitions**

- Serotonin: Biological peptide
- Somatostatin: Protein which binds to somatostatin receptor to regulate the amines and peptides secreted
- Octreotide is a synthetic somatostatin analog (SSA)
- Trade name is Sandostatin and Sandostatin LAR
Outline

1. Presentation
   - Many discovered incidentally
   - Symptoms due to:
     - Local tumour mass
     - Tumor-engendered fibrosis
     - Carcinoid Syndrome:
       - Secretion of biologically active amines and peptides
       - Carcinoid crisis
       - Carcinoid heart disease

2. Diagnostic Work up and Follow
3. Role of Surgery/ RFA/ Cryo
4. Role of Peptide Receptor Radionuclide Therapy
5. Role of Biologics and Somatostatin Analogs
6. Role of Systemic Therapy
   - Chemotherapy and Novel drugs

Molecular biology to clinical features

<table>
<thead>
<tr>
<th>Primary-site (Pt with met dz)</th>
<th>Median survival (months)</th>
<th>Described molecular abnormalities</th>
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<tbody>
<tr>
<td>Lung</td>
<td>13.1</td>
<td>Chr 11q, 3p loss</td>
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<td>Stomach</td>
<td>9.7</td>
<td>Chr 11q, 18, X loss</td>
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<td>Pancreas</td>
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<td>Chr 11q deletion, karyotypic instability, MEN 1</td>
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<td>Small bowel</td>
<td>50.7</td>
<td>Chr 18 loss, 18q loss</td>
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<td>Appendix/ileum</td>
<td>42.0</td>
<td>Chr 18 loss, 18q loss</td>
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<tr>
<td>Colon/rectum</td>
<td>8.6</td>
<td>NRP-2 loss</td>
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</table>
Carcinoid Crisis

- Life-threatening
- Spontaneously or precipitated by anesthesia, chemotherapy, infection or embolization procedures
- Severe flushing, diarrhea, hypo/hyper tension, tachycardia
- Immediate therapy iv octreotide
- Close monitoring before, during, and after surgical treatment

Carcinoid Heart Disease

- 40% metastatic carcinoid tumors usually with liver metastases
- Pathology:
  - Thickening of right heart valves: fibrotic plaques
  - Valve insufficiency, RHF

Carcinoid Heart Disease: Mechanisms

- Serotonin plays important role
- Serotonin receptors subtype 1B present in subendocardial cells
- Significant correlation between carcinoid heart disease and urinary 5-HIAA
• 1. Presentation
• 2. Diagnostic Work up and Follow

Work Up
• Biopsy
• Pathology: Ki 67 < or > 10 %
• CT/ MRI/ Ultrasound
• Octreotide and MIBG Nuclear Scans
• 24 hour urine 5HIAA
• Serum Chromogranin A
• PET (Europe)

Diagnosis: CT/MRI

Nuclear Peptide Scans
• Both MIBG and somatostatin receptors are on carcinoid tumors and overexpressed
• Diagnostic Studies
• Indium 131 or I123 MIBG: sens 50%
• Indium 111 Octreotide sens 80%

Contrast-enhanced CT scan (top) and MRI (bottom) of patient with metastatic small bowel carcinoid
Diagnosis: OctreoScan

Anterior

Posterior

Diagnosis: Biochemical markers

• 5-HIAA Urine
  • Normal 3–15 mg/24 h urine
  • Baseline and 3- to 4-month in first year
  • Repeat if:
    * Disease progression is found
    * Change in therapy is being considered

• CgA Serum
  • Measure every 3 months in first year, then as per disease progresses
PET

• FDG-PET helpful in localizing high grade neuroendocrine but not low grade
• 18F-DOPA PET better but less available
• Swiss : 11C-5HTP (5-hydroxytryptophan) for PET 5HTP precursor in serotonin
• 90% localized but 20 min half life

PET with 11C-5-hydroxytryptophan showing insulinoma in head of pancreas

Definition of the Problem

• 75% will develop liver metastases
• 80% with liver mets will die < 5 years
• Progressive liver mets leading cause of mortality (replaced hormone excess)
• Surgery :
  • Local tumor obstruction, bleeding, perforation
  • Symptoms from fibrosis
Controversial

- Role of extended, radical or en bloc resection of the primary tumor
- Role of metastatic resections?
  - Morbidity and mortality?
  - Symptom control?
  - Survival benefit

Aggressive Resections

- Norton et al. 2003: 20 patients with advanced WDET
  - 15/20 (75%) underwent complete resections
  - Pancreaticoduodenectomy – 8
  - Superior mesenteric vein resection/reconstruction – 3
  - Splenectomy – 11
  - Nephrectomy – 2
  - Liver resections – 6
  - Morbidity = 30%
  - Mortality = 0
  - Actuarial 5 yr-survival = 80%
  - Disease free-survival: all recurred by 7 years

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<th>Year</th>
<th>Patients</th>
<th>Operative Mortality(%)</th>
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<td>Sarmiento/Mayo</td>
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**Hepatic Artery Embolization**

Moertel et al, 1994  
Embolization  
Chemoembolization (Doxo, DTIC, STZ, 5FU)

Embolization  
Chemoembolization  

Eriksson B et al, 1998  
Embolization  

Kim YH et al, 1999  
Chemoembolization  

Diamandidou et al, 1998  
Chemoembolization  

<table>
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<th>Author</th>
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<td>60%</td>
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<td>38%</td>
<td>7 mo</td>
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<tr>
<td>Kim YH et al, 1999</td>
<td>n=30</td>
<td>Chemoembolization</td>
<td>37%</td>
<td>24 mo</td>
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<tr>
<td>Diamandidou et al, 1998</td>
<td>n=20</td>
<td>Chemoembolization</td>
<td>78%</td>
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**Chemoembolization: Carcinoid Crisis**

- Response of carcinoid crisis to somatostatin analogue therapy.
Radiofrequency Ablation: Results

Percutaneous: 43 neuroendocrine metastases in 21 pts
- 7 complications
- 5% recurrence at 6 months
- 4/15 had no residual tumor

Laparoscopic RF: 34 neuroendocrine metastases
- 88% had decreased symptoms
- 60% decreased hormonal tumor markers
- 20% developed new lesions
- 41% stable disease

Liver transplantation in malignant neuroendocrine tumors

(Lehnert T. Transplantation 1998;66:1307)

| Total no. of patients | 103 |
| EPT                 | 48  |
| Carcinoids          | 43  |

2-year survival 60%
5-year survival 47%
Recurrent free survival 24%

Surgical Conclusions

• Aggressive resections can be done, acceptable morbidity and mortality
• Improved symptom control and extended survival likely
• Patients to benefit the most are those rendered disease free
• Precise patient selection and disease extent
• Ultimate disease recurrent and progression likely
• An initial period of medical therapy is often recommended to allow time for observation and make surgery or ablation safer

Outline

• 1. Presentation
• 2. Diagnostic Work up and Follow
• 3. Role of Surgery
• 4. Role of Peptide Receptor Radionuclide Therapy
Nuclear Peptide Targeted Therapy

- Diagnostic 113I MIBG: If positive: potential treat with high dose 131-iodine-MIBG
- 111 Indium-Octreotide: If positive: potential treat with high dose
  - 111 Indium-octreotide
  - 90 Yttrium-octreotide
  - 177 Lutetium-octreotide
- RR 10-40% Survival Benefit?
- Considered Investigational

Tumor targeted irradiation in neuroendocrine tumors

- $^{111}$Ind-DTPA-octreotide n=38 (Krenning et al, 1999)
  - Total dose 20 Gbq
  - Radiological response 30%
  - Disease stabilization 40%

- $^{90}$Y-DOTATOC n=22 (Valkema et al, 2000)
  - Phase I
  - Radiological response 10%
  - Disease stabilization 45%

- $^{90}$Y-DOTATOC (6000 MBq/d) n=41 (Waldherr et al, 2001)
  - CR+PR 24%
  - MR+SD 61%

Outline

- 1. Presentation
- 2. Diagnostic Work up and Follow
- 3. Role of Surgery
- 4. Role of Peptide Receptor Radionuclide Therapy
- 5. Role of Biologics and Sandostatin Analogs (SSA)
**Biologics: Interferon**

- Biochemical response in 40%
- Tumor response seen in <10%
- Side effects: fever, fatigue, anorexia, weight loss, alopecia, myelosuppression, liver dysfunction, clinical depression
- Used in Europe not North America

**Somatostatin Analogs: SSA**

- Somatostatin analogs bind to somatostatin receptors
- Biochemical responses > 70%
- Objective response < 5 %
- No survival benefit? Cytostatic
- ? Super high doses
Sandostatin BCCA 2007

• Symptomatic, 5HIAA high: Approved
• Symptomatic, 5HIAA low: Approved
• No symptomatic, 5HIAA high: Approved
  • Goal: prevent carcinoid heart
• No symptomatic, 5HIAA low: Not Approved
  • Goal: Improve survival
  • Controversial not proven

Somatostatin Analogs

• Start with Octreotide 100 ug sc tid for 4 weeks
• At two weeks overlap with Sandostatin LAR at 20 mg q 4 weeks
• Increase at 10 mg increments q3-4 weeks if symptoms not improving or 5 HIAA not dropping

Somatostatin Analogs

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• At two weeks overlap with Sandostatin LAR at 20 mg q 4 weeks
• Increase at 10 mg increments q3-4 weeks if symptoms not improving or 5 HIAA not dropping

Outline

• 1. Presentation
• 2. Diagnostic Work up and Follow
• 3. Role of Surgery
• 4. Role of Biologics and Sandostatin
• 5. Systemic Treatment
  * Chemotherapy and Novel Therapy

Cytotoxic therapy in carcinoids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose, regimen</th>
<th>Pts</th>
<th>OR(%)</th>
<th>Median duration (mo)</th>
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<td>Single agents:</td>
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<tr>
<td>Doxorubicin (DOX)</td>
<td>60 mg/m² q 3-4 w</td>
<td>81</td>
<td>21</td>
<td>6</td>
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<tr>
<td>5-FU</td>
<td>500 mg/m² x 5 d q 3-5 w</td>
<td>20</td>
<td>17-26</td>
<td>3</td>
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<tr>
<td>Streptozotocin (STZ)</td>
<td>580-1000 mg/m² x 5 d q 2-3 w</td>
<td>14</td>
<td>0-17</td>
<td>2</td>
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<tr>
<td>Decarbazine (DTIC)</td>
<td>250 mg/m² d x 5 d q 4-6 w</td>
<td>15</td>
<td>13</td>
<td>4.5</td>
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<tr>
<td>Cisplatin/5-FU 90 mg/m² q 3-4 w</td>
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<tr>
<td>Combinations:</td>
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<tr>
<td>Streptozotocin + 5-FU</td>
<td>STZ 500 mg/m² x 5 d q 3-6 w</td>
<td>175</td>
<td>7-33</td>
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<td>Doxorubicin</td>
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<td>10</td>
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<td>Cyclophosphamide (CTX)</td>
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<td>+ Etoposide</td>
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Cytotoxic therapy in carcinoids

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**Carcinoid: Chemotherapy**

- Chemotherapy
  - E1281 (JCO 2005)
  - 5FU/doxorubicin
    - PFS = 4.5 months, OS = 15.7 months
  - 5FU/streptozocin
    - PFS = 5.3 months, OS = 24.3 months

**BCCA**

- **ENDO 1:**
  - Streptozocin/ Adriamycin
  - Streptozocin/ 5 FU
- **ENDO 2:**
  - Carmustine/ 5 FU

**New Drugs**

**mTOR**

mTOR (mammalian target of rapamycin) is an intracellular protein (enzyme) that acts as a central regulator for cell growth, transcription, proliferation, and angiogenesis in cancer
**mTOR**

**Controls Cell Growth, Proliferation and Angiogenesis**

- mTOR is a kinase in the PI3-K/Akt signaling pathway
- Integrates multiple signals
  - Growth factor receptor activity
  - Cellular energy, nutrients, and oxygen levels
  - Signals from other cellular signaling pathways
  - Estrogen receptor signaling
- Controls production of proteins regulating cell growth, cell division, and angiogenesis in response to these signals

**RAD001 (everolimus)**

**Single Agent Activity in NET**

ASCO 2006: Dr J. Yao, MD Anderson (IIT)

17 patients with disease progression at study entry

- 3 PR, 10 SD, 4 PD with RAD001 5 mg/d (10 mg/d ongoing)
- 11 (65%) progression-free at 6 mos

Phase II RADIANT 1 Study in Advanced Pancreatic Islet Cell after Chemotherapy Failure, started in 2006 Ph III in 2007, post-interim analysis of RADIANT 1
Increased VEGF expression is associated with poor prognosis in neuroendocrine tumors.

**Inhibiting VEGF**

Bevacizumab

- VEGF
- VEGFR-2
- PI3K
- Akt/PKB
- p38MAPK

BAY 43-9006

SU011248 - Sunitinib

- Small molecule TKI
- 50mg daily 4 weeks on – 2 weeks off
- Good oral bioavailability, unaffected by food
- Metabolized in liver via CYP4503A4 (t1/2 40hr, metabolite 80 hr)
- Potential CYP4503A4 interactions
- Active metabolite SU012662
- Linear PK within tested doses (25-150mg)
- ATP site–directed competitive inhibitor
- Directly binds to kinase domain to prevent phosphorylation and activation of substrates

**Bevacizumab (BV; rhuMAb VEGF)**

- Recombinant humanized anti-VEGF mAb
- Binds and neutralizes all forms of VEGF A
- T1/2 17-21 days

Hair color changes with Sutent

Other VEGF Inhibitors

- Other targeted agents in trial or about to start trials in neuroendocrine tumors
  - SU011248
  - PTK/ZK
  - BAY 43-9006
  - GW788034

Conclusion

• Multimodality approach: Surgery, Medical Oncology, Nuclear medicine, radiology
• Somatostatin Analogs has resulted in significant advances in the management of neuroendocrine tumors
• Therapeutic nuclear treatments evolving and encouraging
• Future lies in new drugs