Targeted Therapy for Adrenocortical Cancer: From Bench to Bedside

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Nothing to Disclose
Topics

1. Introduction to endocrine neoplasms and Endocrine Oncology Branch (EOB) protocols.
2. Targeted systemic therapy for cancer
3. New protocol for adrenocortical cancer:
   - A Phase I/II Trial of IL-13-Pseudomonas Exotoxin in Patients with Treatment Refractory Malignancies with a Focus on ACC
Introduction to endocrine neoplasms

- Thyroid neoplasms (goiter, nodules, cancer)
- Parathyroid tumors (adenoma, hyperplasia, cancer)
- Adrenal neoplasms
  - Functioning: cortisol, aldosterone, sex hormones, catecholamines
  - Non-functioning
- Pancreatic neuroendocrine tumors
- Paraganglioma
Thyroid Nodules

- Palpable thyroid nodules: 4%-7% \(^1\)
- At the age of 55, 45% of women and 32% of men have at least one thyroid nodule.
- Incidentaloma: (<5% are thyroid cancer)
  - 16% of neck CT scan
  - 1.2%-2.3% of FDG-PET scan (30% are thyroid cancer)

1. Hedegus. NEJM 2004
Thyroid cancer

- Estimate 60,000+ new cases in 2013: Increased diagnosis of small papillary thyroid cancer.
- ATA guideline: FNA thyroid nodule > 1cm. But small can be mighty.
- Thyroidectomy, lymphadenectomy
- Radioiodine ablation
- 1%-2% mortality: steadily increasing
EOB Protocols for Thyroid Cancer

1. Clinical and Genetic Studies in Familial Non-medullary Thyroid Cancer
2. A Phase II Trial of Valproic Acid in Patients With Advanced Thyroid Cancers of Follicular Origin
3. A Phase II Study of Ponatinib in Advanced or Metastatic Medullary Thyroid Cancer
EOB Protocols for Thyroid Cancer

3. A Phase II Study of GI-6207 (CEA Vaccine) in Patients With Recurrent Medullary Thyroid Cancer

4. A Phase I/II Trial of Crolibulin (EPC2407) Plus Cisplatin in Adults With Solid Tumors With a Focus on Anaplastic Thyroid Cancer (ATC)
Primary Hyperparathyroidism

**Definition:** Inappropriately elevated parathyroid hormone in the presence of hypercalcemia
Indications for Parathyroidectomy

• Symptomatic – metabolic complication
• “Asymptomatic”
  – NIH criteria
  – “sub-clinical or non-specific” symptoms
• Parathyroidectomy is the only curative treatment
## Asymptomatic Guidelines

<table>
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<th>Measurement</th>
<th>Guidelines ‘08</th>
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<tr>
<td>Serum Ca</td>
<td>&gt; 1 mg/dl</td>
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<tr>
<td>24-hr U Ca</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Creat clearance</td>
<td>Reduced &lt; 60 ml/min</td>
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<tr>
<td>BMD</td>
<td>t-score &lt;-2.5 (any site)</td>
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<tr>
<td></td>
<td>Previous fracture</td>
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<tr>
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<td>&lt; 50</td>
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Pancreatic Neuroendocrine Tumors (PNETs)

- Biologically active hormonal production
  - Non-functioning: PP, CGA, NSE, Ghrelin
  - Functioning: gastrin, insulin, glucagon, VIP, CRH

- Inheritance
  - Sporadic:
  - Syndromic: MEN1, VHL, NF-1, TSC
Pancreatic Neuroendocrine Tumors (PNETs)

• Clinical presentation
  – Excessive hormonal secretion
  – Mass effect, invasion, metastasis
  – Incidental finding

• Imaging studies
  – Contrast enhanced CT scan, MRI
  – Functional studies: octreotidide scan, FDG-PET
  – Endoscopic ultrasound.
EOB Protocol for PNETs

1. Evaluation of the Natural History and Management of Pancreatic Lesions Associated With Von Hippel-Lindau

2. Evaluation of $^{68}$Gallium-DOTATATE PET/CT for Detecting Primary and Metastatic Neuroendocrine Tumors
60 yo male with MEN1 and metastatic gastrinoma found on 68 Gallium Dotatate PET/CT
A. Octreoscan with visible lung lesion
B. Dotatate scout with lung lesion and metastatic gastrinoma
C. Dotatate PET/CT with duodenal gastrinoma and a metastatic lymphnode (red arrows)
D. Arterial phase CT with duodenal gastrinoma and metastatic lymphnode (red arrows)
• **Indications**

  – Functioning tumor
    • Pheochromocytoma
    • Cushing's
    • Conn's
  
  – Nonfunctioning tumor
    • ?risk of primary malignancy
    • ?risk of metastasis
Adrenocortical Cancer

- Rare: 1.5 - 2 per million people per year\textsuperscript{1-3}.
- Overall 5-year mortality rate of 75 - 90% and an average survival time of 14.5 months\textsuperscript{1}.
- Presentation: >50% Hypercortisolism is common. Virilizing is rare.
Adrenocortical Cancer

• Mass effects, local invasion
• Incidentally identified.
• Pathological diagnosis (Weiss criteria) can be difficult unless gross invasion or metastasis is present.
• 40% presents with resectable tumor; however, 60% of these die from recurrent disease.
Risk Stratification for ACC by Imaging Studies

- Size is most important
  - >90% of ACC >5cm.
- CT Hounsfield unit >20
- MRI bright on T2 wt
- Heterogeneous (necrosis/calcifications)
- Growing
Adrenocortical Carcinoma

- Poor prognosis
  - Overall 5-year survival of less than 35%
  - 50% 5-year survival for patients with resectable tumors
  - Median survival of <1 year for patients with metastatic disease
  - *Rare, lethal and neglected!*
EOB Protocols for Adrenal Neoplasm

1. Evaluation of Diagnostic and Prognostic Molecular Markers in Adrenal Neoplasm.

2. A Phase I/II Trial of IL-13-PE in Patients with Treatment Refractory ACC.
Targeted Systemic Therapy for Cancer
Definition:

• Drugs targeted at pathways, processes and physiology which are uniquely and preferentially expressed in cancer cells:
  – Receptors
  – Genes
  – Angiogenesis
  – Tumor pH
Rationale for Targeted Therapy in Cancer

• Increase therapeutic efficacy:
  – Drug resistance mechanisms in tumor cells.
  – Utilize unique characteristics of tumor cells to enhance drug delivery ➔ maximize effects.

• Reduce systemic toxicity:
  – Effective drug delivering system
  – Tumor specific targeting system ➔ enhancing tumor tissue level, reducing toxicity.
Six Essential Alterations in Cell Physiology in Malignancy: Targets for Novel Drugs

- Self-sufficiency in growth signals
- Evading apoptosis
- Insensitivity to anti-growth signals
- Sustained angiogenesis
- Tissue invasion & metastasis
- Limitless replicative potential

Radioiodine Ablation in Thyroid Cancer

- *Is* a targeted therapy for differentiated thyroid cancer
- Utilize unique ability to concentrate iodine of thyroid cancer cells.
The Ideal Targets

- Highly expressed and prevalent in cancer, low in other tissues.
- Critical for desire phenotypic effects (cell proliferation, apoptosis, metastasis).
Existing Targets used Clinically.

- **RET-tyrosine kinase**: medullary thyroid cancer, PNETs
- **c-Kit**: for GIST
- **bcr/Abl**: for CML
- **Steroid receptors**: for ER+ breast cancer, prostate cancer, and lymphoma
- **HER2**: for breast and gastric ca
- **CD20**: for B-cell lymphoma
- **B-RAF**: for melanoma
Imatinib Mesylate in CML

- Bcr-abl is the root cause of CML which is considered a "monogenetic disease"
- Imatinib Mesylate specifically targets the bcr-abl tyrosine kinase.
Imatinib Mesylate in CML: Response

- 55% of patients with CML-blast crisis and 70% of ALL-blast crisis patient responded.
- 10.5% of CML and 20% of ALL patients had complete remission.

Targeted Therapy in Solid Tumors: Limitations

- Most solid tumors have complex genetic abnormalities → genetic heterogeneity.
- Molecular and pathway heterogeneity.
- Hitting one narrow target is not likely to be that beneficial.
A Phase I/II Trial of IL-13-Pseudomonas Exotoxin in Patients with Treatment Refractory Malignancies with a Focus on ACC
IL13Rα2 as a Candidate Target

- Genome-wide expression analysis of adrenocortical tumors demonstrated overexpression of Interleukin-13 receptor subunit alpha-2 (IL13Rα2) in ACC.
- Low or absent expression of IL13Rα2 in normal cells and tissues
- IL13Rα2 is a high-affinity receptor of Th2-derived cytokine interleukin -13 (IL-13).
Functions of IL13Rα2 in ACC

- IL-13 signals through IL13Rα2 and influences ACC cell invasion
- IL-13 signals through IL13Rα2 and influences ACC cell proliferation
IL-13 Pseudomonas Exotoxin

- A chimeric fusion of recombinant ligand-targeted cytotoxins, *Pseudomonas exotoxin A*, and IL-13
- In phase I trial of IL-13 PE in 12 patients with metastatic renal cell carcinoma, 3 developed acute renal failure at 4 ug/kg.
Pre-clinical Studies in ACC

- IL13-PE is effective in ACC cells (NCI-H295R) and a renal cell carcinoma cells (PM-RCC) and specific to cells that express IL13Rα2, siRNA knockdown of IL13Rα2 in NCI-H295R cells resulted in a loss of sensitivity.

- *In vivo* study of IL13-PE in ACC xenografts: 50%-70% reduction in tumor sizes and increased survival with no observed toxicity.
Study Objectives and Eligibility

- **Objectives**
  - Safety and maximal tolerated dose of IL-13-PE
  - Response rate, and progression-free survival
  - Tumor response
  - Association with IL13RA2 expression

- **Eligibility**
  - > 18 years of age
  - Pathology confirmed tumors with IL13RA2
  - Measurable disease
  - Last treatment > 4 weeks
  - Mitotane is allowed.
Study implementation

• **Pre-treatment evaluation**
  – Tumor (+) for IL13RA2 by IHC
  – Axial imaging studies and FDG-PET scan
  – Check human PE antibody
  – Acceptable lab values
  – Baseline EKG.

• **Drug administration**
  – Starting 1 ug/kg IV, will be escalated up to 3 ug/kg.
  – Day 1,3,5 of a 4 week cycle, up to 4 courses
  – IV hydration before and after infusion.
Monitoring

• **Allergic reaction:**
  - Q2H vital signs during infusion then Q4h for 24h

• **Kidney function:**
  - 24-hr urine for creatinine clearance and UA
  - Serum creatinine

• **Evidence of thrombotic microangiopathy**
  - Low plts, anemia, kidney injury

• **Heart:** EKG baseline and 2h post infusion

• **Systemic toxicity:**
  - CBC, BMP, LFTs

• **Human PE antibody:**

• **Pharmacokinetics:**
  - Blood: Days 1 and 3 of course #1 and on Day 1 of course #2.
Thank You.

• “To raise new questions, new possibilities, to regard old problems from a new angle, requires creative imagination and marks real advance in science.”

Albert Einstein