Patient Care Conference

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Neuroendocrine Tumors

- Second most prevalent cancer of the GI tract behind colorectal cancer\(^1\)
- Over 170,000 patients are living with NETs in the United States
- 6-fold increase in incidence over 4 decades
- Principles of care are different/unique compared to other solid tumors


Incidence of Neuroendocrine Tumors Over Time is Increasing

Analysis of SEER database (1973–2004)

Pommier’s Classic vs NET Paradigm
(excludes pheo/paras, some pNETs)

* Singh S et al. Patient-reported burden of a neuroendocrine tumor (NET) diagnosis: results from the first global survey of patients with NETs. J Glob Oncol. 2016;2:43-53
NETs: Three Patterns of Presentation

1. Hormonal syndrome
   Need to put 2 and 2 together (requires expertise)

2. Tumor symptoms (from growth)
   Usually present late (with mets)

3. Asymptomatic (incidental finding)
   Locoregional (resectable) vs. Widespread

Early diagnosis has prognostic implications as surgery is the **ONLY** curative treatment modality
Requires astute physician with a high index of suspicion (mean delay 5-7 yrs)
Functional NET Syndromes

- Carcinoid syndrome
  - Flushing, diarrhea, wheezing, pellagra, cardiac disease
- Zollinger-Ellison syndrome (Gastrinoma)
  - Gastric acid hypersecretion (pain, ulcers, diarrhea)
- Insulinoma Syndrome
  - Neuroglycopenia, sympathetic overdrive, obesity
- Glucagonoma
  - Hyperglycemia, rash (MNE), anemia, hypoaminoacidemia, weight loss, thromboembolism, glossitis
- VIPoma
  - Watery diarrhea, hypokalemia, achlorhydria and others (hyperglycemia, hypercalcemia, flushing)
- Others:
  - ACTHoma – Cushing’s syndrome
  - GRFoma - acromegaly
  - Somatostatinoma – hyperglycemia, steatorrhea, gallstones
  - Rare syndromes (calcium, erythropoeitin, etc)
Management Principles

• Confirm the diagnosis
• Control the hormonal syndrome (if present)
• Determine MEN-1 status
• Determine extent of disease
• Consider surgery
  – For cure (if possible)
  – For debulking (if not)
• Long term management
  – Hormonal syndrome (if present)
  – Growth
Kunz P, J Clin Oncol 33:1855-1863
Multidisciplinary Care is Ideal

• Many options and no standard algorithm exists (therapy should be individualized)
• Tumor Board is **ESSENTIAL** component
• Flexibility is **KEY**
WHAT ABOUT PRRT???
Thera(g)nostics

A treatment strategy that combines therapeutics with diagnostics.

It associates both a diagnostic test that identifies patients most likely to be helped or harmed by a new medication, and targeted drug therapy based on the test results.
PROMID: Time to Progression

CLARINET (Lanreotide) trial with similar outcome

Caplin M et al. Clarinet NEJM
Gallium Dotatate PET CT

Courtesy Thomas Hope, MD
Peptide Receptor Radiation Therapy (PRRT)

Somatostatin-analog linked Radiopeptide

Somatostatin Receptor

KEY

LOCK
Netter 1: Progression-Free Survival

N = 229 (ITT)
Number of events: 90

- $^{177}$Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard ratio: \(0.21\) [0.129 – 0.338] \(p < 0.0001\)

79% reduction in the risk of disease progression/death

Estimated Median PFS in the Lu-DOTATATE arm ≈ 40 months
Managing the Effects of Therapy

• Pancreatic surgery (Distal or Whipple’s)
  – Pancreatic insufficiency
  – Dumping syndrome
  – Diabetes
  – Immunity (spleen)

• Terminal ileal resection
  – B12 deficiency
  – Bile Salt Diarrhea
  – Overgrowth

• Somatostatin Analogs (SSAs)
  – Gallstones
  – Steatorrhea
  – Dysmotility
  – Diabetes

• Others
  – Adhesions
  – Anemia
  – Hepatorenal fn.
The Extended NET Community

- Even widely metastatic NETs should be considered a chronic disease state (i.e., aim to live with the disease)
- Increasing focus on the non-medical aspects of care (i.e., support services, financial toxicity, support groups, educational activities, etc)
  - Run for the Stripes (Andy Steinfeld, Lori & Dave Canzanese)
  - Patient support meetings (Diann Boyd)
  - Navigator expansion (Bonnie Bennett and Diann Boyd)
  - Yearly patient care meeting (live streamed)
  - Professional provider organizations (NANETS, ENETS)
  - Other support organizations
    - Carcinoid Cancer Foundation – Grace Goldstein
    - NETRF, NCAN, HNF, INCA
NET Awareness Day 11/10
Run for the Stripes
CAR T, Azedra, etc.
Conclusions

• NETS present in varied ways but have many features in common and differ significantly from other solid malignancies
• Clinical management is complicated and requires attention to tumor growth, pattern of presentation, syndromic symptoms and side effects of therapy
• Surgery is the only curative therapeutic modality (also effective for debulking, as is liver directed therapy)
• SSAs are drugs of choice for syndromic management (except ZES/insulinoma) and initial tumor growth
• No clear algorithm yet for regional (debulking/LDT) or systemic therapies (chemo, small molecules, PRRT)
• Multidisciplinary care is essential
• NETs are **CHRONIC** conditions that need a holistic approach.
Management of Pheochromocytoma & Paraganglioma

March 6, 2020

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Pheochromocytoma/Paragangliomas

• Pheochromocytoma/Paragangliomas (PCC/PGL) are rare neuroendocrine tumors
• Approximately 1000 new cases annually in the US
• We are seeing an increasing number of patients due to identifying more family members with inherited asymptomatic disease
• Inherited mutations are autosomal dominant
  • A 50% chance of inheritance for every pregnancy
• Each patient is unique and treatment needs to be individualized
PCC/PGL Clinical presentation

• Classic – labile hypertension, palpitations, headaches and sweating
• Patients can have minimal symptoms and BP is not always elevated
• Tumor size does not correlate with symptoms
• Early diagnosis has prognostic implications because surgery is the ONLY curative treatment modality
Management Principles

- Confirm the diagnosis
- Control the BP before and during surgery
- Surgery is the definitive treatment
- Can use adjunctive treatment with MIBG, chemotherapy and newer experimental therapies
MIBG scan of paraganglioma in organ of Zuckerkanndl

New therapies with Azedra, PRRT
Paraganglioma

Pheochromocytoma
Genetics of PCC/PGL

Genetics of PCC/PGL

• Now over 13 genetic mutations identified to be associated with PCC/PGL
• Screening family members -> identifying more asymptomatic patients
• Leads to early disease detection and better clinical outcomes
• About 30-40% of patients have a genetic mutation without a positive family history
• Very important that ALL patients get genetic testing
The Cancer Genome Atlas (TCGA): Comprehensive Molecular Characterization of Pheochromocytoma and Paraganglioma

Future Directions

- Currently few options for treating metastatic disease
- Azedra – FDA approved in 2018
- Diversity of single drivers among PCCs/PGLs makes these tumors a model for future targeted therapy
- Potential for multi-modality treatment with immunotherapy or targeted therapies
Conclusions

• Important to have a multidisciplinary approach and be treated at a specialized center dedicated to care of PCC/PGL patients
• Individualize treatment
• Genetic testing for all patients
• Surgery is only curative treatment
• Annual lifetime screening is essential after surgery
• New promising therapies for recurrent/metastatic disease