Update: Management of Small Bowel Neuroendocrine Tumors

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Disclosures

- None

Well differentiated NETs

- Grade 1 (low)
  - Mitotic count < 2 / 10 HPF &/or
  - Ki-67 < 3%
- Grade 2 (intermediate)
  - Mitotic count 2-20 / 10 HPF &/or
  - Ki-67 3-20%
- Grade 3 (high)
  - Mitotic count > 20 / 10 HPF &/or
  - Ki-67 > 20%, but usually < 50-55%

Sporadic NETs

- ~ 33% arise in lungs or thymus
- ~ 67% arise in GI tract
  - Small intestine, stomach, appendix & rectum are most common

Management of Metastatic NETs

- Promid Study
  - *JCO 27:4656, 2009; Neuroendocrinology 104:26; 2017*
- 85 patients with well-differentiated metastatic midgut NETs randomized to Sandostatin LAR 30 mg IM monthly or placebo
- Primary endpoint: Median time to progression
  - 14.3 vs 6.0 months (HR 0.34; 95% CI, 0.20-0.59; P < 0.0001)
  - Stable disease at 6 months: 66.7% vs 37.2%
- Placebo patients could cross-over to Sandostatin LAR
- Median overall survival: 84.7 vs 83.7 months

Management of Metastatic NETs

- Clarinet study
  - Advanced nonfunctioning, somatostatin receptor–positive NET Ki-67 <10%) w/ documented disease-progression status
  - Pancreas, midgut, hindgut or unknown origin (n=204)
  - Randomized to lanreotide 120 mg subQ monthly or placebo x 96 weeks; then open label extension + cross-over
  - Median progression free survival: 38.5 mo vs 19 months
    - HR 0.47; 95% CI 0.30-0.73, p < 0.001
  - PFS at 2 years: 65.1% vs 33.0%
    - *N Engl J Med 371:224; 2014; Proc ASCO 2017: abstract 4089*

Other Questions: Somatostatin Analogs

- Continuation of somatostatin analogs if disease progresses?
  - Functional tumors: continue SSA for control of disease symptoms
  - Non-functioning tumors: continuation of SSA is controversial
- Patient has an increase in flushing &/or diarrhea toward the end of a 4-week SSA cycle-options?
  - Consider increasing the frequency of SSA to every 3 weeks
- Inadequate control of carcinoid symptoms?
  - Consider dose escalation of SSA

Persistent carcinoid symptoms despite optimal SSA ?

- Telotristat etiprate (Xermelo)
  - Inhibitor of tryptophan hydroxylase, an enzyme involved in the conversion of tryptophan to serotonin
- FDA approved in combination with SSA therapy for the treatment of adults with carcinoid syndrome diarrhea uncontrolled by SSA therapy
  - 12-week, double-blind, placebo-controlled trial in 90 patients with well-differentiated metastatic NETs & carcinoid syndrome diarrhea
    - 4-12 daily bowel movements despite the use of SSA (stable dose for ≥ 3 months)
    - average reduction of 2 BMs per day: 33% vs 4%
      - *doi: 10.1634/theoncologist.2018-0236*

Telotristat etiprate

- most common side effects:
  - nausea, headache, increased levels of the liver enzyme gamma-glutamyl transferase, depression, peripheral edema, flatulence, decreased appetite, fever
  - may cause constipation

Management of Metastatic NETs

- Everolimus:
  - MOA: inhibits mammalian target of rapamycin (mTOR), a serine–threonine kinase that stimulates cell growth, proliferation, angiogenesis
  - Toxicities: stomatitis; rash; diarrhea; fatigue; upper respiratory infections; anemia; hyperglycemia; pulmonary interstitial inflammation
    - Dexamethasone oral rinse can reduce stomatitis (Lancet Oncol 19:654; 2017
      - 10 mL of alcohol-free dexamethasone 0.5 mg per 5 mL oral solution (swish for 2 min and spit, four times daily for 8 -16 weeks)

Management of Metastatic NETs

- Everolimus: advanced, non-functional NETs of the lung or GI tract (Gr 1-2)
  - Randomized 2:1 everolimus 10 mg PO daily vs placebo (n=302)
  - Median PFS 11.0 vs 3.9 months (HR 0·48; 95% CI 0.35–0.67, p<0.00001)
    - *Lancet 387: 968, 2016*

Management of Metastatic NETs

- Everolimus + octreotide LAR: advanced NETs with carcinoid syndrome (Gr 1-2): Radiant 2 Trial
  - 426 patients randomized 1:1 to everolimus 10 mg PO daily or placebo (both groups received 30 mg IM octreotide LAR); cross-over allowed
    - *Lancet 378: 2005; 2011*

Radiant 2 Trial

	Everolimus + Octreotide LAR	Placebo + Octreotide LAR
Number	216	213
PR + SD	5 + 182 (86.6%)	4 + 172 (82.6%)
Median PFS (Central Review) HR	16.4 mo 0.77 (95% CI 0.59-1.00)	11.3 mo
Normalization or ≥ 50% ↓ from baseline Chromogranin A 5HIAA	 46% 61%	 36% 54%

Lancet 378: 2005; 2011

Management of Hepatic Metastasis from NET

- Surgical resection of liver metastasis
- Ablation (oligometastatic disease; tumors < 3 cm)
  - Cryoablation
  - Microwave ablation
  - Radiofrequency

Management of Hepatic Metastasis from NET

- Transarterial Embolization
  - Bland embolization or Chemo-embolization
  - Requires inpatient hospitalization: overnight to several days
    - Functional NET? Octreotide acetate 100 µg IV bolus → 75 µg/hr x 24 hr
    - Acute toxicities: Pain; Post-embolization syndrome; Hepatic abscess (caution if altered biliary anatomy)
    - Can be repeated in patients who responded to prior hepatic arterial embolizations
      - Caution: potential chronic liver injury

Management of Hepatic Metastasis from NET

- Radio-embolization (Sir Spheres; Theraspheres)
  - **Yttrium-90** (^{90}Y)
  - In general, fewer short-term toxicities than bland or chemoembolization
  - Usually done in outpatient setting
  - Some patients develop chronic liver damage: features of cirrhosis on imaging studies: hyper-bilirubinemia & portal hypertension

Treatment: Metastatic Well Differentiated Gr 3 NETs

- Can try standard options as for well differentiated gr 1-2 NETs
  - Somatostatin receptor (SSTR) positive disease
    - SSAs; PRRT (^{177}Lu-dotatate)
  - Everolimus
  - Sunitinib (pancreas NET)
  - Pembrolizumab (if MSI-H, dMMR, or TMB-high (≥ 10 mut/MB)

Treatment: Metastatic Well Differentiated Gr 3 NETs

- Chemotherapy
  - Temozolomide ± Capecitabine
  - Oxaliplatin-based: FOLFOX or CAPEOX
  - Cisplatin or Carboplatin + Etoposide
  - Irinotecan-based: FOLFIRI; cisplatin +irinotecan
- Immunotherapy
  - Nivolumab + Ipilimumab

Systemic Radiotherapy: Beta Particles

- Small, fast-moving particles with a negative electrical charge
- Emitted from an atom’s nucleus during radioactive decay
- Beta particles are more penetrating than alpha particles, but are less damaging to living tissue and DNA because the ionizations produced are more widely spaced

Management of Metastatic Disease: Netter 1
^{77}Lu-Dotatate in midgut NET

- Progression on somatostatin analogs
- ^{177}Lu-Dotatate + Octreotide LAR (30 mg) vs Octreotide LAR (60 mg)
  - *N Engl J Med 2017;* ***376:*** *125–35*
  - *Lancet Oncol 2021; 22: 1752–63*

Netter 1

- PFS at 20 months: 65.2% vs 10.9%
- Response: 18% vs 3%
- OS: 48.0 vs 36.3 months (HR 0.84; 95% CI 0.60–1.17; p=0.30)
- Toxicities: Gr 3-4 neutropenia (1%) / thrombocytopenia (2%) lymphopenia (9%)
- 2 patients developed MDS

Netter 2 Trial

- [^{177}Lu]Lu-DOTA-TATE plus long-acting octreotide (30 mg IM) vs high-dose long-acting octreotide (60 mg IM)
- Newly diagnosed, advanced well-differentiated grade 2 (Ki-67 10-19%) or grade 3 (Ki-67 20-55%) Gastroenteropancreatic neuroendocrine tumors SSTR +
- 2:1 randomization
- Cross-over to ^{177}Lu-dotatate allowed
    - *Lancet 2024; 403: 2807–17*

Netter 2 Trial

	^{177}Lu-dotatate	Control
Number	151	75
Median PFS 95% CI	22.8 mo 19.4–NE	8.5 mo (7.7–13.8)
CR + PR 95% CI	8 + 65 (43%) (35.0-51.3)	0 + 7 (9.3%) (3.8-18.3)
SD	72 (48%)	42 (56%)

Lancet 2024; 403: 2807–17

Systemic Radiotherapy: Alpha Particles

- Positively charged particles that consist of two protons and two neutrons from the atom's nucleus.
- Alpha particles come from the decay of the heaviest radioactive elements
- Are very energetic, but are so heavy that their energy is used up over short distances from the atom

^{212}Pb-DOTAMTATE: targeted alpha therapy

- J Nucl Med 2022;63(9):1326-1333: Phase I trial
- Phase II Trial (Cohort 1)
- PRRT-näıve histologically confirmed unresectable or metastatic GEP-NETs
- Positive somatostatin analogue imaging
- ≥ 1 site of measurable disease per RECIST 1.1

^{212}Pb-DOTAMTATE: targeted alpha therapy

- N = 36
- 67.6 mCi/kg per cycle (maximum 5.5 mCi Q 8 weeks x 4 cycles
- 17 of 36 pts with objective response = 47.2% (95% CI: 32.0-63.0%)
  - *Proc ASCO 2024: abstract 4020*
  - NCT05153772
- Cohort 2: patients with progression on prior PRRT: pending

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