Chemotherapy, biotherapy, and targeted therapy for advanced Gastrointestinopancreatic neuroendocrine tumors

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Gastrointestinopancreatic neuroendocrine tumors (GEP-NET) are frequently diagnosed at a late stage, with approximately more than 60% of patients presenting with unresectable or metastatic disease; as a result, these patients have a poor prognosis. The median survival time for patients with distant metastatic disease is 24 months, and limited treatment options are available for this population. In general, GEP-NET has been divided to pancreatic neuroendocrine tumors (P-NET) and carcinoid tumor based on the difference nature and efficacy to variable treatment options.

Chemotherapeutic treatments for P-NET have therapeutic value in the literature, with series demonstrating response rates varying from only 8 to 45%. Streptozotocin was the only approved therapy for PNETs in the US prior to 2011, despite the debate over its efficacy. Trials are ongoing to find improved chemotherapeutic treatments for unresectable PNETs. Recently Strosberg et al. reported a 70% tumor response rate and 18-month median progression free survival in 30 patients with metastatic pancreatic endocrine carcinomas treated with temozolmide and capecitabine.

Octreotide is the most widely studied of the somatostatin analogues and acts primarily upon the SST2 receptor. Multiple studies show benefit in the treatment of hormone-mediated symptoms from functional P-NETs and carcinoids. The PROMID study has already confirme the antitumor effect of octreotide in functional and nonfunctional well differentiated metastatic midgut carcinoid. This study has established octreotide as a standard option for patients with midgut carcinoids, both functional and nonfunctional. However, the antitumor activity of somatostatin analogue treatment in PNETs has not been fully characterized.

Two new drugs have been recently approved by the FDA for treatment of unresectable PNETs, everolimus and sunitinib. Everolimus, an oral inhibitor of the mammalian target of rapamycin (mTOR), showed promising results in two phase 2 studies of patients with P-NETs. The RADIANT-3 trial was conducted to determine whether everolimus, as compared to placebo, would prolong progression-free survival among patients with advanced PNETs, and resulted in eventual FDA approval of everolimus for the treatment of unresectable pancreatic neuroendocrine carcinomas]. Yao et al. reported 410 randomly

assigned patients with advanced, low or intermediate-grade PNETs with radiologic progression within the preceding 12-month period to receive everolimus at a dose of 10mg daily or placebo, both in combination with best supportive care, which included the use of somatostatin analog therapy in roughly 40% of study patients. This study demonstrated significant improvement in progression-free survival as compared to placebo (11 versus 4.6 months, respectively, P <0.0001). The most common adverse events associated with everolimus noted in this study were stomatitis, rash, diarrhea, fatigue, infections and pneumonitis, and these were primarily grade 1 or 2 drug-related adverse events. The most common grade 3 or 4 drug-related adverse events were anemia, hyperglycemia, stomatitis, trombocytopenia, diarrhea, hypophosphatemia, and neutropenia. Sunitinib is an oral, small-molecule, multitargeted tyrosine kinase inhibitor with activity against vascular endothelial growth factor. Raymond et al. reported on the evaluation of sunitinib in a multinational, randomized, controlled trial of 171 patients with advanced, well differentiated pancreatic neuroendocrine carcinomas that demonstrated RECIST-defined progression within 12 months prior to the study. Patients were randomized to receive sunitinib at a dose of 37.5mg daily or placebo, both with best supportive care. This study was discontinued early when independent data and safety monitoring noted more serious adverse events and deaths in the placebo group as well as a significant difference in progression-free survival (11.4) months in the sunitinib group versus 5.5 months in the placebo group, P<0.0001). Adverse events associated with sunitinib in this trial were diarrhea, nausea, asthenia, vomiting, fatigue and hypothyroidism; grade 3 or 4 adverse drug related events in patients who had received sunitinib were most commonly neutropenia and hypertension.

The discovery of multiple molecular mechanisms associated with P-NETs combined with clinical data to support drug efficacy against these targets, makes this a very exciting time in the investigation and clinical management of GEP-NETs. Clinical trials assessing various combinations of somatostatin analogues, mTOR inhibitors, tyrosine kinase inhibitors, and cytotoxic agents are ongoing, and there is substantial promise that a multitargeted approach to therapy will translate into improved patient outcomes