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HIGHLIGHT ARTICLE

Novel Agents in Gastroenteropancreatic Neuroendocrine Tumors

Highlights from the "2013 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 24-26, 2013

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Summary

Neuroendocrine tumors (NET) are a diverse group of tumors that derive from epithelial cells with neuroendocrine differentiation. Gastroenteropancreatic neuroendocrine tumors are a subset of NET that arises in the gastrointestinal tract. Clinical symptoms and presentations vary depending on the location and hormones produced by the tumor. Treatment of advanced and metastatic gastroenteropancreatic NETs has traditionally been difficult with few systemic treatment options. In 2011, two new targeted therapies, everolimus and sunitinib were approved for treatment of pancreatic NET leading to increased interest in novel agents active in gastroenteropancreatic NETs. At the 2013 ASCO Gastrointestinal Cancers Symposium two abstracts presented new data regarding novel therapies. Lombard-Bohas *et al.* (Abstract #224) presented new data from the RADIANT-3 trial and Shen *et al.* (Abstract #322) looked at the use of octreotide in elderly patients with carcinoid syndrome.

What we Knew Prior to the 2013 ASCO Gastrointestinal Cancers Symposium

Gastroenteropancreatic neuroendocrine tumors (NET) are a clinically diverse group of diseases that arise from tissue throughout the gastrointestinal tract. Symptoms are often related to molecules secreted by the tumors. Well differentiated tumors, traditionally referred to as carcinoid and islet cell tumors or pancreatic NET, often have more indolent courses compared to other epithelial carcinomas, whereas poorly differentiated tumors have a more aggressive course [1]. The incidence and prevalence of these tumors have increased over the past 30 years and a significant percentage has distant disease at diagnosis [1, 2]. Five-year survival is approximately 60%, but no significant improvement has been made on overall survival over the past 30-40 years [1].

Recently, treatment of advanced gastroenteropancreatic NET has made significant advancements, with new approved agents and new drug combinations. Everolimus, a mammalian target of rapamycin (mTOR) inhibitor showed benefit in pancreatic NET. In the RAD001 in Advanced Neuroendocrine Tumors (RADIANT)-3 study, patients with unresectable pNET treated with everolimus had improved progression free survival compared to placebo (11.0 *vs.* 4.6 months) [3]. Similarly, patients with advanced pNET treated with sunitinib *vs.* placebo showed improvement in progression free survival (11.4 *vs.* 5.5 months) [4]. Along with these targeted therapies, somatostatin analogs, long used to control symptoms in carcinoid tumors, have been shown to have antitumor effect. Octreotide was compared to placebo in the PROMID trial in patients with metastatic carcinoid tumors of the midgut, showing improved time to tumor progression (14.3 *vs.* 6 months) [5]. Heightened interest in systemic treatment of gastroenteropancreatic neuroendocrine tumors has been increased due to these recent advancements.

Key words Carcinoid Tumor; Neuroendocrine Tumors; Octreotide; TOR Serine-Threonine Kinases; Therapeutics

Abbreviations RADIANT: RAD001 in Advanced Neuroendocrine Tumors

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What We Learned from the 2013 ASCO Gastrointestinal Cancers Symposium

Efficacy and Safety of Everolimus in Patients with Advanced Low- or Intermediate-Grade Pancreatic Neuroendocrine Tumors Previously Treated with Chemotherapy: RADIANT-3 Subgroup Analysis. (Abstract #224).[6]

Lombard-Bohas *et al.* presented data from a planned exploratory analysis of the phase III RADIANT-3 trial. Patients with low or intermediate grade pancreatic NET (pNET) were stratified prospectively by prior chemotherapy use. The patients were then randomized to receive either everolimus 10 mg daily or placebo plus best supportive care. Results are summarized in Table 1. Best overall response was stable disease in 73% of everolimus treated patients in both groups. Disease stabilization and decreased disease progression was seen with everolimus regardless of prior chemo-

Table 1. Results. Baseline characteristics (age, sex, race, tumor type, histological grade and baseline tumor biomarkers) were similar between the two groups (Lombard-Bohas *et al*. 2013 [6]).

	Chemotherapy naïve (n=204)	Prior chemotherapy use (n=206)
Patients initially diagnosed within last 6 months	50 (25%)	7 (3%)
Patients with prior somatostatin treatment	92 (45%)	111 (54%)
Progression free survival	Everolimus: 11.4 months Placebo: 5.4 months HR=0.42; P<0.001	Everolimus: 11.0 months Placebo: 3.2 months HR=0.35; P<0.001
Drug related side effects in everolimus group	Rash (52%) Stomatitis (56%) Diarrhea (52%) Fatigue (51%)	Rash (53%) Stomatitis (52%) Diarrhea (41%) Fatigue (37%)

therapy. This subgroup analysis shows a benefit of everolimus in low and intermediate grade pNETs independent of prior chemotherapy use and supports possible first-line use of everolimus.

Octreotide LAR Use Among Elderly Patients with Carcinoid Syndrome and Survival Outcomes: A Population-Based Analysis (Abstract #322) [7].

Shen *et al*. performed a retrospective study evaluating octreotide LAR use in elderly patients with carcinoid syndrome and survival differences. NET patients were identified using the Surveillance, Epidemiology and End Results (SEER)-Medicare database from July 1999 to December 2007 (http://healthservices.cancer.gov/seermedicare/). Indications for octreotide use included 2 or more claims for carcinoid syndrome, flushing, diarrhea or malignant islet cell neoplasm within one year of diagnosis and the first claim within 6 months of diagnosis. Patients were excluded if under age 65, enrolled in a health maintenance organization (HMO) or without continuous part A and B enrollment (http://www.medicare.gov/Pubs/pdf/11219.pdf) within 12 months of diagnosis. Cox proportional hazard model and multivariate logistic regression analysis were used to evaluate factors associated with octreotide use and effect of octreotide on survival. The study found that among patients with indications for octreotide use, only 264/539 (49.0%) distant stage patients and 83/850 (9.8%) local/regional stage patients were started on therapy within 6 months of diagnosis. Patients living in southern regions were less likely to be treated. A significant 5-year survival benefit was seen with distant stage disease (HR=0.80; P=0.047) but no benefit in local/regional stage disease (HR=0.97; P=0.89). This study shows a potential survival benefit to octreotide use in elderly patients with distant stage carcinoid syndrome and that many elderly patients with indications for octreotide are not receiving therapy early in the disease course.

Discussion

The treatment of advanced gastroenteropancreatic NETs continues to rapidly evolve. Targeted therapies have a significant role in this advancement. mTOR inhibitors, such as everolimus target cell proliferation and angiogenesis and sunitinib, a multikinase inhibitor, inhibit vascular endothelial growth factor (VEGF). Agents that disrupt angiogenesis have shown significant activity in pancreatic NETs. Table 2 summarizes the use of everolimus in gastroentero-pancreatic NETs. Lombard-Bohas *et al*. showed in a planned subgroup analysis of the RADIANT-3 trial that everolimus improved progresssion free survival irrespective of prior chemotherapy use with no significant difference in side effect profiles [6]. This data further supports upfront use of everolimus for advanced pancreatic NETs.

Therapies for carcinoid tumors were also addressed at the 2013 ASCO Gastrointestinal Cancers Symposium. Octreotide LAR has long been used for treatment of carcinoid syndrome symptoms, but more recently has shown to also delay tumor progression [5]. The retrospective analysis presented by Shen *et al*. found a possible 5-year survival advantage of octreotide LAR use in elderly (age older than 65 years) patients with distant stage disease [7]. The group also found that a minority of patients with symptoms of carcinoid syndrome are receiving prompt treatment of their disease. Further prospective trials are needed to evaluate these findings.

Conflict of interest The authors have no potential conflict of interest

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Table 2. Use of everolimus in gastroenteropancreatic NET.

Type	Stage	Improved progression free survival	Trial
Pancreatic NET	Unresectable locally advanced or metastatic disease	Everolimus: 11 months Placebo: 4.6 months P<0.001	Yao *et al*., 2011 (RADIANT-3) [3]
NET associated with carcinoid syndrome	Unresectable locally advanced or metastatic disease	Everolimus + octreotide LAR: 16.4 months Placebo + octreotide LAR: 11.3 months P=0.025	Pavel *et al*., 2011 (RADIANT-2) [8]

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