Old and New Therapies for GEP NETs

Written by Brian Hoyle

Ian Chau, MD, The Royal Marsden Hospital, London & Surrey, United Kingdom, discussed the conventional and newer, targeted treatment of gastroentero-pancreatic neuroendocrine tumors (GEP NETs).

Systemic therapy for GEP NETs centers on the tumor grade. Treatment of grade 1 and 2 tumors (also known as well-differentiated tumors and defined as a mitotic count < 2 per high-power field [HPF] and 2 to 20 per HPF, respectively, and Ki67 ≤ 2% and 3% to 20%, respectively) that are asymptomatic (nonfunctional) can be immediate or involve watchful waiting. Grade 3 neuroendocrine carcinomas (defined as > 20 per HPF and Ki67 > 20%) that have metastasized must be treated immediately, given the low median survival of these patients [Sorbye H et al. *Cancer.* 2014].

Treatment of grade 3 NETs consists of platinum-based chemotherapy (cisplatin–etoposide or carboplatin–etoposide). Second-line chemotherapy might include temozolomide or the FOLFIRI regimen. Treatment is hindered, however, by the lack of randomized controlled trials on first-line and subsequent therapy, given the relative rarity of patients. Published studies of second-line chemotherapy for grade 3 NETs have involved fewer than 100 patients [Sorbye H et al. *Ann Oncol.* 2013; Hentic O et al. *Endocr Relat Cancer.* 2012; Welin S et al. *Cancer.* 2011].

For grade 1 and 2 tumors, the immediate treatment is symptom directed. Interferon therapy dates back to the 1980s. The use of somatostatin receptor analogues (SSRAs) reflects more recent studies that have shown the high prevalence of expression of some or all of the 5 known somatostatin receptors on carcinoid tumors. Two novel SSRAs are octreotide and pasireotide, which bind particularly avidly to receptors 1 and 4, with pasireotide binding being relatively stronger. In a small, phase 3 randomized study [Wolin EM et al. *J Clin Oncol.* 2013 (abstr 4031)], neither drug met the primary end point of symptoms response at 6 months in the 110 patients, with patient numbers being too small to evaluate drug effects on individual symptoms. Of note, however, tumor response occurred for both drugs, particularly pasireotide, with pasireotide significantly prolonging progression-free survival (PFS; 11.8 vs 6.8 months; HR, 0.46; 95% CI, 0.20 to 0.98; $P = .045$).

Data are more equivocal concerning the antiproliferative effects of SSRAs. The PROMID [Rinke A et al. *J Clin Oncol.* 2009] and CLARINET [Caplin ME et al. *N Engl J Med.* 2014] placebo-controlled, randomized controlled trials involving 85 and 204 patients, respectively, established the antiproliferative efficacy of octreotide LAR for mainly grade 1 primary tumors in the midgut and lanreotide for mainly grade 1 primary tumors located predominantly in the pancreas and midgut. The median time to progression for octreotide LAR vs placebo was 14.3 vs 6.0 months, respectively (HR, 0.34; 95% CI, 0.20 to 0.59; $P = .000072$), and the median PFS for lanreotide vs placebo has not yet been reached for lanreotide but is 18 months for placebo (HR, 0.47; 95% CI, 0.30 to 0.73; $P < .001$).

PROMID, however, did not find an improvement in overall survival (OS), with a median OS of 77.4 months for octreotide vs 73.7 months for placebo (HR, 0.85; 95% CI, 0.46 to 1.56; $P = .59$) [Arnold R et al. *J Clin Oncol.* 2013 (abstr 4030)]. The OS data for CLARINET are pending, but no superiority of lanreotide is evident. In addition, neither trial found a significant improvement in quality of life with improved PFS. This supports the view that there may be asymptomatic disease progression, and that disease progression may not equal worse symptoms. But the literature is sparse, and no conclusions can be made. Watch and wait may still be an option.

For nonfunctional GEP NETs that are receiving immediate treatment, their origin (ie, pancreatic or nonpancreatic) can be an important consideration, because median survival can vary widely depending on the location of the primary tumor.

Pancreatic tumors can receive targeted therapy with sunitinib or everolimus. A pivotal placebo-controlled phase 3 study involving 171 patients with well-differentiated advanced pancreatic NET randomized to sunitinib (n = 86) or placebo (n = 85) [Raymond E et al. *N Engl J Med.* 2011] reported

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a significant treatment benefit on the primary end point of PFS (median PFS, 11.4 vs 5.5 months; HR, 0.42; 95% CI, 0.26 to 0.66; $P < .001$). There was no difference in median OS (33 vs 26.7 months; HR, 0.71; 95% CI, 0.47 to 1.09; $P = .11$) [Vinik A et al *J Clin Oncol.* 2012 (abstr 4118)]. Concerning everolimus, the pivotal phase 3, placebo-controlled RADIANT 3 trial [Yao JC et al. *N Engl J Med.* 2011] that randomized 410 patients with well- or moderately differentiated NET to receive everolimus (n = 207) or placebo (n = 203) met the primary end point of PFS (median PFS, 11.0 vs 4.6 months; HR, 0.35; 95% CI, 0.27 to 0.45; $P < .001$), whereas OS was not significantly affected. As reported by Yao et al. [ESMO 2014 (abstr 1132O)], these trends continued through the trial's conclusion.

Should nonpancreatic gastrointestinal NETs also be considered for targeted therapy? Is it too early to make a case for sunitinib? Concerning everolimus, the RADIANT 2 phase 3 study [Pavel ME et al. *Lancet.* 2011] evaluated everolimus plus octreotide LAR (n = 216) vs placebo plus octreotide LAR (n = 213), and it reported an everolimus benefit on median PFS (16.4 vs 11.3 months; HR, 0.77; 95% CI, 0.59 to 1.00) but did not achieve significance ($P = .026$).

Cytotoxic chemotherapy for pancreatic NETs includes streptozocin, temozolomide, fluoropyrimidines, and platinum compounds. These have been studied in many small-scale studies, with an objective response rate of 40% or more evident, including in 3 randomized studies [Meyer T et al. *Eur J Cancer.* 2014; Moertel CG et al. *N Engl J Med.* 1992; Moertel CG et al. *N Engl J Med.* 1980]. The approach can be useful for nonpancreatic NETs, with the caveat of a lower objective response rate (20% to 30%) in the many studies that have been performed [Costa FP et al. *Best Pract Res Clin Gastroenterol.* 2012].

With both targeted and cytotoxic therapies amenable for the treatment of nonfunctional pancreatic NETs, the question becomes which should be performed first. The results of the SEQTOR trial [NCT02246127] will be instructive. In the trial, patients will be randomized to everolimus therapy first, with a switch to streptozocin plus 5-FU on disease progression or the reverse order. The primary end point will be the second PFS following the second disease progression.