The Changing Paradigm of Treating Pancreatic Neuroendocrine Tumors

Neuroendocrine tumors (NETs) are a rare group of malignancies arising from the neuroendocrine cell system that have a wide spectrum of variability in terms of presentation, embryology, histology, disease course, and treatment. The annual incidence is estimated at 5.25 per 100,000 population. Incidence and prevalence are on the rise due to the increasing use of cross-sectional imaging. Most pancreatic NETs (PNETs) are nonfunctional and detected at later stages. Patients with early-stage tumors often have symptomatic disease from hormonal secretion, which is the usual trigger for further workup. The subset of PNETs is a little more aggressive in behavior compared with carcinoids, and treatment is often also warranted because of the symptoms arising from functioning PNETs. These symptoms are caused by hypersecretion of gastrin, glucagon, insulin, somatostatin, pancreatic polypeptide, and vasoactive intestinal peptide. Treatment for these tumors has progressed despite their rarity and variable biologic behavior, partially because of better-defined patient populations for clinical trials, better understanding of tumor biology, and effective targeted therapies.

Changing Classification systems

For decades, numerous classification systems have been put forth for NETs. Earlier reports classified these tumors based on embryology, histology, chemical secreted, grade, and stage of disease. These systems help to differentiate tumors but do not contribute toward choosing therapy. The recent WHO classification has incorporated the elements that are needed to refine understanding and establish much-needed uniformity before deciding on treatment. Further work to validate the prognostic value of these systems is still needed.

Therapy

PNET Therapy Before 2011

Before the discovery of molecular targeted agents, the mainstay of treatment for NETs was initial debulking surgery for early-stage disease and a wide spectrum of options, from observation to locoregional therapy or a wide spectrum of systemic medications. Somatostatin analogues were and still are an important component of treatment to control symptoms and for antineoplastic effects. Interferon-based regimens, either alone or in combination with somatostatin analogues, have been tried, with poor response rates.

Cytotoxic streptozocin-based regimens with combinations of cyclophosphamide and doxorubicin, and 5-fluorouracil have shown efficacy in treating advanced NETs. Radiologic regression of tumors and increase in survival rates were seen with these regimens, but their use has been limited because of severe adverse events and the complexity of administration.

A combination of temozolomide and thalidomide has been used, with modest response rates (46% in PNETs) and encouraging progression-free survival (PFS). Temozolomide and capecitabine have also shown promising activity (objective response rates, 70%). In patients with PNETs in whom tumor shrinkage is needed, these regimens have high response rates with acceptable toxicity profiles. Although impact on long-term survival has not yet been defined clearly in the phase III setting, these drugs remain in the armamentarium for these patients.
PNET Therapy After 2011

With the advent of molecular targeted therapy comes a promising new horizon for treatment of advanced PNETs. Two recent phase III trials, one using everolimus\(^8\) and the other sunitinib,\(^9\) have shown clinical benefit in delaying progression and prolonging survival in advanced PNETs that progressed on other therapies. This has lead to FDA approval of these agents.

The oral mammalian target of rapamycin (mTOR) inhibitor, everolimus, which was previously shown to have efficacy in a phase II trial, was recently prospectively evaluated in a phase III trial (RADIANT-3).\(^8\) In this trial, 410 patients were randomized to receive drug or placebo. PFS was prolonged by 6.4 months with therapy (11.6 vs. 5.2 months) in the treatment group. Most patients in this trial had well-differentiated tumors and radiologically confirmed disease progression in the past 12 months while on other regimens. Previous liver-directed therapy was an exclusion criterion. Median treatment duration was 8.79 months in the everolimus group compared with 3.7 months in the placebo group. The most frequent treatment-related adverse events were stomatitis, rash, fatigue, diarrhea, and respiratory infections. Everolimus benefit was due to tumor stabilization in most cases.

Promising phase II data prompted another randomized phase III trial comparing sunitinib, an oral multitargeted tyrosine kinase inhibitor, with placebo. The mean PFS was 11.4 months in the sunitinib group compared with 5.5 months in the placebo group.\(^9\) The study was terminated early because the study drug showed a clear benefit (more serious adverse events and death were seen in the placebo arm). The sample size was comparatively small (N = 171) and patients with previous liver-directed therapy were also included in this trial. The most frequent adverse events were diarrhea, nausea, vomiting, asthenia, and fatigue. Median treatment duration was 4.6 months in the sunitinib group compared with 3.7 months in the placebo group.

Median time from diagnosis was more than 2 years in both trials; this is worth mentioning and should be included as an independent prognostic variable when estimating PFS through multivariate analysis in future trials. Both studies allowed crossover to the treatment arm, and meaningful clinical benefit was seen despite radiographic shrinkage with both drugs.

Future

For clinicians who treat these tumors, access to these new drugs has been a testament to the motivation of patients to participate in clinical trials. A death rate of 10% in the sunitinib study and 6% in the everolimus study, even after progression on these agents, suggests remaining work needs to be done to identify the correct sequence of therapy. Liver-directed therapies and debulking surgery remain treatment options when feasible. Until long-term follow-up data become available, these newer agents are best used for progressing PNETs as selected for inclusion in the phase III trials. Sunitinib and everolimus for treatment of progressive PNETs are included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Neuroendocrine Tumors published in 2011 (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).\(^10\) Temozolomide-based regimens play a role in palliation because of high response rates, and their role in the treatment of PNETs needs further study.

The ever-changing field of medicine stimulates further questions. Issues that remain unanswered are: Should we offer these drugs to all patients with NETs, irrespective of stage or grade of disease? Should the agents be used as first-line therapy earlier, when disease burden is lower, or as rescue therapy after other debulking measures are exhausted? Would a combination have greater clinical benefit if preclinical synergy or different molecular pathways are targeted?
Recently completed trials involving vatalanib, thalidomide, temozolomide, and pemetrexed, and ongoing clinical trials with sorafenib, AMG 479, bevacizumab, and temozolomide in the treatment of advanced NETs (available at www.ClinicalTrials.gov), are expected to further our understanding and refine our practices.

References