Current Chemotherapy Use in Neuroendocrine Tumors

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KEYWORDS

• Chemotherapy • Neuroendocrine tumors • Metastatic

KEY POINTS

- Advanced grade 3 (G3) poorly differentiated neuroendocrine carcinomas (NECs) are usually treated with platinum/etoposide chemotherapy in the first-line setting.
- There is no consensus regarding "well-differentiated G3 gastroenteropancreatic neuroendocrine tumors"; a platinum doublet or capecitabine (CAPTEM) are reasonable options in this setting.
- Chemotherapy is not routinely used as first-line therapy for G1 to G2 neuroendocrine tumors (NETs). The combination of CAPTEM and temozolomide shows promise in this setting as later-line therapy.
- There is little evidence for adjuvant chemotherapy for resected G1 to G2 NETs; adjuvant platinum/etoposide is often given for resected G3 NETs.

INTRODUCTION

The incidence of neuroendocrine tumors (NETs) has increased over the past 30 years,[1] and they are the second most prevalent gastrointestinal tumor behind colorectal cancer. NETs are heterogeneous neoplasms that most commonly arise from the gastrointestinal tract, pancreas, and lung. Their biological behavior can vary widely, and for this reason characterization of NETs relies as much on their histologic grading as the primary site of disease. Grade 1 (G1) NETs may display extremely indolent behavior, whereas grade 3 (G3) NETs may grow over a matter of weeks and require urgent treatment. Gastrointestinal tumors are graded using the World Health Organization (WHO) 2010 system, using a combination of the mitotic count and Ki-67 index. The WHO

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2017 system published earlier this year provides minor modifications to the grading cutoffs, as well as separating G3 pancreatic NETs into well-differentiated and poorly differentiated tumors.[2] This is due to new evidence showing that patients with G3 poorly differentiated pancreatic neuroendocrine carcinomas (PDNECs) have worse outcomes, even though the Ki-67 index of these tumors overlaps considerably with G3 well-differentiated NETs (WDNETs).[3,4]

NETs are generally treated by a multidisciplinary team, as treatments are complex and varied.[5] These may include surgery (both curative and debulking), external beam radiotherapy and peptide receptor radionuclide treatment (PRRT), liver-directed therapies (embolization, radiofrequency ablation), systemic treatments, and clinical trials. Sequencing of these modalities is a major clinical and logistical challenge due to the number of services involved. Although surgery is the standard of care for resectable NETs, up to 50% of patients present with metastatic or unresectable disease,[6] and systemic therapy is the mainstay of therapy for these patients.

Chemotherapy was one of the few systemic treatments available for NETs for much of the twentieth century. The development of other systemic treatments (such as somatostatin analogs and the targeted agents everolimus and sunitinib) have decreased the prominence of chemotherapy in the treatment of low-grade (G1–G2) NETs; however, it is still the first-line treatment of choice in high-grade NETs. Cytotoxic chemotherapy disrupts the mitotic processes of dividing cells and thus is more likely to affect rapidly proliferating malignancies. Different classes of agents exist, alkylating agents (cisplatin, temozolomide), topoisomerase inhibitors (etoposide), and thymidylate synthase inhibitors (capecitabine), for instance, with the possibility of synergistic efficacy between different classes. There remains considerable debate over the utility and sequencing of chemotherapy in the role of systemic therapy in NETs overall.

AN OVERVIEW OF RANDOMIZED CHEMOTHERAPY TRIALS IN NEUROENDOCRINE TUMORS

A systematic review investigating randomized trials of chemotherapy for NETs showed that the vast majority of trials were conducted in the 1980s and 1990s (**Table 1**).[7] These generally involved the comparison of streptozocin (usually in combination with 5-fluorouracil [5-FU]) with another chemotherapeutic regimen, as streptozocin had shown signs of clinical activity in prior single-arm trials and became adopted as a standard treatment at that time. There were no placebo-controlled randomized trials identified. Most of the trials failed to show a significant difference between the 2 treatment arms in terms of overall survival (OS) and progression-free survival (PFS), although ascertainment of response varied tremendously during this time period. The only trials that demonstrated significant differences in outcomes were Moertel and colleagues[8] and Sun and colleagues.[9] Both trials showed an OS advantage for streptozocin and doxorubicin compared with streptozocin and 5-FU, although there was no significant difference in PFS in the trial by and colleagues.[9]

It is important to note that the previously described trials need to be interpreted with caution, given the evolution in both classification and monitoring of NETs over the past 2 decades. These trials often included a very heterogeneous population of NETs, which would not be considered appropriate in today's environment. As the 3-grade system for classifying gastroenteropancreatic NETs (GEPNETs) was only published in 2007, trials before this were often limited to analysis by the degree of differentiation alone rather than using the mitotic rate and Ki-67 index, as is standard practice today. Even the most recent trial, Meyer and colleagues,[10] enrolled patients with all 3 grades of NET, perhaps reflecting the difficulty in conduct of well-designed NET trials. There