Randomized Controlled Trials in Neuroendocrine Tumors

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KEYWORDS

• Neuroendocrine tumor • Somatostatin • Clinical trial • Carcinoid

KEY POINTS

- Neuroendocrine tumors are a diverse group of tumors with variable clinical presentation and biological behavior, making evaluation, diagnosis, and treatment planning difficult in the absence of an experienced multidisciplinary team.
- Treatment is predicated on accurate staging and biologic work-up; namely, the differentiation, grade, and presence of somatostatin receptors.
- Somatostatin analogues, mammalian target of rapamycin inhibitors, receptor tyrosine kinase inhibitors, antiangiogenics, targeted radiopeptides, immune therapy, and cytotoxic chemotherapy have shown efficacy in the treatment of neuroendocrine tumors.
- Multidisciplinary evaluation and treatment are recommended to give patients with neuroendocrine tumors the best chance at a durable survival with optimal quality of life.

INTRODUCTION

Carcinoid tumor was identified more than 100 years ago. The term carcinoid described a carcinomalike tumor with an indolent course. These tumors arise from the resident endocrine cells with the gastrointestinal (GI) tract and lung as the predominant sites of occurrence, and are designated endocrine tumors because of their endocrine and paracrine function and the resemblance to endocrine cells elsewhere, as in the pancreas. Submucosal endocrine cells can be found in multiple organs, including pancreas, lungs, thymus, upper respiratory tract, ovary, uterine cervix, bladder, prostate, kidney, and biliary tree, but the great preponderance are in the GI tract.

Well-differentiated neuroendocrine malignancies are referred to as tumor, neoplasia, carcinoid, or neuroendocrine tumor, whereas poorly differentiated tumors

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represent small cell carcinoma. At present, neuroendocrine tumors are divided into grade 1 and grade 2 based on their proliferative rate and are also discriminated by their differentiation (**Table 1**). This pathologic reporting is paramount in a multidisciplinary discussion regarding management of neuroendocrine tumors.

Localized tumors rarely produce symptoms unless obstructive. Many of these tumors are found incidentally during endoscopic evaluation or cross-sectional imaging and are already metastatic. Up to 35% of these tumors release vasoactive peptides such as serotonin, histamine, or tachykinins, causing clinical syndromes, including carcinoid syndrome.[1] Typical manifestations of functional neuroendocrine tumors are episodic flushing, wheezing, diarrhea, glycemic instability, hypertension, weight change, cosmetic change, and heart disease.[2] Discussion of these syndromes is beyond the scope of this article, but astute physicians must assess for symptoms to appropriately evaluate patients with neuroendocrine tumors.

The prevailing axiom in the management of neuroendocrine tumor is that treatment should be influenced by the distribution and bulk of tumor, the biology of the tumor, and the severity and manner of the associated symptoms. Once determined to treat, physicians target the systems that propel the metastatic machinery of neuroendocrine tumor: DNA repair, somatostatin receptor signaling, receptor tyrosine kinase signaling, and mammalian target of rapamycin (mTOR) signaling. There are no curative interventions for metastatic neuroendocrine tumor. Therefore, managing the patient's expectations of observation or therapeutic intervention remains a critical aspect of cancer care in this disease. This article provides a review of the important randomized controlled trials that have shaped the management of neuroendocrine tumor over the last 2.5 decades (**Table 2**).

CYTOTOXIC CHEMOTHERAPY

In 1992, a multi-institutional study conducted by the Eastern Cooperative Oncology Group (ECOG) was published presenting the outcomes of the randomized controlled trial studying the effect of streptozocin plus fluorouracil, streptozocin plus doxorubicin, or chlorozotocin alone in the treatment of advanced pancreatic neuroendocrine tumor.[3] Previous reports supported the use of these agents in the treatment of neuroendocrine tumor and provided the rationale for this randomized control trial. Patients were randomly assigned after stratification according to the ECOG performance score to 1 of the 3 arms. After failure of therapy, patients were randomly assigned to receive alternative arms of therapy. An intention-to-treat analysis was performed on the outcome measures to determine efficacy. One-hundred and twenty-five patients were enrolled between 1978 and 1985. However, only 105 patients received therapy.

Table 1
Classification of neuroendocrine tumors

Grade	GI and Pancreatic	Lung and Thymic Tumors	Differentiation
Low (G1)	<2 mitoses/10 HPF and/or <3% Ki-67 index	<2 mitoses/10 HPF and no necrosis	Well
Intermediate (G2)	2–20 mitoses/10 HPF and/or 3%–20% Ki-67 index	2–10 mitoses/10 HPF and/or foci of necrosis	Well
High (G3)	>20 mitoses/10 HPF and/or >20% Ki-67 index	>10 mitoses/10 HPF	Poor

Abbreviation: HPF, high-power field.