Clinical Trial Design in Neuroendocrine Tumors

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KEYWORDS

• Neuroendocrine tumors • Clinical trials • Patient homogeneity
• Standardized response assessment • Study design and interpretation

KEY POINTS

- Neuroendocrine tumors (NETs) present tremendous opportunities for productive clinical investigation, but substantial challenges as well.
- NETs are relatively rare, heterogeneous, and typically indolent tumors that are imperfectly visualized by most common imaging techniques, and have historically had minimal standardization of care.
- Investigators must be aware of common pitfalls in study design, informed by an understanding of the history of trials in the field, to make the best use of available data and our patient volunteers.
- When previous studies are considered as instructive not only about disease biology and management, but also about study design and interpretation, investigators are poised to continue iteratively refining our methods for the benefit of our patients with these diseases.
- We believe the salient issues in clinical trial design and interpretation in the NET field are patient homogeneity, standardized response assessment, and rigorous design and execution. Whether designing or interpreting a study in patients with NET, these principles should drive assessment.

INTRODUCTION

The field of neuroendocrine oncology has grown significantly over the past decade. Over that time, substantial collaborative efforts have allowed the successful conduct of multiple randomized controlled trials that have changed both the clinical practice of oncology and the scientific practice of conducting future studies. These studies provide ample opportunity for learning in study design and execution, and our intent in this article is to consolidate the lessons learned and offer direction as the field continues to advance.

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We would submit that the key principles for neuroendocrine tumor (NET) clinical trials moving forward are the selection of homogeneous patient populations, assessment of standardized criteria for progression and response by real-time centralized review, and rigorous study design. These principles arise from a history of rigorous clinical investigation that has evolved together with improvements in technology that enable us to conduct ever more sophisticated investigations. Similarly, we believe that these issues are central to interpretation of any given study, and should be reviewed when considering the results of any clinical trial.

HISTORICAL OVERVIEW

The earliest clinical trials for patients with NET evaluated conventional chemotherapy, and highlight many of the salient issues of clinical trial design in this patient population. These issues include grouping tumors by primary site and clinical aggressiveness, selection of response criteria, and assessment of those criteria.

One of the first studies tested streptozocin in 52 patients with metastatic pancreatic NETs (pNETs) in the 1970s.[1] This relatively large study for the era was conducted after an initial evaluation of the drug in 4 patients with pNET and 4 patients with extrapancreatic NET (carcinoid) revealed 1 response in a patient with pNET and no responses in the carcinoid patients.[2] This later study required the collaboration of 50 investigators to accrue 52 patients, and is notable for its inclusion of exclusively patients with pNET. Following their accrual, patients received standardized doses of the therapy and were followed for response. Response criteria were strictly defined to incorporate both improvements in hormone secretion and tumor volume assessed by physical examination of the assessing investigator. By its nature, this study was uncontrolled, but given the lack of alternative therapies, evidence of relevant activity established streptozocin as the standard therapy for advanced pNET.

Subsequently, 2 randomized studies of approximately 100 patients each were conducted by the Eastern Cooperative Oncology Group (ECOG) to develop streptozocin-based chemotherapy further.[3,4] The first demonstrated superiority of 5-fluorouracil combined with streptozocin over streptozocin alone[3] in a population of patients with pNET, although it continued to use a composite endpoint of biochemical and measureable response, with approximately one-third of patients eligible for classification of response based on biochemical parameters, and an unknown proportion eligible based on physical examination. Secondary endpoints of progression-free survival (PFS) and overall survival were not statistically different between the 2 arms. The second study evaluated 3 regimens: streptozocin with 5-fluorouracil, streptozocin with doxorubicin, and single-agent chlorozotocin, with doxorubicin/streptozocin demonstrating superiority. Nearly half of all patients in that study could be classified as responders based on biochemical criteria. However, both PFS and overall survival were significantly improved with the combination ($P<.005$ for both endpoints and both comparators).[4] These studies established the standard therapy for pNETs until 2011, although notably, later evaluation in the modern era of cross-sectional imaging would suggest that the radiographic response rate of pNETs to streptozocin-based doublet chemotherapy is actually less than 10%.[5,6] Importantly, these studies highlight some of the key study design issues that continue to arise in the field. Multi-institutional cooperation was required to achieve even modest accrual of a homogeneous group of patients and intermediate endpoints, such as objective radiographic response rate, were used due to feasibility. Also of note, given the challenges of patient accrual, the time lapse between each of these studies was approximately 10 years.