Chemoradiation in the Management of Pancreatic Neuroendocrine Tumors (PNET)
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Introduction

Pancreatic Neuroendocrine Tumors (PNET)
Pancreatic neuroendocrine tumors represent a heterogenous group of tumors with varying tumor biology and prognosis. The incidence of PNETs has increased over the past two decades to approximately 5,000,000 persons. Advanced PNETs remain a difficult therapeutic challenge because of high malignant potential and resistance to conventional chemotherapy. As a result, there are limited effective treatment options for patients with advanced disease.

There have been recent new developments with promising results with the use of novel molecular targeted agents for the treatment of this disease. Traditional conventional chemotherapy agents included regimens based on etoposide, platinum agents, anthracyclines, streptozocin, and 5-FU based agents.

Combined modality chemoradiation is not widely used in the management of locally advanced pancreatic endocrine tumors.

University of Maryland School of Medicine, Baltimore, MD and Johns Hopkins University School of Medicine, Baltimore, MD presented a series of series of 11 patients with histologically confirmed PNET (T3/ T4) who received external beam radiation therapy to the primary tumor or resection bed to a median dose of 50.4 Gy. Of these 11 patients, 7 received concurrent capecitabine (1000mg/m² bid). Among 9 patients with locally advanced disease, two were able to undergo surgical resection. At a median follow-up of 30.4 months, 3 patients were dead with progressive disease, 2 had died without progressive disease, 3 were alive with metastases, and 3 were alive without metastases (1 stable, 1 partial response, 1 complete response). Only two grade 3 toxicities were noted. The authors concluded that local radiation therapy may convert initially unresectable, locally-advanced tumors to disease amenable to surgical resection, which would theoretically improve local control.

To further augment these data, we present our experience in treating patients with PNET with chemoradiation.

Methods

Patients with biopsy proven, previously untreated PNET were treated with capecitabine (median dose 600 mg/m² po bid; range: 600-800 mg/m²) or infusional 5-FU (175 mg/m²/day) and concurrent radiation

Radiotherapy began on the first day of week 1 of capecitabine or 5-FU. The target volume received external beam radiation at 180 Gy/day delivered Monday through Friday for a total dose of 50.4 Gy. The treatment volume consisted of the gross tumor volume (GTV), defined by pancreatic and locoregional radiographic abnormalities identified by contrast-enhanced computed tomography (CT), the clinical target volume (CTV) defined as the area at risk for subclinical microscopic disease, and the planning target volume (PTV), typically consisting of a 0.5 cm margin outside of the CTV.

Results

Six patients (2 females: 4 males), median age was 52 years (range: 38 to 63 y), with ECOG PS 0-1, grade 0-1 weight loss, and grade 0-1 pain are included in this series. Three patient underwent attempted resection, 1 with negative margins, 2 with positive margins, and 3 patients had unresectable locally advanced disease. All patients completed the intended course of therapy.

The treatment was tolerable with 2 cases of grade 2 hand-foot syndrome (1 requiring capecitabine dose reduction), 1 case of grade 3 diarrhea (5-FU held for 3 days), and 2 cases of grade 1 mucositis. Local control was achieved in 5 patients. All 3 patients with locally advanced disease demonstrated sustained partial radiographic response and improved symptoms.

Three distant recurrences occurred from 12 to 27 months following treatment. Progressive disease was observed in 2 patients with positive margins (1 associated with local recurrence), and 1 with unresected disease. Two of these patients succumbed to PNET and one is alive at 4.5 y with disease controlled on Sandostatin-LAR®. Two patients remain alive without recurrence, 1 remains alive with controlled metastatic disease, 2 patients are dead of progressive disease at 2.5 and 9 years, and 2 patients without evidence of recurrence were lost to followup at 3 years.

Conclusions

Local chemoradiation for PNET is tolerable and results in excellent local control. Our results are in agreement with the other report, including one by Strosberg et al. in which 6 patients were treated with induction chemotherapy followed by concurrent radiation with infusional 5-FU or capecitabine resulted in an 80% objective radiographic response rate and the chemoradiation was well-tolerated. Prospective studies to further investigate the role of chemoradiation in this setting are warranted.