CASE REPORT

**Everolimus and Octreotide in a Patient with High-Grade Pancreatic Neuroendocrine Carcinoma**

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**ABSTRACT**

**Context** Peritoneal dissemination is an important prognostic factor for patients with metastatic pancreatic adenocarcinoma. For an improved prognosis and quality of life, more effective treatment for ascites is necessary. **Case report** We describe a seventy-one-year-old Japanese man with pancreatic adenocarcinoma with malignant ascites who had responded to treatment with Nab-paclitaxel plus gemcitabine after novel cell-free and concentrated ascites reinfusion therapy. For ascites control, keisuke matsusaki cell-free and concentrated ascites reinfusion therapy was performed twice. After that, systemic chemotherapy was initiated. His performance status improved since keisuke matsusaki cell-free and concentrated ascites reinfusion therapy could control the refractory ascites, which allowed chemotherapy to be administered. As a result, the patient survived for 11 months and was able to live without hospitalization for most of this time. **Conclusion** Keisuke Matsusaki cell-free and concentrated ascites reinfusion therapy may be an effective treatment for refractory ascites associated with cancerous peritonitis of pancreatic adenocarcinoma.

**INTRODUCTION**

Pancreatic Neuroendocrine Tumors (PNETs) are overall rare tumors with incidence of ≤ 1 case per 100,000 individuals per year and account for 1 to 2 percent of all pancreatic tumors [1, 2, 3]. The incidence and prevalence of PNET in the United States and elsewhere have increased likely due to detection of asymptomatic disease on cross-sectional imaging and endoscopy done for other indications [3, 4]. The World Health Organization (WHO) classifies neuroendocrine neoplasm arising within the digestive system, according to proliferative rate, into two broad categories. Well-differentiated neuroendocrine tumors (Ki-67 <20%), this category is further separated, into low-grade (Ki-67 <3%), intermediate-grade (Ki-67 =3 to 20%) and poorly differentiated high-grade neuroendocrine carcinomas (Ki-67 >20%) [5].

Prognosis for unresectable PNETs is generally poor when compared to classic carcinoid of the small bowel; however, the histological grade can affect the prognosis where 5-year survival rates for low-, intermediate-, and high-grade tumors are 75%, 62%, and 7%, respectively. When considered based on stage of disease per American Joint Committee on Cancer (AJCC) classification, 5-year overall survival (OS) rates for stages I, II, III, and IV were 92%, 84%, 81%, and 57%, respectively [6].

The current guidelines for the management of well-differentiated metastatic PNETs recommend streptozocin plus 5-fluorouracil/doxorubicin or, temozolomide, with or without capcitabine, as chemotherapy, and everolimus or sunitinib as targeted agents [7, 8, 9, 10, 11, 12, 13]. There is a general lack of data from prospective trials to guide clinical decision-making regarding treatment of high-grade metastatic PNETs. Current treatment approaches include chemotherapy that is based on the pattern of small cell lung cancer with cisplatin and etoposide. Alternative regimens substituting carboplatin for cisplatin or irinotecan for etoposide have been validated in metastatic small-cell lung cancer and are therefore thought to be acceptable options [14, 15]. Temozolomide-based chemotherapy is commonly used as a second-line treatment [16].

Everolimus, an orally administered mammalian target of rapamycin (mTOR) inhibitor, has demonstrated antitumor activity in patients with low- or intermediate-grade PNET who have experienced treatment failure with prior chemotherapy [17]. Subsequently, further investigation in this patient group was initiated with the prospective, randomized, phase III RADIANT-3 trial. RADIANT-3 was
conducted to assess the efficacy and safety of everolimus compared with placebo among patients with low- or intermediate-grade PNETs and radiologic documentation of disease progression. Results showed that the median progression-free survival to be significantly longer among PNETs patients who received everolimus than among those with Placebo (11.0 vs. 4.6 months; hazard ratio, 0.35; 95% confidence interval (CI), 0.27–0.45; p < 0.001). Stable disease was observed in 73% of everolimus-treated patients compared with 51% of those receiving placebo, and tumor shrinkage was also greater in the everolimus arm (64%) compared with the placebo arm (21%). Everolimus was generally well tolerated; adverse events were mostly graded 1 or 2 in severity, consistent with known mTOR side effects, and generally reversible [18]. Median OS was 44.0 months for those randomly assigned to everolimus and 37.7 months for those assigned to placebo, although this finding was not statistically significant; crossover of patients likely confounded the OS results [19]. Also, everolimus has been reported to have activity in progressive metastatic medullary thyroid cancer in a case report [20]. On the other hand, the multitargeted tyrosine kinase inhibitor sunitinib has also shown activity against pancreatic neuroendocrine tumors; it was compared with placebo in a phase III trial. Median PFS was 11.4 months in the sunitinib group as compared with 5.5 months in the placebo group [21]. In a later report, median overall survival favored sunitinib (38.6 vs 29.1 months), but the difference was not statistically significant, potentially due to crossover from placebo to sunitinib in 69 percent of the control group [22]. Herein, we present a case of Stage IV, high-grade pancreatic large-cell neuroendocrine carcinoma who achieved long term survival benefit and prolonged clinical response for more than 28 months to everolimus plus octreotide as a third line treatment.

CASE REPORT

In April 2013, a fifty-two-year-old man presented with four months’ history of Gastroesophageal reflux disease (GERD) symptoms that are not relieved with prescription medications of proton pump inhibitors (PPI). Computed tomography (CT) scan of the abdomen, pelvis and chest revealed a 5×8 cm lobulated mass in the body and the tail of the pancreas with enlarged peri-pancreatic lymph nodes that occluded the splenic vein, a numerous hypervascular lesions throughout the hepatic parenchyma (the largest lesion measured approximately 9 cm in diameter) and two dominant left lower lobe pulmonary nodules measuring up to 1.5 cm. The patient underwent Fine Needle Aspiration (FNA) of the liver lesion which showed sheets of loosely cohesive malignant cells exhibiting significant cellular and nuclear pleomorphism with numerous bizarre forms, many cells were multinucleated and contained intranuclear and cytoplasmic vacuoles. The tumor cells were positive for cytokeratin, synaptophysin and weakly positive for chromogranin, Ki-67 proliferative index stains approximately 35% of tumor cells. CK7, CK20, TTF1, CDX2 and S100 were all negative.

As a part of his work up he did have tumor markers done and of significance, his CA-19-9 was 10 (range: 0-37 U/ml), and Chromogranin A was 2778 (range: 0-93 ng/ml). Octreotide scintigraphy revealed increased focal activity in the pancreatic mass, liver parenchyma, and in the left lower lobe. These findings were consistent with the diagnosis of Stage IV, high grade large-cell neuroendocrine carcinoma of the pancreas with liver and lung metastases. Platinum based chemotherapy was initiated in April 2013 (Cisplatin at 75 mg/m² on day 2 and Etoposide at 100 mg/m² on day 1 through day 2) with pegfilgrastim support for six cycles until August 2013 when his CT scans showed stable disease and the patient was followed up every three months. Later in August 2014, the patient presented with increased reflux symptoms and right upper quadrant abdominal pain. As a result, he underwent further workup, which showed disease progression, as assessed by CT scans and serum markers. Gastrin and chromogranin A were measured at 917 pg/mL (range: 0-100 pg/ml), and 8240 ng/mL, respectively. Subsequently, second line treatment with capectabine (1000 mg/m² on days 1–14 on every 28-day basis) and temozolomide (200 mg/m2 on days 10–14 on every 28-day basis) was initiated, however after 7 cycles the patient experienced significant peripheral neuropathy and fatigue and the treatment was discontinued with radiologic imaging showed stable disease (Figure 1a).

DISCUSSION

In this case, we report activity of everolimus in a patient with large cell pancreatic neuroendocrine carcinoma and high Ki67 (35%) who progressed after cytotoxic chemotherapy and achieved a very prolonged stable disease. Because of the activity of the mTOR pathway in the pathogenicity of PNET, everolimus has been investigated as a second line therapy in patients with advanced disease with evidence activity leading to...
its evaluation and later approval in 1st line settings. The
activity of everolimus was evaluated in patients with well
and moderately differentiated PNET, and in the pivotal
study 82% had well differentiated disease. The high Ki-67
level and the histology of large cell carcinoma represent
poor risk features with poor prognosis and median survival
of 21 months [6]. Our case raises the question whether there
is an activity of mTOR pathway inhibitors even in large cell
neuroendocrine tumors, and whether Ki67 as a marker
should be the determining factor for trial enrollment as
opposed to more modern genomic signature. In the case
presented here, a patient with high-grade, stage IV large-
cell pancreatic neuroendocrine carcinoma was treated
with multiple lines of treatments and achieved long-term
survival for more than 52 months and reduction in disease
biomarkers. The combination of everolimus plus octreotide
LAR demonstrated markedly improved clinical response and
an addition of 28 months of progression-free survival. The
clinical and radiologic benefits were unexpected considering
that a poor prognosis features existed given the disease stage,
high-grade tumor and two failed prior lines of therapies. Our
patient tolerated everolimus plus octreotide LAR very well
with manageable toxicity (grade 1: rash, mouth sores, nail
changes, nasal bleeding, diarrhea).

CONCLUSION

In summary, this case report suggests that the
combination of everolimus plus octreotide LAR may
offer a valuable treatment strategy for patients with
heavily pretreated, advanced, high-grade pancreatic
neuroendocrine tumors and warrant further investigation
of this regimen. Randomized phase III studies remain the
gold standard to determine the efficacy of such a regimen.

Conflict of Interest

The authors have declared that no competing interests
exist.

References

1. Kloppel G, A Perren, PU Heitz. The gastroenteropancreatic
neuroendocrine cell system and its tumors: the WHO classification. Ann
2. Klimstra DS. Nonductal neoplasms of the pancreas. Mod Pathol
2007; 20:S59-112. [PMID: 17486055]
rising incidence of neuroendocrine tumors: a population-based analysis
of epidemiology, metastatic presentation, and outcomes. Cancer 2015;
121:589-97. [PMID: 25312765]
hundred years after “carcinoid”: epidemiology of and prognostic factors
for neuroendocrine tumors in 35,825 cases in the United States. J
Clin Oncol 2008; 26:3063-72. [PMID: 18565994]
5. Rindi G, Arnold R, Bosman FT. Nomenclature and classification
of neuroendocrine neoplasms of the digestive system. In: Bosman FT,
Carneiro F, Hruban RH, Theise ND, et al., editors. WHO classification of
al. Prognostic validity of a novel American Joint Committee on Cancer
Staging Classification for pancreatic neuroendocrine tumors. J Clin Oncol
2011; 29:3044-9. [PMID: 21709192]
gastroenteropancreatic tumours: ESMO Clinical Practice Guidelines
20555086]
Fluorouracil, doxorubicin, and streptozocin in the treatment of patients
with locally advanced and metastatic pancreatic endocrine carcinomas. J
P, et al. The doxorubicin-streptozotocin combination in treatment of
advanced well-differentiated pancreatic endocrine carcinoma; a judicious
diagnostic and treatment strategies for pancreatic neuroendocrine
ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine
line chemotherapy with capecitabine and temozolomide in patients with


