CASE SERIES

Gemcitabine as Salvage Treatment in Patients with Poorly Differentiated Pancreatic Neuroendocrine Tumors: A Case Series

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ABSTRACT

Context Poorly differentiated neuroendocrine carcinoma of the pancreas is a rare and aggressive tumor. The combination of etoposide and cisplatin is considered as the first-line treatment, but no recommendations exist for further treatment after progression. **Case series** We report here case series of three patients who received gemcitabine as salvage chemotherapy in patients with poorly differentiated neuroendocrine carcinoma of the pancreas. All the three patients achieved clinical benefit with manageable toxicities. The survival was 5.5, 8, and 9 months respectively after the beginning of gemcitabine in these three patients. **Conclusions** This case series of patients with poorly differentiated neuroendocrine carcinoma of the pancreas who received gemcitabine as salvage chemotherapy suggests that gemcitabine could be an effective salvage treatment. Future studies to investigate gemcitabine in this setting are warranted.

INTRODUCTION

Pancreatic neuroendocrine tumors (pNETs) account for 3 to 5% of pancreatic malignancies with an incidence of around 1,000 cases per year in the United States [1]. They represent a heterogeneous group of tumors with varying biology and clinical behavior based in their functionality and differentiation. The neuroendocrine tumors (NET) are classified by WHO (Table 1) based on their differentiation in order to assess their biological behavior and their potential for a malignant phenotype [2].

Across all types of neuroendocrine neoplasms, prognosis is dependent on both histology and disease extent [3]. Well-differentiated NETs generally are associated with less-aggressive behavior and poorly differentiated NETs are characterized by extremely aggressive tumor biology and poor prognosis. The alternate and historical names to identify poorly differentiated NETs include: high grade neuroendocrine carcinoma, large cell neuroendocrine carcinoma, oat cell carcinoma, poorly differentiated endocrine carcinoma, or small cell carcinoma. Diagnosis is confirmed on pathology that may include: small cells with scant cytoplasm, fine chromatin, nuclear molding, diffuse pattern of growth, numerous mitotic figures (by definition >20/10 HPF), and abundant necrosis. Immunohistostaining is usually positive for synaptophysin and/or chromogranin. The poorly differentiated NETs of the pancreas are characterized by aggressive tumor biology, similar to that of small-cell carcinoma of lung and carry a poor prognosis. In patients with distant metastases, the 5-year survival probability for patients with poorly differentiated NETs is 4% *versus* 35% for well-differentiated NETs [2] (Table 2).

Poorly differentiated pNETs are characterized by their aggressive tumor biology, absence of somatostatin receptors, and poor prognosis [4]. Neuron-specific enolase (NSE) might be a good tumor marker, whereas chromogranin-A (CgA) is generally negative. Conventional imaging studies, such a computed tomography (CT) scan are usually sufficient for localization of the primary tumor and hepatic metastases. ^{18}F-fluorodeoxyglucose positron emission tomography (PET) can provide additional information in some cases.

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Abbreviations ECOG: Eastern Cooperative Oncology Group; FOLFIRI: irinotecan, 5-fluorouracil and leucovorin
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Table 1. WHO 2010 classification of neuroendocrine tumors.

Differentiation	Grade	Mitotic rate	Ki-67	Classification
Well differentiated	Low grade (G1)	<2 per 10 HPF	<3%	Neuroendocrine tumor, grade 1
	Intermediate grade (G2)	2-10 per 10 HPF	3-20%	Neuroendocrine tumor, grade 2
Poorly differentiated	High grade (G3)	>20 per HPF	>20%	Neuroendocrine carcinoma, grade 3, small cell Neuroendocrine carcinoma, grade 3, large cell

HPF: high-power fields

Surgery is only recommended for resectable primary tumors, whereas the presence of hepatic metastases excludes a curative surgery. Although, cytoreductive procedures are generally not recommended, transcatheter arterial chemo-embolization or transarterial chemoembolization (TACE) may be indicated in selected patients. Systemic chemotherapy is the main stay for patients with systemic disease. The combination of etoposide and cisplatin, the same chemotherapy regimen that is used for patients with small-cell carcinoma of lung is usually offered to these patients. A study by Moertel *et al*. reported that etoposide plus cisplatin produced a remission in 55-80% of patients, with response duration of 8-11 months [5]. This regimen was further confirmed by more studies [6, 7]. If the combination of etoposide and cisplatin as the first-line chemotherapy fails to treat these patients, no consensus exists to define second or further treatment recommendations.

We report here a case series of three patients with poorly differentiated pNETs who were treated with gemcitabine as third-line/salvage chemotherapy.

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Case #1

A 67-year-old Hispanic male with locally advanced poorly differentiated pNET (encasement of superior mesenteric vessels and lymph nodes), was treated with a combination of etoposide and carboplatin as first-line chemotherapy. Carboplatin was chosen instead of cisplatin due to renal dysfunction. He achieved a partial response that persisted for a total of six months. A CT scan at the end of sixth months showed progressive disease with liver metastases. He was given a combination of capecitabine with temozolomide that kept his cancer in stable disease for another two months. The patient remained in Eastern Cooperative Oncology Group (ECOG) performance status of 1. Phase I studies were offered which he declined and therefore, other treatment options including irinotecan, gemcitabine and paclitaxel were offered. He preferred gemcitabine as he has a baseline diarrhea of 3-4 per day despite being on octreotide.

We chose gemcitabine at 1,000 mg/m^2 on days 1, 8 every 3 weeks due to history of neutropenia and thrombocytopenia with previous regimens. Restaging CT scan was performed every three cycles (9 weeks). After three cycles of gemcitabine, a CT scan showed stable disease. He continued gemcitabine for another three cycles (18 weeks) when the restaging CT scan showed 18% increase but stable disease. Therefore, we added erlotinib (100 mg) orally every day. CT scan after an additional three cycles (9 weeks) showed stable disease but patient requested to stop therapy. He decided to go for holistic treatment. He died 78 days later.

Case #2

A 56-year-old Caucasian male with a diagnosis of metastatic poorly differentiated pNET (para-aortic lymph nodes) was treated with a combination of etoposide and cisplatin as first-line chemotherapy. He achieved a minor response (18% shrinkage) that persisted for a total of four months. A CT scan at the end of the fourth month showed progressive disease with new liver metastases, bone lesions and mediastinal lymph nodes. He was treated with FOLFIRI (irinotecan, 5-fluorouracil and leucovorin). This regimen led to stable disease in pancreas, bones, lymph nodes and improvement in the liver. He continued FOLFIRI for a total of six months and then developed lung metastases. His ECOG performance status was 2 and gemcitabine was administered.

The patient received 1,000 mg/m^2 gemcitabine on days 1, 8 and 15 every 4 weeks. This schedule was chosen because of relatively young age and excellent performance status. After two cycles of gemcitabine (8 weeks), a CT scan of his abdomen showed stable disease. He continued gemcitabine for a total of six months, though required dose

Table 2. The table shows the median survival and 5-year survival rates reported for all NETs according to disease grade and stage.

		Local disease (50%)	Regional disease (23%)	Distant metastases (27%)
Well differentiated neuroendocrine tumors (G1, G2)	- Median survival duration	223 months	111 months	33 months
	- 5-year survival	82%	68%	35%
Poorly differentiated neuroendocrine carcinomas (G3)	- Median survival duration	34 months	14 months	5 months
	- 5-year survival	38%	21%	4%

Adapted from Yao JC *et al*., 2008 [2]

reduction (700 mg/m^2) from third cycle onwards due to recurring neutropenia and fatigue. At the end of the sixth month, the patient progressed with worsening liver metastases and declined in performance status. The patient was placed on hospice and died after 49 days.

Case #3

A 63-year-old Caucasian female with advanced poorly differentiated pNET (liver, lymph nodes, peritoneal), was treated with a combination of etoposide and cisplatin as first-line chemotherapy. She achieved partial response, but patient requested to stop chemotherapy due to nausea and fatigue after six months. She was followed with a CT scan every two months and the imaging at eighth month from the start of chemotherapy showed progressive disease with new liver metastases and prominent peritoneal studding. She received temozolomide monotherapy that resulted in stable disease. She continued temozolomide for approximately four months and then progressed with worsening liver metastases and ascites. The patient had ECOG performance status of 2. Among choices offered to her including phase I studies, she elected to receive gemcitabine.

The patient received 1,000 mg/m^2 gemcitabine on days 1, 8 and 15 every 4 weeks. After two cycles of gemcitabine (8 weeks), a CT scan of her abdomen showed minor response (overall 22% shrinkage). She continued gemcitabine for a total of six months. Although there was some increase in size of liver metastases at that time, overall her CT scan showed stable disease. The patient requested that the therapy would be stopped because of malaise and fatigue. She died 90 days later due to progressive cancer.

DISCUSSION

Gemcitabine is a deoxycytidine analog similar to the pyrimidine antimetabolite cytarabine, with activity against solid tumors. Gemcitabine is approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with pancreatic cancer, non-small-cell lung cancer and bladder cancer [8]. It is also commonly used in other gastrointestinal malignancies [9]. Poorly differentiated pNET is a rare neoplasm, associated with poor prognosis.

The review of literature revealed only one similar report in which the patient received gemcitabine as third-line therapy [10]. Another case reported benefit in a patient who received gemcitabine/ cisplatin based chemoembolization [11] and two cases treated with gemcitabine plus S-1 [12, 13]. Gemcitabine is an effective active agent against untreated and recurrent small-cell carcinoma of lung [14, 15]. The response rate to gemcitabine was reported to be 27% in patients with previously untreated small-cell carcinoma of lung [14]. In patients with previously refractory or recurrent small-cell carcinoma of lung, gemcitabine produced a response rate of 6-17% [15]. The efficacy of gemcitabine for poorly differentiated NET of the pancreas remains unclear and we believe that our case series provide more evidence that gemcitabine can offer palliative benefit to patients who have ECOG performance status 0-2 and are willing to receive more therapy.

The survival was 5.5, 8, and 9 months, respectively after the beginning of gemcitabine in these three patients. The median survival duration is 5 months in the patients with poorly differentiated pNET with the presence of distant metastases and our patients clearly lived longer by the addition of more chemotherapeutic agents to their treatment: the overall survival was 15.9, 17.5 and 19 months, respectively.

Other possible chemotherapeutic agents that may be used in this setting include paclitaxel, topotecan and irinotecan [16, 17, 18]. Each drug carries its specific side effects, but gemcitabine has the least gastrointestinal side effect and modest effect on bone marrow. In addition, gemcitabine is the most commonly used drug to treat pancreatic adeno-carcinoma and gives an ease to the treating oncologists as well [19]. Kulke *et al*. performed a phase II trial of gemcitabine for the treatment of metastatic NETs, but this study included various histological subtypes of NETs, and only two of the 18 patients had poorly differentiated NETs [20]. They reported stable disease in 65% of the patients and the median overall survival was less than one year. Gemcitabine was well tolerated.

FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) regimen has been investigated in a small trial of 39 patients [21]. Among the 19 patients treated with the FOLFIRI regimen, 6 (31.6%) had objective response, 6 (31.6%) had stable disease, and 7 (36.8%) had disease progression. Disease control (objective response + stable disease) was achieved in 8 of the 14 patients (57.1%) who received FOLFIRI after progression with etoposide-platinum combination. Median progression-free survival under FOLFIRI was 4 months. Overall survival was 18 *vs*. 6.8 months in non eligible patients. However, this regimen is only limited to patients with near-normal liver function tests [21]. Recent data also indicated a modest activity of temozolomide in pNET. A study by Welin *et al*. [22] showed that temozolomide alone or in combination with capecitabine and bevacizumab resulted in objective response or stabilization in 71% of pNET patients who failed on first-line chemotherapy.

We suggest that gemcitabine is a reasonable salvage therapy for patients with poorly differentiated

PNET. Most oncologists have experience administrating gemcitabine; its toxicity profile is quite favorable and both the dose and schedule can be modified if needed. Since the prognosis of this population is terribly poor, our case series and other reports provide a growing evidence supporting benefit of chemotherapy after first-line failure in selected patients with good performance status. In order to establish an effective second-line treatment options for these patients, we need cooperative efforts among institutions.

Declaration of interest The authors state no conflict of interest and have received no payment in preparation of this manuscript or conduct of the study

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