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Effect of Endostar combined with chemotherapy in advanced well-differentiated pancreatic neuroendocrine tumors

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Abstract

The aim of the present study was to assess the effect of Endostar and temozolomide or dacarbazine plus 5-fluorouracil (5-FU) in patients with advanced pancreatic neuroendocrine tumors (pNETs).

Phase II study of 14 patients with locally advanced or metastatic well-differentiated pNETs treated between April 2013 and September 2016. Patients received temozolomide or dacarbazine plus 5-FU, and Endostar. The primary outcome was the radiographic response rate.

All 14 patients had nonfunctional pNETs. Six patients received temozolomide and 8 received dacarbazine + 5-FU, combined with Endostar. Thirteen patients were assessable for treatment response: 1(7%) with complete response, 5 (39%) with partial response, 5 (39%) with stable disease, and 2 (15%) with progression. The median progression-free survival was 12 months. The most common grade 1/2 toxicities were neutropenia (43%) and leucopenia (21%).

Endostar combined with temozolomide or dacarbazine + 5-FU was effective in the treatment of advanced pNETs. The combinations were well tolerated.

Abbreviations: CAMS = Chinese Academy of Medical Sciences, CR = complete response, DTIC = dacarbazine, ECOG = Eastern Cooperative Oncology Group, 5-FU = 5-fluorouracil, mTOR = mammalian target of rapamycin, NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, NSCLC = nonsmall cell lung cancer, ORR = objective response rate, OS = overall survival, PD = progressive disease, PFS = progression-free survival, pNETs = pancreatic neuroendocrine tumors, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease, TEM = temozolomide, VEGF = vascular endothelial growth factor, VEGFR-TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitor, WHO = World Health Organization.

Keywords: dacarbazine, endostar, 5-fluorouracil, pancreatic neuroendocrine tumors, survival, temozolomide

1. Introduction

Advanced pancreatic neuroendocrine tumors (pNETs) have a more indolent course than other pancreatic malignancies, but they can be aggressive.[1] Analyses from the SEER data from 2000 to 2012 showed a median survival time of 60 months among patients with metastatic disease, and the 3- and 5-year survival rates were 62% and 50%, respectively.[2]

Randomized trials demonstrated antitumor activity of streptozotocin-based chemotherapy,[3,4] molecular-targeted agents (such as everolimus and sunitinib),[5,6] and somatostatin analog[7] in advanced pNETs. Nevertheless, the best sequence of therapies and patient stratification to different treatments remains challenging. Chemotherapy is especially used in pNETs with progressive nature or associated with higher tumor burden.[1,8,9] Retrospective studies revealed response rates of 25% to 42% with streptozotocin, supporting its role in the era of novel-targeted drugs,[10–12] but streptozotocin is not available in China. Some small studies reported promising results for temozolomide (TEM), another alkylating agent, as single or combination therapy in the treatment of unresectable pNETs, with response rates ranging from 30% to 70%.[13] Although TEM is less toxic and can be conveniently taken orally, it is expensive and not reimbursed by public health insurance in China. As a result, it cannot be afforded by many patients. Dacarbazine (DTIC) is an intravenous alkylating agent sharing the active metabolite metozolomide with TEM, but DTIC is much less expensive than TEM. Different regimens of DTIC (including DTIC monotherapy or in combination with 5-fluorouracil [5-FU] and epirubicin) have been used in NETs for more than 3 decades. The largest monotherapy study so far included 75 patients with NETs predominantly of pancreatic origin (50 patients) treated with 650 mg/m^2 DTIC every 4 weeks.[14] The objective response rate (ORR) was 32% and the treatment was well tolerated.

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pNETs are characterized by abundant vasculature and high levels of vascular endothelial growth factor (VEGF) expression. Targeting pathways involved in angiogenesis (e.g., using VEGF receptor tyrosine kinase inhibitors [VEGFR-TKIs] such as sunitinib) is of potential value in advanced pNETs. Endostatin is an endogenous angiogenesis inhibitor.[15] Endostar is a novel recombinant human endostatin expressed and purified in *Escherichia coli* with an additional 9 amino acid sequence forming another his-tag structure.[16] Endostar combined with chemotherapy prolonged overall survival (OS) compared with chemotherapy alone in advanced nonsmall cell lung cancer (NSCLC), and was approved by the State Food and Drug Administration of China in 2005 for the treatment of NSCLC.[17,18]

Nevertheless, the benefits of Endostar in pNETS are currently poorly known. Therefore, the present single-center phase II trial aimed to assess the treatment effect of a combination regimen of Endostar and TEM or DTIC plus 5-FU in a cohort of patients with advanced pNETs. All patients were followed for evidence of radiologic response, toxicity, and survival.

2. Materials and methods

2.1. Study design and patients

This was a phase II study (ClinicalTrial.gov #NCT01845675, retrospectively registered). The study population consisted of patients treated at the Department of Medical Oncology of Peking Union Medical College Hospital between April 2013 and September 2016. The study was approved by the ethics committee of Peking Union Medical College Hospital (S-530). The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

The inclusion criteria were: patients with histologically confirmed, locally advanced or metastatic pancreatic well-differentiated NETs (G1, G2, G3)[19,20] with radiologic progression within the previous 12 months; at least 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria[21] (lesions previously treated with radiation, cryotherapy, or chemoembolization were not considered measurable); Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better; life expectancy of at least 3 months; adequate hepatic, renal, and bone marrow function; one line of prior chemotherapy was allowed, with the exception of prior treatment with TEM, DTIC, 5-FU, or Endostar within the past 6 months; and prior systemic therapy (somatostatin analogs, VEGFR kinase inhibitor, or mammalian target of rapamycin [mTOR] inhibitor) other than chemotherapy and local therapy (chemoembolization or cryotherapy) was permitted if completed for at least 4 weeks before initiation of the trial.

The exclusion criteria were: concurrent use of therapies that may have treatment effect in NETs; or any severe and/or uncontrolled medical conditions or other conditions that could affect participation in the study.

2.2. Treatment strategy

Chemotherapy regimens were TEM or DTIC plus 5-FU. TEM was administered orally at 150 to 200 mg/m^2 per day on days 1 through 7. DTIC and 5-FU were both administered intravenously at 250 mg/m^2 per day and 500 mg/m^2 per day, respectively, on days 1 to 5. Endostar was administered intravenously at 15 mg/d on days 1 to 14. This cycle was repeated every 21 days. Dose adjustments for chemotherapy agents were made based on hematologic toxicity. Treatment was held if patients developed an absolute neutrophil count $<1000/mm^3$ or a platelet count $<50{,}000/mm^3$, and was not resumed until full hematologic recovery. On recovery, TEM treatment was resumed with a dose reduction of 50 mg/m^2, and with a 25% reduction in doses of DTIC and 5-FU. Treatment was also held for all nonhematologic toxicities of grade 2 or higher and resumed until recovery to grade 1 with a dose reduction of chemotherapy agents as in patients with hematologic toxicity. Patients who were unable to resume therapy within 4 weeks were removed from study treatment.

2.3. Imaging evaluation

Radiologic tumor assessments with contrast computed tomography or magnetic resonance imaging were performed at baseline and every 9 weeks after initiation of treatment. Radiologic response was classified according to the RECIST 1.1 criteria.[21] Chemotherapy and Endostar were given for no more than 8 cycles. Patients with evidence of response (complete response [CR] or partial response [PR]) to treatment or stable disease (SD) could receive TEM alone as maintenance therapy until there was evidence of progressive disease (PD) or unacceptable toxicity.

2.4. Definitions and outcomes

Progression-free survival (PFS) was defined as time from initiation of treatment until PD or death. OS was defined as time from initiation of treatment until death or last known follow-up.

The primary outcome of this study was to determine the radiographic response rate for the combination of Endostar and chemotherapy. Secondary outcomes included assessment of toxicity, PFS, and OS. Toxicities were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 4.0 criteria.

2.5. Statistical analysis

The statistical methods of this study were reviewed by XYY from Department of Biostatistics, Peking University Clinical Research Institute. This study used the Simon's minimax 2-stage design. Fourteen patients were required to reject a null hypothesis of an ORR $<15\%$ vs an alternative hypothesis of $\geq 45\%$. The study had an overall power of 80% and overall type I error of 0.05. Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NY). Continuous data were presented using median (range). Categorical data were presented as frequency (percentage). PFS and OS estimates were calculated using the Kaplan–Meier method.

3. Results

3.1. Characteristics of the patients

Between April 2013 and September 2016, 14 patients were enrolled in the study. Baseline characteristics of the patients are listed in Table 1. All patients had nonfunctional pNETs. Among the 14 patients, 9 had prior surgeries including 3 with primary tumor resection, 4 with primary tumor with liver metastases resection, 1 with liver metastasis resection, and 1 with palliative choledochojejunostomy with gastrojejunostomy.

3.2. Treatment

The patients received a median of 6 treatment cycles (range, 2–8 cycles). Of the 14 patients, 6 received TEM and 8 received DTIC +5-FU as chemotherapy combined with Endostar. Two patients

Table 1

Baseline characteristics of the patients.

Characteristics	Patients (n = 14)
Age, y, median (range)	48 (37–71)
Sex, n (%)	
Male	8 (57)
Female	6 (43)
ECOG performance status, n (%)	
0	14 (100)
Extent of disease, n (%)	
Locally advanced	2 (14)
Metastatic	12 (86)
Tumor grades, n (%)	
2	12 (86)
3	2 (14)
Ki67 index, median (range)	6 (3–30)
Organ type involved, n (%)	
Liver	11 (79)
Lymph nodes	4 (26)
Adrenals	1 (7)
Previous treatments, n (%)	
Surgery	9 (64)
Locoregional and ablative therapies	6 (43)
Somatostatin analog	5 (36)
Targeted therapy	5 (36)
Chemotherapy	1 (7)
Number of prior systemic therapy, n (%)	
0	6 (43)
1	5 (36)
2	3 (21)

(1 with PR and 1 with SD) underwent resection of liver metastases after 8 and 4 cycles of therapy, respectively. Five patients used TEM as maintenance therapy, for a median of 6 cycles (range, 2–18 cycles). Three patients discontinued maintenance therapy due to adverse events, 1 due to PD, and 1 due to economic reasons. Three patients with SD after 6 to 8 cycles of therapy were on observation instead of maintenance therapy, according to the patients' own decision.

Doses of TEM, DTIC, and 5-FU were adjusted to minimize the number of tablets or ampoules required. Thus, the actual average doses/cycle/day of TEM was 171 mg/m^2 daily (days 1–7). The actual average doses/cycle/day of DTIC and 5-FU were 245 mg/m^2 daily (days 1–5) and 475 mg/m^2 daily (days 1–5), respectively.

3.3. Treatment effect and survival

Thirteen out of 14 patients were assessable for treatment response. Five patients experienced PR and 1 experienced CR. One patient with radiologic PR response was revealed to be pathologic CR after liver metastases resection. The overall radiologic response rate was 46%. Five (39%) patients experienced SD, and only 2 patients (15%) experienced PD as their best response to therapy (Fig. 1).

In July 2017, the median follow-up time of the patients was 20 months (range, 10–51 months). Eight patients developed PD. The median PFS was 12 (95% confidence interval 0.000–30.118) months (Fig. 2), while median OS was not reached.

3.4. Toxicities

All 14 treated patients were assessable for toxicities (Table 2). Only 1 patient developed grade 3 lymphopenia (nadir 490/mm^3) and subsequent grade 2 herpes zoster limited to 1 dermatome after 15 months of maintenance therapy. One (7%) patient discontinued treatment because of recurrent grade 2 liver enzyme elevation after 2 cycles of therapy (DTIC + 5-FU + Endostar). The most common grade 1/2 toxicities were neutropenia (43%) and leucopenia (21%). One patient developed transient grade 2 rash during the second cycle, was resolved after taking antihistamine medicine, and did not recur during the following 4 cycles. All of the toxicities except for rash were attributed to chemotherapy.

4. Discussion

In this study, we observed an objective radiographic response rate of 46% among patients with advanced pNETs treated with Endostar combined with chemotherapy. Of the 13 assessable patients, 1 patient (Endostar with TEM) achieved radiologic CR and had a disease remission of 25 months. One patient (Endostar with DTIC + 5-FU) who achieved radiologic PR was revealed to be a case of pathologic CR after liver metastases resection, and had

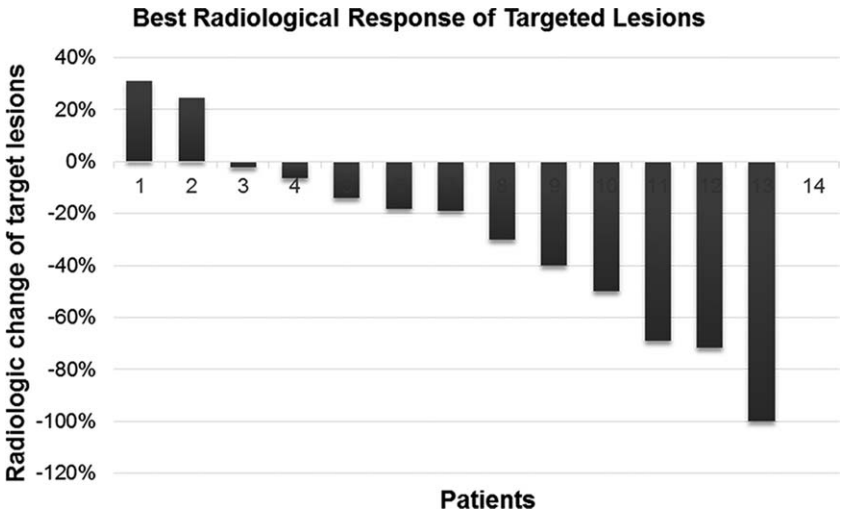

Figure 1. Waterfall plot illustrating the best radiologic response in each patient.

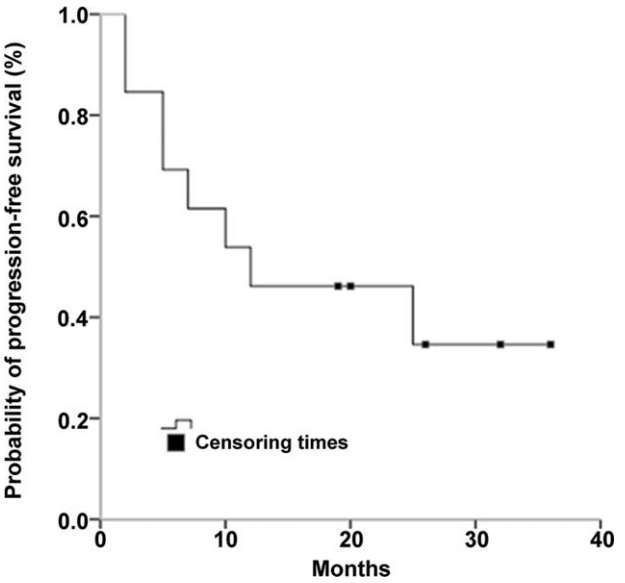

Figure 2. Progression-free survival of the patients.

been disease free for 28 months. Taken together, the results suggest that the study regimen could effectively reduce the tumor burden. Although the optimal sequence of treatments for pNETs has not yet been determined, the ORR seemed not affected by prior systemic therapies (no therapy vs prior therapy: 33% vs 50%).

In the present study, 2 patients with Ki67 index >20% (25% and 30%, respectively) were classified as NET G3 according to the World Health Organization (WHO) classification criteria of 2017 and enrolled in this study. Their best response was SD and PR, respectively, suggesting that the study regimen may be active for NET G3. NETs G3 are more commonly originating from the pancreas than from the gastrointestinal tract or lung.[2,22,23] They are more progressive than NET G1 and G2, and generally have a poorer prognosis.[22,23] Although the ENETS guideline recommends streptozotocin-based chemotherapy for pNETs G3,[24] there is no evidence-based treatment for this group of patients so far, and a clinical trial (ClinicalTrial.gov #NCT02113800) using everolimus after progression of chemotherapy is currently ongoing.

Prospective randomized clinical trials of chemotherapy in advanced NETs are rare. The E2211 trial suggests that TEM and capecitabine led to a better PFS than TEM alone in advanced low or intermediate grade pNETs.[25] A number of small prospective and retrospective studies have shown an anti-tumor effect of chemotherapy regimens comprising alkylating agents such as streptozotocin, TEM, DTIC, and other cytotoxic agents in well-differentiated pNETs (reviewed by Krug et al[9]). The reported response rates of chemotherapy were higher than the response rates demonstrated in phase III randomized trials of somatostatin analogs or molecular-targeted drugs, which were <10%. The TEM-based chemotherapy combination regimen includes TEM with capecitabine, thalidomide, or bevacizumab.[26–29]

Our study initially used Endostar combined with TEM, but the high cost of TEM limited the enrollment; thus, DTIC combined with 5-FU was used as an alternative to TEM. Previous studies of DTIC-based chemotherapy included monotherapy and combination therapy, with response rates in pNETs ranging from 32% to 58%.[14,30,31] Taking into account the 3-week cycle of Endostar and the toxicity of DTIC-based therapy, DTIC combined with 5-FU for 5 days every 3 weeks was applied. Although more than half of the patients used the DTIC+5-FU regimen, the results showed a low incidence of adverse reactions, with only 1 patient developing grade 3 lymphopenia after 15 months of TEM maintenance. No grade 3 or grade 4 nonhematologic adverse events occurred. As an anti-angiogenic agent, Endostar showed good safety profile and tolerance in previous studies, without toxicities commonly seen with other VEGF or VEGFR inhibitors, such as hypertension and proteinuria.[17,18,32–34] Chan's phase II study used the combination of TEM and bevacizumab for the treatment of advanced NETs (15 patients with pNETs), and the incidence of grades 3 and 4 lymphopenia and thrombocytopenia was 53% and 18%, respectively.[29] The ORR in pNETs patients was 33%, and the median PFS was 14.3 months.[29] Similar to our study, the study also used a combination of chemotherapy and anti-angiogenic-targeted agent, but with more toxicities, while the efficacy was not superior to what was seen in the present study. The higher incidence of toxicities was probably attributed to the higher dose density of TEM in their study.

Except for above-mentioned chemotherapy agent combination or chemotherapy with angiogenesis inhibitor, phase II studies using combination of mTOR inhibitor and bevacizumab also showed high response rates in patients with advanced pNETs. The CALGB 80701 phase II trial showed that treatment with everolimus and bevacizumab led to superior ORR than treatment with everolimus alone (31% vs 12%, $P = .005$) in patients with pNETs, but also led to more adverse events.[35] A phase II trial by Hobday et al[36] showed that the combination of temsirolimus and bevacizumab had substantial activity and reasonable tolerability with ORR of 41% in patients with progressive metastatic pNETs. Thus the wide selection of available agents for combination is a challenge and additional studies are necessary to determine the optimal approach.[37]

The present study is not without limitations. First, the patients used different chemotherapy regimens and the comparison of the 2 regimens was not possible due to the small number of patients. Secondly, although Endostar has few side effects, the 14-day infusion regimen would affect patients' compliance. Subcutaneously injected Endostar is being tested in a phase I study (ClinicalTrial.gov #NCT02652234) in NSCLC. If the efficacy of subcutaneous Endostar is comparable to the intravenous form, it would be easier for clinical use. Thirdly, 3 patients in our study were unable to afford the maintenance therapy of TEM and discontinued treatment. Although the optional treatment cycles and duration of chemotherapy are still unknown, a retrospective study of TEM plus capecitabine showed that maintenance

Table 2

Adverse events.

Adverse events	Grade 1	Grade 2	Grade 3
Hematologic, n (%)			
Anemia	1 (7)		
Leucopenia	3 (21)		
Neutropenia	6 (43)		
Lymphopenia		2 (14)	1 (7)
Thrombocytopenia	2 (14)		
Nonhematologic, n (%)			
Nausea	2 (14)		
Elevated liver enzyme		2 (14)	
Herpes zoster		1 (7)	
Fatigue	2 (14)		
Rash		1 (7)	

therapy until progression is appropriate for patients who were progression free at 6 months and had good tolerance to treatment.[38] The early discontinuation of chemotherapy may be one of the reasons for the relatively short PFS in this study.

In conclusion, the present study showed a high ORR and low toxicity rates of Endostar combined with chemotherapy for the treatment of advanced pNETs. These results probably warrant the implementation of multicenter clinical trials using the same approaches.

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