

Combination of capecitabine and oxaliplatin is an effective treatment option for advanced neuroendocrine tumors

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Abstract

The role of chemotherapy in well differentiated neuroendocrine tumors (NET) has been questioned. It was recently demonstrated that everolimus and sunitinib have activity in low and intermediate grade pancreatic NET. The aim of this study was to evaluate the activity of capecitabine and oxaliplatin (CapOx) combination in treating NET in an unselected population. In this regard, we retrospectively evaluated 24 patients diagnosed with metastatic NET treated with CapOx at two Brazilian institutes that are reference centers in cancer care. Tumor response was measured by RECIST criteria. Median age at diagnosis was 56 years, 71% had ECOG 0 or 1, the majority of tumors were primary from pancreas (67%) followed by lung (17%), and 29% were functional. According to WHO classification criteria, 25% were grade 1, 37.5% grade 2 and 37.5% grade 3. Most patients received CapOx as second-line therapy, with a median of 6 cycles. Twenty-nine percent of patients had partial response by RECIST criteria. No association was observed between response rate and tumor grade, primary site or line of CapOx. The median time to progression was 9.8 months and median time to treatment failure was 12.1 months. Seventy-five percent of patients are alive at the time of this analysis; therefore, median overall survival was not reached. The CapOx combination was shown to be active in an unselected population with metastatic NET and may be a good platform for the incorporation of the newer molecular targeted agents being investigated for the treatment of this entity.

Introduction

Neuroendocrine tumors (NET) make up a broad spectrum of malignancies with different biological behavior, varying from indolent to highly proliferative and aggressive disease.

They can arise from neuroendocrine cells throughout the body and may produce active peptides that cause hormonal syndromes.¹

According to the SEER database, the incidence and prevalence of NET has increased substantially over the past 30 years, which may in part reflect the availability of better diagnostic techniques, advances in immunohistochemistry, new diagnostic biomarkers and a better understanding of this entity.^{1,2}

Approximately 30% of patients present when symptoms become evident and are found to have distant metastatic disease. Prognostic factors include differentiation, grade, disease stage, and primary site.² According to the recently published WHO grading system based on mitotic rate and Ki67 index, NET can be classified as: grade 1, <2 mitoses per 2 mm² and/or Ki-67 index ≤2%; grade 2, 2-20 mitoses per 2 mm² and/or Ki-67 index between 3% (intended as >2%) and 20%; or grade 3 with >20 mitoses per 2 mm² and/or Ki-67 index >20%.³ The median overall survival (OS) of patients with metastatic NET is nearly three years for grade 1 tumors, approximately twenty-four months for grade 2, and in the range of ten months for grade 3.²

Due to the heterogeneity of disease biology, there is no standard approach to the management of metastatic NET. Therapeutic options include cytoreductive surgery, somatostatin analogs, peptide receptor radionuclide therapy (PRRT), liver-directed therapy such as arterial embolization, chemoembolization, radiofrequency ablation or cryotherapy and cytotoxic therapy.⁴ Biologics and chemotherapy agents that have been mostly evaluated in NET include interferon (IFN) associated with somatostatin analogs, temozolomide associated with thalidomide or capecitabine, dacarbazine, bevacizumab and fluorouracil. However, the only FDA approved cytotoxic combination is the fluorouracil, adriamycin and streptozotocin (FAS) regimen that demonstrated some activity in grade 1 or 2 pancreatic NET.⁵⁻⁷ For grade 3 disease, chemotherapy combinations based on cisplatin or carboplatin associated with etoposide (VP-16) or irinotecan (CPT-11) have been used in analogy to small cell carcinoma of the lung.⁸ Recently, sunitinib and everolimus have been approved for the treatment of grade 1 or 2 pancreatic NET, showing increased progression free survival (PFS) when compared to placebo.^{9,10}

The majority of patients with metastatic NET are not curable and will eventually need chemotherapy in the course of their disease, either by presenting as an aggressive, poorly differentiated tumor or by transformation of a previous indolent, well differentiated neoplasia into a more aggressive carcinoma. Considering the few effective systemic therapeutic options available for this emerging population, and based on previous data showing

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encouraging results of the capecitabine and oxaliplatin combination in the metastatic NET scenario, we aimed to evaluate the activity of capecitabine and oxaliplatin (CapOx) in treating unselected patients with metastatic NET.¹¹

Materials and Methods

Patients

We retrospectively evaluated 24 patients diagnosed with metastatic NET treated with CapOx at two Brazilian institutions: Hospital SíríoLibanês (HSL) and Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina, Universidade de São Paulo (ICESP) between November 2003 and February 2011. Approval for data collection and analysis was obtained from each institutional ethics committee. Patients were eligible if they had biopsy proven metastatic NET with measurable disease on computed tomography (CT) or magnetic resonance imaging (MRI), pathology description of the proliferative Ki67 index determined by immunostaining, had radiological evidence of disease progression and had received at least two cycles of CapOx.

Chemotherapy

The regimen consisted of oral capecitabine 2000 mg/m² starting on Day 1 for 14 consecutive days, and intravenous 100 to 130 mg/m² bolus oxaliplatin on Day 1, repeated every three weeks. Full blood counts and biochemistry were obtained before each chemotherapy cycle in all patients. Dose reductions were performed if grade 3 or 4 toxicity was observed. Toxicity information was collected retrospectively from the medical notes and classified according to the National Cancer Institute Common Toxicity Criteria Version 4.0. Only grade 2 or more adverse events reported in the patient chart were considered for analysis. Chemotherapy was continued until disease progression, unacceptable toxicity or patient intolerance.

Evaluation of tumor response

All patients were evaluated for response by complete physical examination and imaging (CT or MRI). The images were reviewed by the same radiologist (LTS). Tumor assessment was performed every 2 or 3 cycles of chemotherapy and toxicity was reported at each cycle as part of standard-of-care. Response to treatment was evaluated using the Response Evaluation Criteria In Solid Tumors (RECIST version 1.0):¹² complete response (CR) was defined as the disappearance of all lesions, partial response (PR) was

defined as at least a 30% reduction in the tumor load, progressive disease (PD) was defined as at least a 20% increase in the tumor load, and stable disease (SD) was defined as disease that showed neither sufficient shrinkage nor increase to qualify as PR or PD.

Statistical analysis

Descriptive statistics were used to report continuous and categorical variables. Time to event variables were analyzed by the Kaplan Meir method. Time to tumor progression (TTP) was defined as the time between the first dose of CapOx and documentation of radiological progression or death. Losses to follow-up were censored. We also calculated the time to treatment failure (TTF) which measured the interval from the first dose of Capox to the first dose of another systemic treatment. This end point was chosen as clinically valuable because some patients achieved long-term stable disease with CapOx and were re-challenged later with the same regimen. Median overall survival was not reached at the cut-off date for analysis (February 20th, 2011). The comparisons between response rate and tumor grade, primary site and line of CapOx were based on χ^2 and Fisher's exact tests, as appropriate. $P < 0.05$ was considered statistically significant, after adjusting for multiple comparisons with the Bonferroni method. All analyses were carried out as intention-to-treat.

Results

We identified 32 patients with metastatic NET who were treated with CapOx. Out of the 32 patients, 24 (17 male and 7 female) met eligibility criteria. Four patients did not have images available for radiology review and 4 patients received one or two cycles of CapOx, and could not be evaluated for response at the cut-off date for this analysis.

The median age at the time of diagnosis was 56 years (range 23 to 73 years) and 71% of patients had ECOG performance status 0 or 1. The most common primary tumor site was pancreas (n=15, 63%), followed by lung (n=4, 17%). Liver was the main site of metastases (96%). Seven patients (29%) had functional syndrome: 1 VIPoma, 2 insulinomas and 4 had carcinoid syndrome. The majority of patients had grade 2 and 3 NET. Patient's characteristics are listed in Table 1.

Treatment

Ten patients (42%) had been previously treated locally: 7 patients underwent surgery (30%), 2 underwent hepatic artery embolization (8%) and one received chemoembolization (4%). CapOx was used as first-line therapy in 50% of patients. The median number of cycles was 6 (range 2 to 13). Out of the 24 patients treated with CapOx, 7 were kept in

Table 1. Patients characteristics.

	N.	%
Sex		
Male	17	71
Female	7	29
Performance status		
ECOG 0	5	21
ECOG 1	12	50
ECOG ≥ 2	7	29
Primary site		
Pancreas	15	63
Lung	4	17
Small intestine	2	8
Unknown	2	8
Rectum	1	4
Functional syndrome		
Carcinoid syndrome	4	17
Insulinoma	2	8
VIPoma	1	4
Grade		
Grade 1	6	25
Grade 2	9	37.50
Grade 3	9	37.50
Metastatic site		
Liver	23	96
Lymph nodes	18	75
Peritoneum	6	25
Bone	4	17
Others	5	21

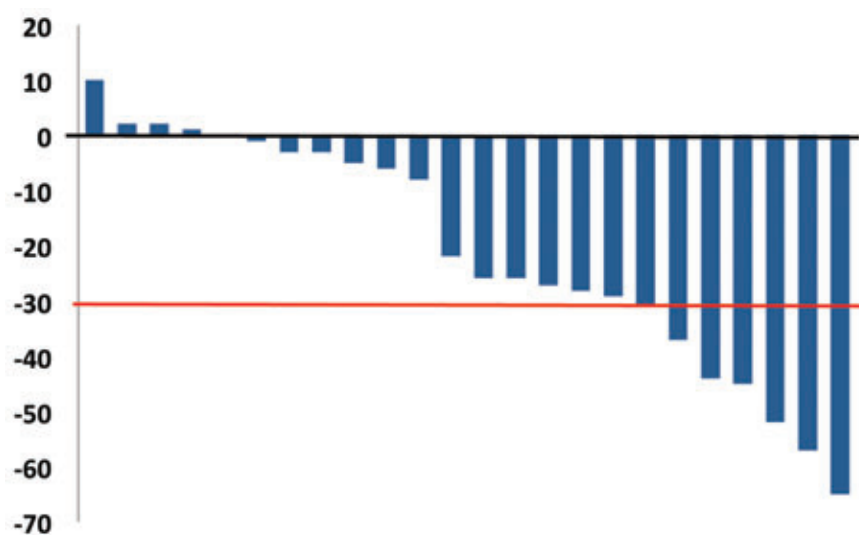


Figure 1. Waterfall plot demonstrating the percentage variation of tumor lesion size. Red line indicates 30% shrinkage (Partial response by RECIST criteria).

maintenance treatment after maximum response: 4 received capecitabine monotherapy, 2 everolimus and 1 somatostatin analog. Treatment characteristics are listed in Table 2.

The CapOx regimen was generally well tolerated. Six patients (25%) experienced grade 3 toxicity and 15 patients (63%) had grade 2 toxicity, with the most common being peripheral neuropathy, hand-foot syndrome and diarrhea. Dose reduction was necessary in 8 patients (33%). Only one patient discontinued treatment due to side effects. There was no hospitalization or death associated to treatment. Toxicity profile associated with the CapOx regimen is described in Table 3.

Clinical outcomes

Out of the 24 patients who were available for analysis, 7 (29%) achieved a partial response (PR). The waterfall plot demonstrating the percentage of tumor size change following CapOx treatment is shown in Figure 1. Stable disease (SD) was the best response achieved by 17 (71%) patients. There was no significant statistical association between RR and either tumor grade, primary site or line of CapOx administration. Median TTP was 9.8 months (range 7.4 to 12.2 months; 8 patients censored) and median TTF was 12.1 months (range 6.9 to 17.2 months; 11 patients censored). Only 6 patients had died until the cut-off date for analysis, so median OS was not reached. Kaplan-Meier curves showing TTP and TTF are presented in Figures 2 and 3, respectively.

Discussion

Our analysis including 24 unselected patients with advanced NET treated with CapOx demonstrated that 29% achieved PR with this chemotherapy regimen. The TTP of

Table 2. Treatment characteristics.

	N.	%
Local treatment pre-CapOx		
Surgery (primary site)	1	4
Metastectomy (hepatic resection)	6	25
Embolization	2	8
Chemoembolization	1	4
Systemic treatment other than CapOx		
Somatostatin analogs +/- INF	11	46
Cisplatin or carboplatin + VP-16 or CPT-11	8	33
Capecitabine	5	21
Lutecium radioligand therapy	5	21
Everolimus	5	21
Others	6	25
Cisplatin or carboplatin + taxane	2	8
5-FU + adriamycin + streptozotocin (FAS)	2	8
Line of CapOx		
First	12	50
Second	6	25
Third or beyond	6	25
Maintenance treatment post-CapOx		
Capecitabine	4	17
Everolimus	2	8
Somatostatin analogs	1	4

Median n. cycles of CapOx 6 (range 2-13). INF, interferon; VP-16, cisplatin or carboplatin associated with etoposide; CPT-11, irinotecan; 5-FU, fluorouracil; FAS, fluorouracil + adriamycin + streptozotocin.

Table 3. Grade 2 and 3 toxicities associated with the CapOx regimen (total n. patients=24).

	Grade 2 (N)	%	Grade 3 (N)	%	Total n.	% of total
Overall toxicity						
Grade 2					15	63
Grade 3					6	25
CapOx dose reduction					8	33
Hospitalizations						
Disease-related					4	17
Treatment-related					0	0
Infection (not due to neutropenia)					3	13
Main reported toxicities						
Neuropathy	7	29	2	8	9	37
Hand-foot syndrome	3	13	1	4	4	17
Diarrhea	1	4	2	8	3	12
Hematologic toxicity (neutropenia)	1	4	0	0	1	4
Nausea	2	8	0	0	2	8
Asthenia	1	4	0	0	1	4
Oxaliplatin hypersensitivity reaction	0	0	1	4	1	4

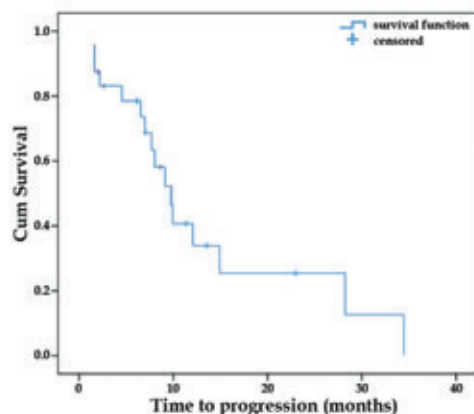


Figure 2. Time to tumor progression (TTP). Blue line demonstrates median TTP of 9.8 m (range 7.4-12.2 m). N. progressions=16; patients censored=8.

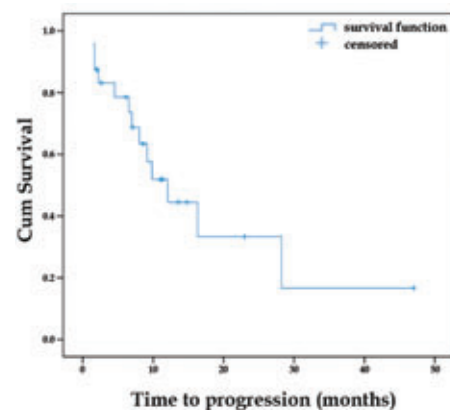


Figure 3. Time to treatment failure (TTF). Blue line demonstrates median TTF of 12.1 m (range 6.9-17.2 m). N. patients who failed CapOx=13; patients censored=11.

9.8 months and TTF of 12.1 months is compatible with an active regimen and is comparable with the current available therapeutic options.^{7,9,13,14}

Somatostatin analogs alone or in combination with IFN can be used to manage hormonal symptoms, and it has recently also been shown to improve PFS in well differentiated, low volume midgut NET, but rarely results in tumor shrinkage.^{15,16} For more advanced grade 2 and 3 tumors, somatostatin analogs offer limited antitumor effect. Combinations including streptozotocin with fluorouracil and doxorubicin (FAS) have yielded variable results with RR varying from 6% to 39% for pancreatic NET, depending on the method used for response assessment.^{5,14,17} Dacarbazine has shown some degree of activity, with RR between 8% and 15% in carcinoid tumors and 33% in pancreatic islet cell carcinoma. However, concerns about toxicity have precluded its widespread use.^{18,19} The combination of temozolomide and thalidomide in 29 patients with metastatic NET demonstrated an objective RR of 25% and better toxicity profile than dacarbazine alone.²⁰ More recently, retrospective data has shown promising activity of the combination of temozolomide and capecitabine in first-line treatment of G1 and G2 pancreatic NET, yielding a RR of 70% (21 in 30 patients) and a median PFS of 18 months, making the temozolomide combinations an attractive option for the treatment of NET.²¹ Other drugs combinations as bevacizumab and pegylated interferon alfa-2b or gemcitabine and oxaliplatin have shown RR of approximately 15%.^{7,13} Single agents such as docetaxel, paclitaxel, gemcitabine and pemetrexed have shown little, if any, activity in the metastatic NET scenario (RR 0-8%) and are not routinely recommended in clinical practice.²²⁻²⁵

In spite of the heterogeneous results obtained with the FAS regimen, it is still the most accepted chemotherapy combination for pancreatic NET. Streptozotocin is not commercially available in Brazil and is fairly toxic, which limits its use. In our study, the CapOx combination evaluated in 15 patients with pancreatic primary tumors resulted in 4 PR according to RECIST criteria (26.7%), which is comparable to the results of the FAS regimen.

The activity of the CapOx combination has been previously evaluated in a phase II Italian study including 40 patients with advanced NET.¹¹ The population consisted of 13 poorly differentiated and 27 well-differentiated NET patients whose tumors had progressed after somatostatin analogs. The RR, evaluated according to the WHO criteria (decrease in 50% tumor burden),²⁶ symptoms and changes in tumor marker, was 23% in the high-grade and 30% in the low-grade populations with a median TTP of 18 months and OS of 32 months. The authors concluded that while

CapOx may be a good option for well-differentiated NET, it may not be a good choice for first-line treatment of high-grade NET when compared to historical data of patients treated with cisplatin and VP-16. However, the RR achieved with cisplatin and VP-16 combination has been inconsistent, varying according to the series between 14% and 67%.^{27,28} Our study included 9 patients with grade 3 NET: 6 received CapOx as first-line and 3 as second or further lines, with a median of 8 cycles. We observed 2 PR and 2 additional patients had at least 25% shrinkage in tumor load, suggesting CapOx may also be a salvage therapeutic option for poorly differentiated NET.

Another fluoropyrimidine-based regimen, FOLFOX (5-fluorouracil, leucovorin and oxaliplatin) associated with bevacizumab, was prospectively evaluated by Venook *et al.* in 13 patients with metastatic NET,²⁹ showing similar results to the CapOx combination (RR of 20% for carcinoid tumors and 33% for pancreatic NET). However, significant toxicity associated with bevacizumab was observed, with one arterial thromboembolic event and one death due to intestinal perforation. Sunitinib, a multi-targeted tyrosine kinase inhibitor, and everolimus, an inhibitor of mammalian target of rapamycin (mTOR), were recently approved for treatment of low or intermediate grade pancreatic NET, showing a RR of approximately 10% and a median PFS of 11 months, which is comparable to our results. These targeted agents were tested in a population that had previously received local treatment or systemic therapy, making these drugs good options for patients who progress after chemotherapy, or as front-line therapy for asymptomatic patients with low disease burden.^{9,10}

Considering the available options, our results demonstrate that the CapOx combination has promising activity in metastatic NET. This study is limited by its retrospective nature, the long period of patient recruitment and recognition that the data is still immature, with a high number of patients being censored and median OS not reached. In spite of this, the results are comparable with the published trial evaluating the same drug combination and has shown similar activity to the FAS and the temozolomide-based regimens.¹¹

Conclusions

Metastatic NET is an heterogeneous and deadly disease, and due to the small patient population, data from large randomized trials are scarce. The CapOx regimen has shown to be active and well tolerated in an unselected population with metastatic NET and may be a good platform for the incorporation of the

newer molecular targeted agents being investigated for the treatment of these tumors. Despite the need for longer follow up to better assess outcomes; the presented data support the inclusion of CapOx as an option in the management of metastatic NET.

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