

Metronomic capecitabine in gastroenteropancreatic neuroendocrine tumors: a suitable regimen and review of the literature

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Background: We present a retrospective analysis of metronomic capecitabine in metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs). A review of the literature is also presented.

Methods: From January 2007 to December 2013, ten patients with metastatic GEP-NETs (four pancreatic and six ileal) who progressed after treatment with somatostatin analogs and other cytotoxic agents received oral capecitabine 1,500 mg/day continuously. The median patient age was 68 (range 29–82) years. The median treatment duration was 8 months.

Results: Five (50%) patients achieved a partial radiographic response, four (40%) showed stable disease, and one (10%) progressed. Median overall survival was 56 months. Three of the four pancreatic patients achieved a partial radiographic response that lasted for a median of 15.5 months; overall survival and progression-free survival in this subgroup was 58 and 6 months, respectively.

Conclusion: Data in the literature show that capecitabine has only occasionally been used as a single agent, with increased toxicity. Only one study using single-agent capecitabine reported a progression-free survival of 9.9 months and overall survival of 36.5 months, without an objective response or major toxicity. In our experience, metronomic capecitabine was well tolerated, although minor side effects may have been underestimated due to the retrospective nature of our study. This regimen also seems to be feasible in elderly people. Although high response rates and prolonged response duration indicate the potential efficacy of this treatment, our results should be interpreted cautiously because of the small number of patients involved. Capecitabine was most effective in the pancreatic subgroup, which would seem to be more sensitive to chemotherapy.

Keywords: capecitabine, gastroenteropancreatic neuroendocrine tumors, metronomic chemotherapy

Introduction

Neuroendocrine tumors (NETs) are neoplasms arising from cells of the endocrine system and represent a heterogeneous group of tumors that originate from the embryological gut. In particular, gastroenteropancreatic (GEP)-NETs are located in the gastric mucosa, small and large intestine, rectum, or pancreas.¹ Although the incidence of these tumors is low (5.25 per 100,000 per year), the incidence has increased significantly in recent years, and because of the long survival of these patients, prevalence is high (35 per 100,000 per year).² A number of these tumors produce hormones, neuropeptides, or neurotransmitters, which cause specific syndromes in relation to the hormone released. The medical approach to metastatic disease depends on the anatomical origin,

degree of differentiation, and endocrine function of the tumor, and includes numerous therapeutic options.^{3,4}

Currently, the most widely used therapeutic option for well and moderately differentiated metastatic NETs after somatostatin analog treatment is targeted therapy (everolimus or sunitinib).^{5,6} However, chemotherapy still plays a role in this type of patient. In fact, although well differentiated NETs do not show high sensitivity to chemotherapy because of low mitotic rates, high levels of the antiapoptotic protein bcl-2, and increased expression of the multidrug resistant gene, pancreatic endocrine tumors appear to be more sensitive to cytotoxic chemotherapy than other types of neuroendocrine malignancies.^{7,8} In particular, in recent years, streptozotocin-based chemotherapy regimens have obtained good objective response rates and led to an improvement in overall survival.^{9,10} Although the pyrimidine analog 5-fluorouracil (5-FU) is often used in combination with streptozotocin, toxicity remains an issue, highlighting the need to improve tolerability without compromising efficacy.^{11,12} Other therapeutic agents such as cisplatin used in association with etoposide or irinotecan would appear to be less effective in well to moderately differentiated NETs than in poorly differentiated ones.^{13,14}

Capecitabine, a 5-FU prodrug, used alone or in combination with other agents, has produced an exceptionally promising response rate and response duration, with acceptable toxicity. In a case report published in 2007, a 51-year-old male with multiple metastatic liver lesions from a moderately differentiated pancreatic NET treated with capecitabine alone achieved a complete remission and showed good tolerance to therapy.¹⁵ In other malignancies, different schedules of capecitabine have been used to improve tolerability without compromising efficacy.^{16,17} Metronomic chemotherapy (MCT) refers to the administration of low doses of cytotoxic agents given orally, in most cases, over a prolonged period of time or with only short drug-free intervals. MCT has proven more effective in overcoming acquired tumor resistance to chemotherapy than standard antitumor regimens and also in counteracting tumor regrowth caused by neoangiogenesis and revascularization, which may occur between chemotherapy cycles.^{18,19} In addition to these mechanisms, some preclinical models of MCT in different tumors have been shown to activate innate immunity, inducing tumor cell cytotoxicity, depletion of regulatory T-cells, and improved antitumor immune response.^{20,21} Recently, several trials were published on the efficacy of metronomic capecitabine used alone or in combination with other agents in different tumor types, such

as breast or hepatocellular carcinoma, showing good response and tolerability.^{22–24}

On the basis of these data, we treated ten patients with low-grade or intermediate-grade metastatic GEP-NETs using a metronomic schedule of capecitabine. The present study retrospectively evaluated the overall response rate, progression-free survival, overall survival, and toxicities of this therapeutic approach. We also performed a review of the literature, focusing on the role of capecitabine alone or in combination with other agents in the treatment of NETs.

Patients and methods

Our study evaluated ten patients with metastatic G1–G2 GEP-NETs who received metronomic therapy with capecitabine from January 2007 to December 2013. All patients were progressing after treatment with somatostatin analogs and other cytotoxic agents. Poorly differentiated tumors were excluded from analysis.

The patients received continuous oral capecitabine 1,500 mg daily in three divided doses. Treatment was discontinued in the event of unacceptable toxicity or disease progression. All patients underwent a computed tomography scan within 9 weeks of starting capecitabine and were followed up every 3 months. Response to treatment was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) parameters. Toxicity was assessed using NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) version 4.0. Progression-free survival was defined as the time from the start of treatment to disease progression or death. Overall survival was defined as the time from the start of treatment until death or last known follow-up. Standard search methods were used to identify publications on the use of capecitabine to treat patients with NETs.

Results

Ten patients (six males, four females) were included in our analysis. Median age at onset of treatment was 68 (range 29–82) years. Sites of the primary tumor were the ileum (six patients) and the pancreas (four patients). All tumors were nonfunctioning GEP-NETs. Patient characteristics are reported in Table 1. Five patients had previously undergone induction therapy with octreotide acetate 30 mg every 28 days because of its antiproliferative effect and continued to receive it during treatment with capecitabine. The median time from diagnosis to the start of capecitabine treatment was 21 (range 8–34) months.

Table 1 Patient characteristics

	n
Median age, years (range)	68 (29–82)
Sex	
Male	6
Female	4
ECOG	
0	9
I	1
Primitive	
Pancreas	4
Ileum	6
Tumor	
Nonfunctioning	10
Functioning	0
Grading	
G1	4
G2	6
Prior treatment	
SST analogs	5
Other CHT	1
PRRT	3
None	2
Metastatic sites	
Liver	10
Nodes	3
Peritoneum	2
Other	3

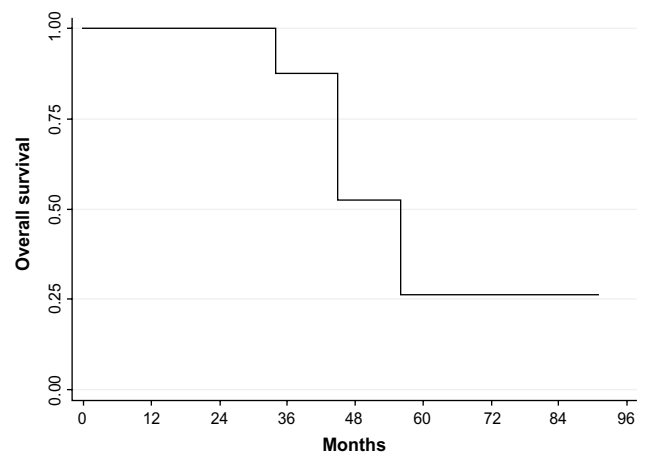
Abbreviations: CHT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; PRRT, peptide receptor radionuclide therapy; SST, somatostatin.

Efficacy

All patients were evaluable for response. Five patients (50%) achieved a partial radiographic response to chemotherapy, four (40%) achieved stable disease, and one (10%) showed progressive disease. The median duration of treatment was 8 months. Only one patient discontinued treatment to shift to a new targeted therapy. Median overall survival was 56 months (see Figure 1) and median progression-free survival was 8 months (see Figure 2). In particular, three of the four patients in the pancreas subgroup achieved a partial radiographic response and maintained it for a median of 15.5 months. Median progression-free survival was the same in the pancreatic and ileal subgroups (6 months), and median overall survival in the two subgroups was 58 and 45 months, respectively (see Figure 3).

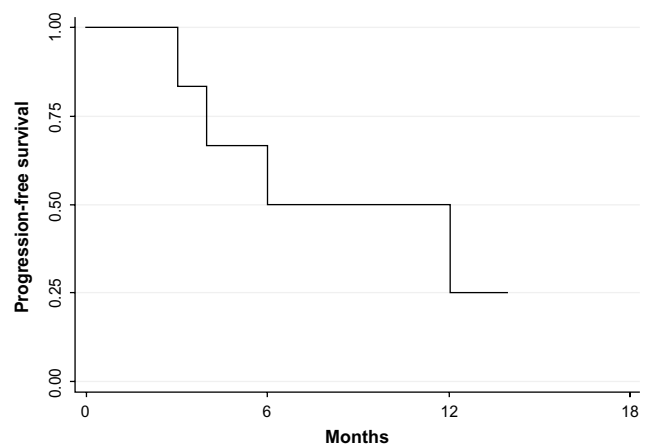
Toxicity

The most common side effects were fatigue and nausea. One patient experienced grade two hand-foot syndrome and one had grade two mucositis. No treatment-related deaths were observed. There were no cases of grade three or four hematological toxicity, and none of the patients discontinued treatment due to unacceptable toxicity (see Table 2).

**Figure 1** Overall survival in all patients.

Literature review

NETs are a group of heterogeneous tumors that vary widely in their presentation and prognosis, which is reflected in the different therapeutic strategies used. Over the years, numerous chemotherapeutic agents, such as streptozotocin, temozolomide, and 5-FU, have been used to treat this tumor, with varying degrees of efficacy and toxicity. Based on the promising data obtained with 5-FU, capecitabine has also been tested alone or in combination with other agents for the treatment of metastatic disease, with good results. The first study using capecitabine was published by Bajetta et al in 2006, and reported on 40 patients with advanced NETs treated with the XELOX regimen (intravenous oxaliplatin 130 mg/m² on day 1 and capecitabine 2,000 mg/m² from days 2–15, every 3 weeks). Thirteen patients had high-grade NETs and 27 had low-grade tumors according to the 2004 World Health Organization classification. Twenty-seven of the 40 patients received concomitant treatment with somatostatin analogs. The most important responses were seen

**Figure 2** Progression-free survival in all patients.

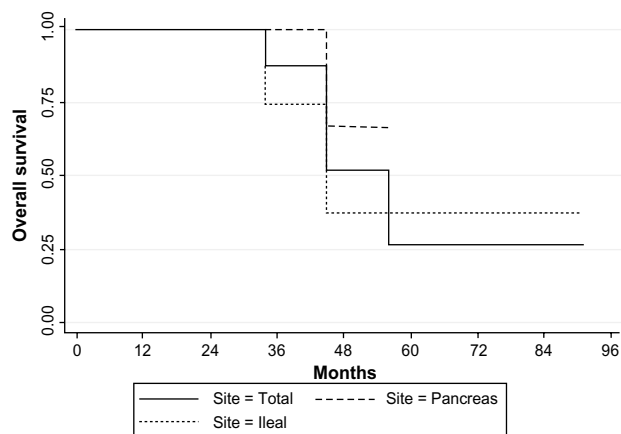


Figure 3 Overall survival in relation to site of origin.

in the group of well differentiated NETs, with a disease control rate of 78% (30% partial radiographic response and 48% stable disease). In contrast, three partial radiographic responses (23%) and one case of stable disease (7%) were obtained in the poorly differentiated NET group, with acceptable toxicity.²⁵

In 2011, a Phase II, open-label, multicenter study was published on the use of single-agent capecitabine for the treatment of metastatic nonpancreatic NETs. Nineteen patients received oral capecitabine 2,000 mg/m²/day divided into two doses for 14 days every 3 weeks. Treatment was safe and well tolerated. Thirteen patients achieved radiologically stable disease according to RECIST criteria, which was maintained by four patients for more than 12 months. No partial

radiographic responses or complete responses were obtained. Median progression-free survival and overall survival were 9.9 months and 36.5 months, respectively.²⁶

In another Phase II study, Claringbold et al investigated the safety and efficacy of capecitabine in association with peptide receptor radionuclide therapy (PRRT) lutetium-177 octreotate, exploiting the radiosensitizing effect of 5-FU and its prodrug. Thirty-three patients with inoperable, progressive, well differentiated NETs of different origin and previously treated with chemotherapy, radiotherapy, and somatostatin analogs received four cycles of lutetium-177 octreotate 7.8 GBq at 8-week intervals in association with capecitabine 1,650 mg/m² daily for 14 days starting on the same day as PRRT. All of the patients received at least one cycle of PRRT and 25/33 completed all four planned therapy cycles. Three patients discontinued capecitabine due to adverse cardiac events but completed PRRT. Hematological toxicity was mild, with only one patient experiencing grade three thrombocytopenia. Grade one to two hand-foot syndrome occurred in three patients. The objective response rate consisted of partial radiographic response (24%), stable disease (70%), and progressive disease (6%), with a response duration of 2 years. One-year and 2-year survival rates were 91% and 88%, respectively.²⁷

The association of capecitabine with temozolomide (the CAPTEM regimen) was investigated in vitro and found to be synergistic when temozolomide was administered after exposure of cells to capecitabine.²⁸ It was hypothesized that this was caused by depletion of the DNA repair enzyme, O6 methyl guanine DNA methyl-transferase, by capecitabine, an event similar to that exerted by 5-FU.²⁹ A retrospective analysis published by Strosberg et al in 2011 investigated the efficacy of capecitabine and temozolomide in 30 patients with well or moderately differentiated metastatic pancreatic endocrine tumors who had not received prior systemic chemotherapy. Capecitabine was given as 750 mg/m² twice a day for 14 consecutive days and temozolomide as 200 mg/m² once daily on days 10–14 every 28 days.³⁰ Twenty-one of the 30 patients achieved an objective radiographic response. Median progression-free survival was 18 months and the 2-year survival rate was 92%. Only one patient underwent a dose reduction before starting treatment because of renal impairment. Four patients required a dose reduction during therapy, two for grade two hand-foot syndrome and two for grade four hematological toxicity (one pancytopenia and one thrombocytopenia). Grade three hypertransaminasemia was observed in one patient. Treatment was otherwise well

Table 2 Overall toxicity

Toxicity grade	Maximum toxicity grade			
	1 n (%)	2 n (%)	3 n (%)	4 n (%)
Hematological				
Hemoglobin	6 (60)	0	0	0
Leukocytes	6 (60)	2 (20)	0	0
Neutrophils	8 (80)	2 (20)	0	0
Platelets	4 (40)	0	0	0
Nonhematological				
Nausea	1 (10)	0	0	0
Fatigue	2 (20)	0	0	0
Hand-foot syndrome	1 (10)	1 (10)	0	0
Diarrhea	2 (20)	0	0	0
Mucositis	2 (20)	1 (10)	0	0
Hypertransaminasemia	1 (10)	0	0	0
Elevated bilirubin	0	0	0	0
Anorexia	2 (20)	0	0	0
Dehydration	0	0	0	0
Dermatitis	0	2 (20)	1 (20)	0

tolerated, with only grade one and two common hematological and nonhematological toxicities.

The CAPTEM regimen was also the focus of another study, recently published by Fine *et al*,³¹ that retrospectively evaluated 18 patients with NETs of different origin and metastatic to the liver, and previously treated with somatostatin analogs, chemotherapy, or a locoregional approach, such as hepatic chemoembolization. Patients received capecitabine 600 mg/m² orally twice daily on days 1–14 and temozolomide 150–200 mg/m² divided into two doses daily on days 10–14 of a 28-day cycle. One patient (5%) with a midgut carcinoid achieved a surgically confirmed complete response, ten patients (55.5%) had a partial radiographic response, and four (22.2%) showed stable disease. Median progression-free survival and overall survival were 14 (11.3–18) months and 83 months, respectively. Two patients experienced grade three thrombocytopenia and one had grade two hand-foot syndrome. There were no grade four toxicities. The remaining patients reported only grade one to two hematological toxicity.

In a recent retrospective study, Saif *et al* tested a modified CAPTEM regimen in seven patients with well or moderately differentiated metastatic pancreatic NETs in progression after different treatments (somatostatin analogs or chemotherapy including doxorubicin, streptozotocin, cisplatin, and gemcitabine).³² Treatment consisted of capecitabine 1,000 mg/m² twice a day on days 1–14 and temozolomide 200 mg/m² on days 10–14 every 28 days. The overall response rate was 43%, with a clinical benefit in 71%. The median response duration was 8 (range 4–13) months, progression-free survival was 12 months, and overall survival was 24 months. Grade three thrombocytopenia occurred in one patient and another experienced grade three fatigue.

Exploiting the radiosensitizing effect of capecitabine, Saif *et al* carried out a study in eleven patients with histologically confirmed resected or locally advanced pancreatic NETs (T3–T4). Of these, seven received a combination of capecitabine 1,000 mg/m² twice daily or infusional 5-FU and external beam radiation therapy to the primary tumor or resection bed at a median dose of 50.4 Gy. Treatment was well tolerated, with only grade two hand-foot syndrome and grade one mucositis observed. All patients showed radiographic progression-free survival and achieved local disease control. Of nine patients with locally advanced disease, two subsequently underwent surgical resection. At a median follow-up of 30.4 months, three patients had died from progressive disease, two had died from other causes, three were alive with metastases, and three were alive without metastases

(one stable disease, one progression-free survival, and one complete response; see Table 3).³³

Discussion

Although NETs are considered to be relatively rare tumors, their incidence and prevalence are increasing in both Europe and the USA. Because of the diversity of this kind of neoplasm, we focused our attention on GEP-NETs, which are endocrine malignancies derived from the gastrointestinal tract. When feasible, radical surgery is the optimal therapeutic approach for this subgroup, whereas somatostatin analogs and targeted agents are the most widely used strategies in a metastatic setting. Systemic chemotherapy also seems to have a certain efficacy in advanced disease. The majority of the studies on the use of chemotherapy in NETs were conducted more than 10 years ago, before the introduction of the new NET classification according to tumor proliferation index.^{34–36}

These factors, in addition to different primary tumor locations that appear to influence the chemoresponsiveness of NETs, should be taken into consideration to optimize the modality and timing of treatment. Several chemotherapeutic drugs, such as streptozotocin, temozolomide, and 5-FU, have been used for this type of neoplasm, with differing efficacy and toxicity. Following the efficacy of 5-FU, capecitabine has been studied alone and in combination for metastatic disease, with good efficacy and an acceptable toxicity profile. It has been shown to exert a synergistic effect when used with drugs such as temozolomide and oxaliplatin, and to act as a sensitizing factor when used in combination with other therapeutic approaches, such as radiotherapy and PRRT. In the studies presented in this review, the schedule of capecitabine was often modified when used in association with other agents or when used alone, to minimize side effects.^{25–28,30–33}

In our experience, metronomic use of capecitabine in metastatic GEP-NETs was safe and well tolerated, with none of the patients showing major side effects. The most frequent minor adverse event was grade one to two nonhematological toxicity, although this may be an underestimation due to the retrospective nature of our study. The regimen used would also appear to be feasible in elderly patients, as documented by the median age of the population. Although the high response rate and prolonged duration of response indicate the potential efficacy of this treatment, our results must be interpreted cautiously because of the small number of patients involved, as this may have influenced the progression-free survival and overall survival data. Treatment was particularly

Table 3 Clinical trials using capecitabine in gastroenteropancreatic neuroendocrine tumors

Reference	Treatment	Patients (n)	Concomitant SST analog	Setting	Grade	Origin	(CR/PR/SD/PR) %	PFS	OS
Fine et al ³¹	Capecitabine 600 mg/m ² twice daily, days 1–14; TMZ 150–200 mg/m ² for 5 days every 28 days	18	Octreotide acetate 30 mg once monthly	Metastatic	G1	Midgut (7 Pancreatic)	(5/55/16/22)	25 months	83 months
Claringbold et al ²⁷	Capecitabine 1,650 mg/m ² daily, days 1–14 + PRRT Lu ¹⁷⁷ octreotate	33	No	Metastatic	G1–G2	10 Pancreatic 15 GI 2 Lung 6 Unknown Pancreatic	(0/24/70/6)	NR	OS 1-year 91% OS 2-year 88%
Strosberg et al ³⁰	Capecitabine 750 mg/m ² twice daily, days 1–14 + TMZ 200 mg/m ² for 5 days every 28 days	30	No	Metastatic (no prior chemotherapy)	G1–G2	Pancreatic	(0/70/27/1)	18 months	OS 2-year 92%
Medley et al ²⁶	Capecitabine 2,000 mg/m ² daily, days 1–14 every 21 days	19	Octreotide acetate 8 patients	Metastatic	G1–G2	Non pancreatic	(0/0/68/16)	9.9 months	36.5 months
Bajetta et al ²⁵	Oxaliplatin 130 mg/m ² day 1 + capecitabine 2,000 mg/m ² daily, days 2–15 every 21 days	40	Octreotide acetate 27 patients	Metastatic	G1–G2 (27/40) G3 (13/40)	15 pancreatic One GI 10 lung 6 other/unknown Pancreatic	G3 (0/23/7/70) G1–G2 (0/30/48/22)	18 months	32 months
Saif et al ³²	Capecitabine 1,000 mg/m ² twice daily, days 1–14 + TMZ 200 mg/m ² , days 10–14 every 28 days	7	NE	Metastatic	G1–G2	Pancreatic	(0/43/28/28)	12	24
Saif et al ³³	Capecitabine 1,200 mg/m ² daily or infusional 5-FU 175 mg/m ² /day and concurrent radiotherapy (50.4 Gy)	6	NE	3 locally advanced 3 positive margins resected	G1–G2	Pancreatic	50% PR	NE	NE

Abbreviations: NR, not reached; NE, not evaluable; 5-FU, 5-fluorouracil; TMZ, temozolomide; GI, gastrointestinal; SST, somatostatin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival; PRRT, peptide receptor radionuclide therapy.

effective in pancreatic NETs, suggesting that this subgroup is more sensitive to chemotherapy. Prospective studies are needed to confirm these findings. Preclinical studies are also warranted to clarify whether the antitumor activity and mechanism of action of capecitabine can be attributed to immunomodulatory or antiangiogenic effects, or both.

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Disclosure

The authors report no conflicts of interest in this work.

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