

Metronomic chemotherapy in patients with advanced neuroendocrine tumors: A single-center retrospective analysis

Giulia Arrivi^{1,2}  | Francesca Spada¹ | Samuele Frassoni^{1,3} | Vincenzo Bagnardi^{1,3} | Alice Laffi¹ | Manila Rubino¹ | Lorenzo Gervaso^{1,4} | Nicola Fazio¹ 

¹Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, IEO, European Institute of Oncology, IRCCS, Milan, Italy

²Department of Clinical and Molecular Medicine, Sapienza University of Rome, Italy

³Department of Statistics and Quantitative Methods, University of Milan-Bicocca, Milan, Italy

⁴Molecular Medicine Program, University of Pavia, Pavia, Italy

Correspondence

Nicola Fazio, MD, PhD, Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, IEO, European Institute of Oncology, IRCCS, Via Ripamonti 435, 20141, Milan, Italy.
Email: nicola.fazio@ieo.it

Abstract

Neuroendocrine tumors (NETs) are more commonly slow-growing, therefore patients often receive chronic systemic therapies for tumor growth control and preservation of quality of life. Metronomic chemotherapy (mCT) is in line with this goal as it leads to stabilization of tumor growth over time without severe systemic toxicity. This is a retrospective analysis of patients with metastatic NETs receiving metronomic capecitabine (mCAP) or temozolomide (mTEM), at a NET-referral center. The aims of the study were to explore activity and safety of mCT and relationships between some characteristics of the patient population and clinical outcomes. Among a total of 67 patients with metastatic well or moderately differentiated (W/M-D) NETs, mostly gastroenteropancreatic (GEP) and nonfunctioning, 1.2 years (95% CI: 0.8–1.8) median progression-free survival (mPFS), and 3.0 years (95% CI: 2.3–4.9) median overall survival (mOS) were observed. Disease control rate was 85%. Grade 3 adverse events occurred in 15% of patients in mCAP and 13% in mTEM, and were mostly hematological and gastrointestinal. At univariate and multivariate analysis none of the variables analyzed (treatment regimen, sex, age at diagnosis, site of primary tumor and metastases, number of previous mCT lines, baseline tumor status before mCT, Ki67 value) were significantly correlated to OS and PFS. Our retrospective study suggested that mCAP and mTEM can be active and well tolerated in patients with metastatic W/M-D NETs, irrespective of the primary site, site of metastases, line of treatment and baseline tumor status.

KEYWORDS

capecitabine, metronomic chemotherapy, neuroendocrine, temozolomide

1 | INTRODUCTION

Neuroendocrine tumors (NETs) represent a group of rare and well differentiated malignancies¹ with a very heterogeneous clinical behavior.

In the majority of cases, advanced NETs are relatively slow-growing, and patients often receive a sequence of systemic therapies in order to achieve tumor growth control and preserve quality of life. Therefore, therapeutic schedules may play a crucial role in achieving these complex goals.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Journal of Neuroendocrinology* published by John Wiley & Sons Ltd on behalf of British Society for Neuroendocrinology.

The therapeutic concept of administering agents continuously at lower doses is known as metronomic therapy.² The ability of tumor cells to mutate, developing resistance to different drugs, makes the metronomic chemotherapy (mCT) a way to potentially overcome possible changes in tumor behavior and evolution.³ This could be mainly related to the reduction of the drug-free period, which represents a trigger for tumor cells to restart their progression.⁴ The regular administration of mCT makes this therapy biologically active at any time point. Since mCT does not provide a cytotoxic effect, it maintains a significant proportion of sensitive alive cells within the tumor, meanwhile limiting the proliferation of the drug-resistant cell population.⁵

The main role of mCT is also derived from its antiangiogenic mechanism of action.^{6–14} In this context, vascular endothelial growth factor (VEGF) is one of the most important factors involved in the process of development of new tumor vessels.¹³ Considering the high levels of VEGF secreted by neuroendocrine cells¹⁵ which result in hypervascularization, NETs could potentially benefit from mCT.^{16,17} A rich vascularization has been observed mainly in low-grade pancreatic NETs (panNETs) in comparison with high grade and other digestive epithelial neoplasms.^{18–20}

In addition, the metronomic schedule has proved to be effective on the immune system. Pre- and clinical studies showed that the antitumor effect has been linked to the depletion of immunosuppressive cells (T regulatory cells and myeloid-derived suppressor cells)²¹ and mainly to the modulation of dendritic cells. Indeed, mCT induces dendritic cell maturation, which are crucial for the activation of an adaptive immune response,²² and then enhances their function and the expression of tumor antigens and antigen-presenting molecules. Moreover, conversely to a conventional chemotherapy schedule, a regular low-dose of drug is deemed to interfere with a tumor's clonal evolution by targeting both tumor initiating cells and cancer stem cells.⁸

The biological characteristics of advanced NETs represents the ideal basis for mCT application, with the aim to integrate the concepts of angiogenesis and angiogenetic machinery, tumoral microenvironment, cancer stem cells, and tumoral immunology. However, to date, most of the published body of evidence in this setting, include case reports, retrospective analyses^{23,24} and very few phase II studies.^{25–28} Furthermore, in these studies, mCT is often associated with other concomitant drugs and the patient population is heterogeneous in terms of primary site, biological features and previous treatments. For these reasons, despite the large use of chemotherapy in NETs, nowadays the use of metronomic schedules is not yet well defined in the main guidelines.²⁹

For these reasons, we conducted a retrospective analysis of patients with metastatic NETs from various primary sites treated with metronomic schedules of capecitabine (CAP) or temozolomide (TEM). The aims were to evaluate the activity and safety of mCAP and mTEM, and to explore the relationships between some characteristics of the patient population and clinical outcomes.

2 | MATERIALS AND METHODS

This was a retrospective analysis of patients with a histological diagnosis of metastatic NET, receiving mCT at the European Institute of

Oncology (IEO), ENETS-certified Center of Excellence (CoE) for gastroenteropancreatic (GEP) NETs. Patients treated with mCAP or mTEM from January 2007 to January 2020 were identified. They should have received mCT over a minimum period of one cycle, namely 12 weeks. The mCAP schedule could be 1000 mg/day continuously or 1500 mg/day continuously or 2000 mg/day continuously or 1000–2000 mg/day 2 weeks on/1 week off, orally taken two or three times per day arbitrarily set by physicians. The mTEM schedule could be 100 mg/day continuously or 100 mg/day 1 week on/1 week off or 2 weeks on / 1 week off, orally taken once per day, as determined by physician choice. The use of mCT was related to patient attitude or aspects such as performance status or comorbidities and represented an alternative option to “conventional” chemotherapy according to physician choice. The mCT was taken until progressive disease (PD) or unacceptable toxicity. Patients receiving concomitant assumption of somatostatin analog (SSA) or concomitant antitumor locoregional treatments were included, whereas those receiving concomitant peptide receptor radionuclide therapy (PRRT) or other systemic antitumor therapies were excluded.

All patients underwent a computed tomography (CT) scan or magnetic resonance imaging (MRI) and ⁶⁸gallium (⁶⁸Ga) positron emission tomography (PET)/CT-DOTA-peptide before starting mCT. For each patient at least one tumor restaging with CT or MRI during mCT had to be available.

According to clinical practice, although the retrospective design of this study and the not fully standardized follow-up programs, computed tomography (CT) or magnetic resonance imaging (MRI) assessments were performed at baseline and approximately every 3-months after starting chemotherapy, unless clinical conditions required shorter intervals. Tumor response was evaluated taking into account the RECIST³⁰ and RECIST version 1.1.³¹ The overall disease control rate (DCR) was calculated as the sum of complete response (CR), partial response (PR), and stable disease (SD).

With respect to the retrospective nature of this analysis, the adverse events were classified in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTCAE, version 3.0).³²

Metronomic treatment is conventionally used in our institution, and all patients signed an informed consent for chemotherapy at their first oncological visit. No additional informed consent for scientific research purpose was required, as ours was a retrospective study collecting clinical information. The present study has been authorized by the IEO Institutional Review Board and by the Data Protection Officer on 02/04/2020 and notified to the Regulatory Office on 08/05/2020 (reference no. UID 2311).

2.1 | Statistical analysis

Continuous variables are reported as median and range, while categorical variables are reported as count and percentage. Progression-free survival (PFS) is defined as the time from treatment initiation until disease progression or last contact without PD; overall survival (OS) is

TABLE 1 Clinicopathological characteristics of patients

Variable	Level	Overall (N = 67)
Sex, N (%)	M	42 (62.7)
	F	25 (37.3)
Age at diagnosis, N (%)	<65	56 (83.6)
	65+	11 (16.4)
	Median (min–max)	54 (12–80)
Site of the primary, N (%)	Pancreas	34 (56.7)
	Midgut	11 (18.3)
	GI extra-midgut	2 (3.3)
	Lung	13 (21.7)
	Missing	7
Histotypes, N (%)	Neuroendocrine tumor	53 (79.1)
	Atypical carcinoid tumor of the lung	5 (7.5)
	Typical carcinoid tumor of the lung	6 (9.0)
	NAS carcinoid	3 (4.5)
Ki-67, median (min–max) ^{a,b}		10 (0.5–70)
Metastases, N (%)	Synchronous	40 (59.7)
	Metachronous	27 (40.3)
Hepatic/extrahepatic metastases, N (%)	Only liver	24 (35.8)
	Only extrahepatic	11 (16.4)
	Liver + extrahepatic	32 (47.8)
Hepatic metastases, N (%)	No liver mets	11 (16.7)
	Unilobar	23 (34.8)
	Bilobar	32 (48.5)
	Missing	1
NF/F, N (%)	NF	51 (76.1)
	F	16 (23.9)
PET-FDG basal mCT, N (%)	Negative	6 (15.8)
	Positive	32 (84.2)
	Missing	29
PET-Ga basal mCT/octreoscan, N (%)	Negative	7 (11.3)
	Positive	55 (88.7)
	Missing	5
Previous surgery, N (%)	No	30 (44.8)
	Yes	37 (55.2)
Type of surgery, N (%)	No	30 (44.8)
	Primary	23 (34.3)
	Mets	1 (1.5)
	Primary + Mets	13 (19.4)
Number of prior therapies antitumor lines, N (%)	0	6 (9.0)
	1	13 (19.4)
	2	13 (19.4)
	3	20 (29.9)

(Continues)

TABLE 1 (Continued)

Variable	Level	Overall (N = 67)
	4	7 (10.4)
	5	5 (7.5)
	6	1 (1.5)
	7	2 (3.0)
Concomitant SSA, N (%)	No	15 (22.4)
	Yes	52 (77.6)
Other concomitant therapies, N (%)	No	59 (88.1)
	Yes	8 (11.9)
Baseline tumor status, N (%)	SD	16 (23.9)
	PD	51 (76.1)
Study treatment regimen, N (%)	Capecitabine	51 (76.1)
	Temozolomide	16 (23.9)
Duration of mCT chemotherapy, N (%)	<6 months	18 (27.3)
	6–12 months	15 (22.7)
	12–24 months	15 (22.7)
	>24 months	18 (27.3)
	Missing	1
Median (min–max)		12.6 (1.5–123.4)

Abbreviations: F, functioning; mCT, metronomic chemotherapy; NF, nonfunctioning; PD, progressive disease; PET-FDG, positron emission tomography-18F-2-fluoro-2-deoxyglucose; PET-Ga, positron emission tomography-gallium; PRRT, peptide receptor radionuclide therapy SSA, somatostatin analog.

^aThe maximum value among Ki-67 of the primary and Ki-67 of the metastases was considered for each patient.

^bFour missing.

defined as the time between start of metronomic therapy and death for any cause or last contact. Survival curves for OS and PFS were estimated using the Kaplan–Meier method. The log-rank test was used to assess differences between groups. Median OS and PFS were reported with 95% confidence intervals (CIs). Univariate and multivariate Cox proportional hazard regression models were used to assess the association between treatment regimen and clinicopathological parameters with OS and PFS. All analyses were performed using SAS software version 9.4 (SAS Institute).

3 | RESULTS

3.1 | Clinic-pathological characteristics

A total of 67 patients with metastatic NETs, with a median age of 54 years (range 12–80 years), predominantly males, were included. The majority had a nonfunctioning NET ($n = 51$, 76%), in 78% of cases from GEP tract and in 22% from lung. Among GEP the most common primary sites were pancreas ($n = 34$, 57%), and midgut ($n = 11$, 18%). All patients presented diagnosis of well or moderately differentiated

(W/M-D) NETs. The demographics and clinic-pathological variables of the investigated patients are listed in Table 1.

Thirty-two patients (48%) had liver plus extra-hepatic metastases, whereas 24 patients (36%) liver-only. The involvement of liver was uni- and bilobar in 23 (35%) and 32 (48%) patients, respectively. In Table S1, all sites of extrahepatic metastases were reported.

All patients received mCT, 76% of them mCAP and 24% mTEM; the various schedules are reported in Table S2. Most patients received mCT as more than a second-line therapy (Table S3). Concomitant SSA was administered in 52 patients (78%), while four patients underwent a concomitant nonsurgical locoregional treatment for liver metastases. About 24% of patients had a baseline stable disease (SD), therefore, receiving mCT as a sort of “maintenance” treatment, whereas the others had a baseline radiological progressive disease (PD) according to RECIST criteria.

3.2 | Activity and safety

All 67 patients were evaluable for tumor response. In the mCAP group, we observed 39 (85%) SD, and one (2%) PR; in the mTEM group 11 (69%) SD, and two (13%) PR. Six (13%) and three (19%) patients showed PD in mCAP and mTEM groups, respectively (Table 2). In the whole population, the median duration of treatment was 12.6 (range 1.5–123.4) months. More than two thirds of patients had a duration of mCT longer than 6 months, and 27% longer than 24 months. A similar treatment duration was reported between mCAP and mTEM: 72% and 75% of patients in the two groups of treatment, were treated for more than 6 months, respectively ($p = .86$). The median duration of treatment was 10.3 (1.5–123.4) months for mCAP, and 15.6 (2.5–76.7) months for mTEM (Table S4).

The DCR in the whole population was 85%, 87% in the mCAP group and 81% in the mTEM group. The analysis of DCR by site of the primary tumor showed rate of 88, 90 and 100% in the pancreas, midgut and GI extra-midgut, respectively, while a DCR of 69% was reported in lung population. Grouped by histological differentiation, a DCR of 82 and 92% was observed in well and moderately differentiated NETs, respectively (Table 3). Although the population of our study was heterogeneous in the site origin, we performed an efficacy analysis by arbitrarily distinguishing the whole population with a cut-off of $Ki67 < 2$, $Ki67 2-10$ by configuring “G2 low” NETs and $Ki67 > 10$ by configuring “G2 high” NETs, which showed an excellent DCR in all histopathological subgroups (Table S5).

Regarding the tolerability, about half of patients did not experience any grade of toxicity, whereas in the remaining patients most adverse events (AEs) were reported as mild to moderate. Six patients (15%) in mCAP group, and two (13%) in mTEM showed grade 3 (G3) AEs, such as diarrhea, neutropenia, stomatitis, renal failure, cutaneous and cardiac disorders (Table 2).

3.3 | Survival analysis

With a median follow-up of 2.8 (Q1–Q3 1.5–5.6) years, there were 46 deaths (69%) and 52 (78%) patients with progressive disease (PD). In the entire study population, mOS was 3.0 (95% CI: 2.3–4.9) years (Figure 1) and mPFS was 1.2 (95% CI: 0.8–1.8) years (Figure 2). When the patients were grouped according to treatment regimen, mOS was 4.2 years (95% CI: 2.3–5.6) and 2.9 years (95% CI: 1.2–5.2), for mCAP and mTEM, respectively with no statistical significance ($p = .213$) (Figure 3). However, mCAP showed a slight advantage in survival. In the mCAP group, the 4-year OS rate was 50.0% (95% CI: 34.8–63.5)

TABLE 2 Response rate and toxicity

Variable	Level	Overall (N = 67)	Study treatment regimen	
			Capecitabine (N = 51)	Temozolomide (N = 16)
Best response, N (%)	CR	0 (0.0)	0 (0.0)	0 (0.0)
	PR	3 (4.8)	1 (2.2)	2 (12.5)
	SD	50 (80.6)	39 (84.8)	11 (68.8)
	PD	9 (14.5)	6 (13.0)	3 (18.8)
	Missing	5	5	0
Max toxicity grade during metronomic, N (%)	No toxicity	25 (45.5)	19 (47.5)	6 (40.0)
	G1 ^a	6 (10.9)	2 (5.0)	4 (26.7)
	G2 ^b	16 (29.1)	13 (32.5)	3 (20.0)
	G3 ^c	8 (14.5)	6 (15.0)	2 (13.3)
	Missing	12	11	1

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

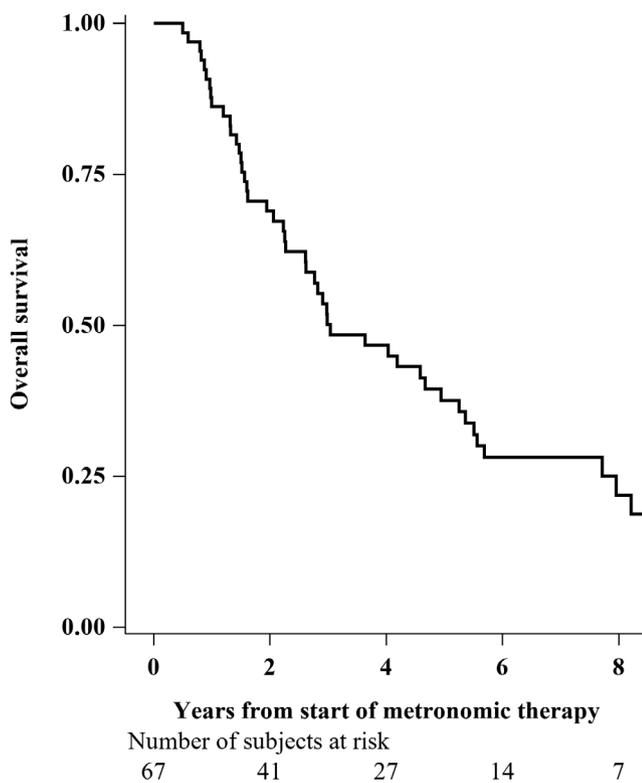
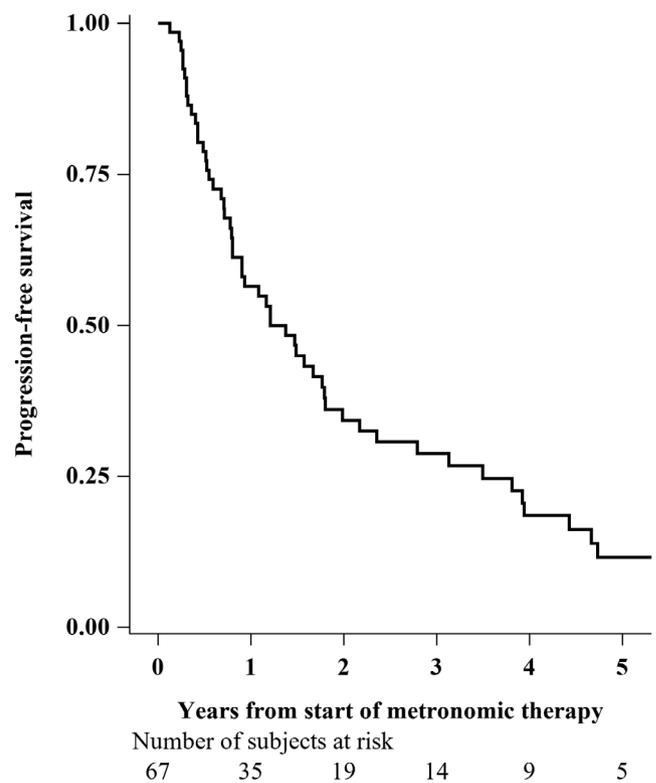
^aHematological (N = 2), increasing levels of transaminases (N = 1), one cardiovascular (N = 1), nausea/diarrhea (N = 1), Other (N = 1).

^bDiarrhea (N = 1), cutaneous rash (N = 6), hematological (N = 2), nausea/vomiting + cutaneous rash (N = 1), increasing levels of transaminases + acute renal insufficiency (N = 1), other (N = 5).

^cHematological (N = 1), diarrhea (N = 1), oral mucositis (N = 1), cutaneous rash (N = 2), cardiovascular (N = 1), other (N = 1), cutaneous rash + acute renal insufficiency (N = 1).

TABLE 3 Response rate by study treatment, site of primary tumor and histological differentiation

Variable	Level	Best response	
		CR/PR/SD, N (%)	PD, N (%)
Overall		53 (85)	9 (15)
Site of the primary	Pancreas	28 (88)	4 (13)
	Midgut	9 (90)	1 (10)
	GI extra-midgut	1 (100)	0 (0)
	Lung	9 (69)	4 (31)
	Missing	6	0
Differentiation	Well differentiated	36 (82)	8 (18)
	Moderately differentiated	12 (92)	1 (8)
	Missing	5	0

**FIGURE 1** Overall survival (OS) in the entire study cohort ($N = 67$)**FIGURE 2** Progression-free survival (PFS) in the entire study cohort ($N = 67$)

and in the mTEM group it was 37.5% (95% CI: 15.4–59.8). Median PFS was 1.4 (95% CI: 0.7–2.0) years in patients received mCAP (2-year PFS 35.3%) and 1.2 (95% CI: 0.4–2.2) years in those receiving mTEM (2-year PFS 31.3%), $p = .36$ (Figure 4).

In patients with SD at baseline the mOS was 8 years whereas in those with PD at baseline the mOS was 2.9 years (p -value = 0.22; Figure S1), with an advantage of about 20% in 4 years OS rate (62.9% in SD group vs. 43.4% in the PD group). Regarding mPFS, no significant difference was observed between the two aforementioned groups (Figure S2).

At univariate and multivariate analysis none of the variables analyzed (treatment regimen, sex, age at diagnosis, site of primary tumor

and metastases, number of pre-mCT lines, baseline tumor status before mCT, Ki67 value) were significantly correlated to OS and PFS. Furthermore, the analysis showed no correlation between SSA before mCT in any line treatment and survival outcomes (Tables S6 and S7).

4 | DISCUSSION

This retrospective study suggests that mCAP and mTEM can be active and well tolerated in patients with metastatic W/M-D NETs.

Interestingly, we observed an 85% DCR and more than 12 months of median treatment duration for more than half of the

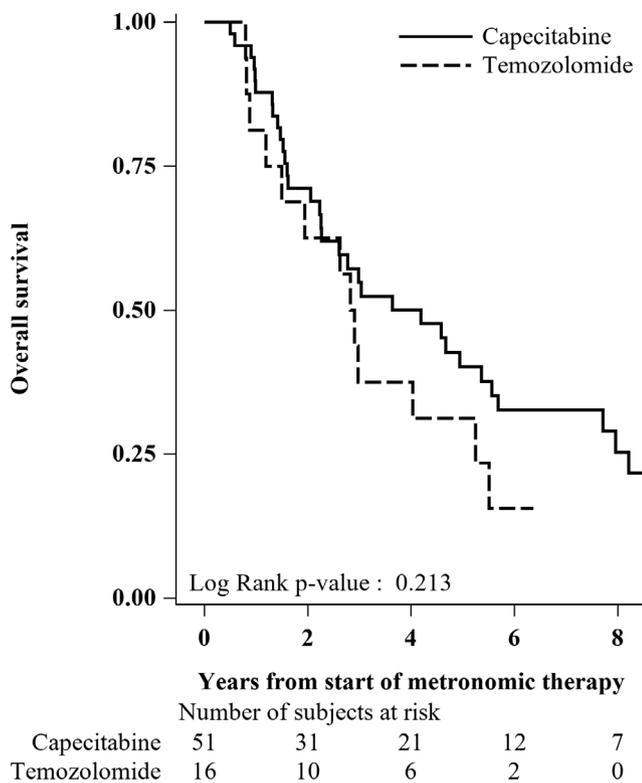


FIGURE 3 Overall survival (OS) by treatment regimen of metronomic chemotherapy (mCT) ($N = 67$)

patients. This result is noteworthy considering the clinical heterogeneity of the population and the percentage of highly pretreated patients.

Our analysis did not show any specific relationships between tumor primary site, tumor grade, line of treatment, type of treatment or other variables and survival, suggesting that mCT is potentially active in all metastatic W/M-D NET patients.

Moreover, the mixed tumor population in terms of primary sites and tumor grades and the different schedules represent a limitation in interpreting the information. However, descriptive results from some subgroups could be more informative.

Currently, mCT does not have a defined role in patients with advanced NETs. In 2016, a less dose intense dacarbazine (DTIC) treatment schedule comprising single intravenous applications of 650 mg/m² DTIC every 4 weeks was reported to be active in patients with metastatic NETs.³³ Although it cannot be considered a mCT experience, it represents a possibility of administering a lower intensity schedule of chemotherapy; however, it did not have a further development.

Since then, other agents have been investigated, including CAP and TEM. Studies conducted with these drugs were heterogeneous in terms of sample size, tumor morphology, tumor grade and number and type of previous treatments^{23,25–27,33–35} making the clinical interpretation of their results at high risk of biases.

Although the median PFS and OS of our study (1.2 and 3.0 years, respectively) are numerically better than those previously reported with biological agents,^{36–39} a selection bias cannot be excluded, letting suppose a tumor population with favourable biological and/or

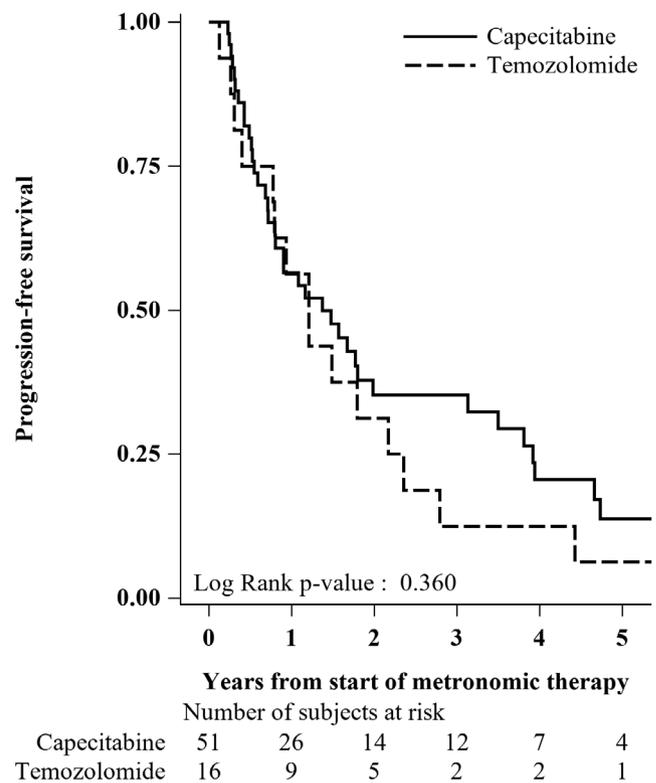


FIGURE 4 Progression-free survival (PFS) by treatment regimen of metronomic chemotherapy (mCT) ($N = 67$)

clinical characteristics. On the other hand, a role of mCT cannot be excluded even in the favourable context of patients with SD at baseline where mCT was used as “maintenance” after a conventional CT. Maintenance mCT after a long period of conventional CT or as part of a stop-and-go policy are validated strategies in the management of various cancers.^{40,41} However, in the context of NETs, few reliable experiences of “maintenance” mCT are available. Consequently, it is still unclear which drug best fits the role of maintenance agent. Previous experiences showed a 21 months advantage in PFS by extended cycle protocol of streptozotocin/5-FU in case of PR or SD after induction chemotherapy.⁴²

We are aware that a comparison between the two subgroups of our retrospective study (mCAP and mTEM) is inconclusive, but just as descriptive results, mCAP patients had a better mOS than those treated with mTEM, with a similar PFS. Our data were in line with those reported in previous studies on the activity and tolerance of mCAP^{43,44} or 5-FU as an intravenous continuous infusion in combination with other drugs in the treatment of advanced NETs.^{27,45} Metronomic TEM was explored as a “week on/week off” schedule at 75 mg/m²/day as second-line treatment in advanced GEP and lung G2-G3 neuroendocrine neoplasms (NENs).²⁴ In our study, about 30% of patients received mTEM as a second-line. Although our population included also G3 NETs ($n = 15$; 58%), mTEM did not show significant relationships between response to therapy and patients or tumor characteristics. Indeed, a potential advantage in ORR and DCR was noticed also in NET G3 patients.

Lastly, the DCR did not differ significantly according to the primary site tumor, although we observed a lower DCR in lung disease than in gastrointestinal neoplasms. The overall DCR was promising, since more than half of the patients were still under treatment after 1 year of mCT.

Although the high rate of SD could be due to the SSA administration before mCT, we know from the literature that mCT also has no great capacity of inducing apoptosis, but due to their low drug levels, senescence can be one mechanism which occurs during mCT.²

We did not observe significant correlations between survival and collected variables – including primary tumor site, treatment regimen, sex, age at diagnosis, presence of hepatic/extrahepatic metastases, number of pre-mCT lines and disease status before mCT. This data is inconsistent with the XELBEVOCT phase II trial results,²⁶ where tumor response was more frequently observed in panNET than in non-panNET. However, it is important to note that in this trial, octreotide LAR and bevacizumab were utilized concomitantly with mCAP. Similarly, the association of mTEM plus bevacizumab and octreotide LAR has been investigated in another study conducted in pancreatic and nonpancreatic NETs.²⁵

High grade AEs are almost unexpected during mCT. However, around 10% of our patients experienced G3 AEs in both the subgroups, suggesting that individual variability in some key factors (absorption, liver metabolism, or drug-to-drug interactions) can play a role in inducing toxicities, even with mCT. Nowadays, the detection of polymorphisms of dihydropyrimidine dehydrogenase (DPYD) in the peripheral blood before starting a conventional fluoropyrimidine-based chemotherapy is recommended by national and international guidelines^{46,47} in order to modulate treatment dosages and avoid potential high-grade AEs. Unfortunately, in our study the DPYD was not specifically checked. The toxicity data from our study suggest that initial patient selection can play a critical role even for mCT.

Temozolomide activity and efficacy has been hypothesized to be linked to the O6-methylguanine-DNA methyltransferase (MGMT) status.⁴⁸ A recent systematic review and meta-analysis suggested that in NETs MGMT status may be predictive of TEM efficacy in NETs. However, according to these results, current evidence is not robust to justify the routine detection of MGMT before starting TEM in NETs care.⁴⁹

A comment on the possible advantage of the mCT compared to the conventional capecitabine plus temozolomide (CAPTEM) schedule of 2 weeks on and 2 weeks off, appears as necessary. Some recent high-quality data of a phase II study⁵⁰ comparing TEM versus CAPTEM in p-NETs showed advantage in survival for combination chemotherapy, while no significant difference was observed between two arms in the response rate. With regard to the tolerance profile, the authors reported an adverse event (G3–4) rate of 22% in the TEM arm compared to 44% in the CAPTEM arm. We therefore assume a better toxicity profile for monotherapy is also easier to adhere to due to its simplified schedule.

Our work presents several limitations. First, it is monocentric and retrospective. Second, the heterogeneity of the population, in terms of primary sites, tumor grades, and previous treatment lines. Third, the lack of a centralized pathological review. Lastly, our analyses have

more descriptive than statistical value. The potential strengths of our study could be the sample size, the homogeneity of tumor morphology and tumor stage. On the other hand, although a central pathology review has not been carried out, all the cases have been reviewed by a NET-dedicated pathologist which represents an important added value in clinical practice.

5 | CONCLUSIONS

Our retrospective study revealed that mCAP and mTEM can be active and well tolerated in patients with metastatic W/M-D NETs from various primary sites. Furthermore, it suggested that mCT could play a role in patients with advanced low-grade NET, slowly growing, with favorable biological and clinical characteristics, although the design and heterogeneity of the study does not allow conclusions in terms of efficacy of mCT or comparison between groups.

The mCT represents an active option when the goal is the tumor growth control over time concomitantly with a very manageable toxicity profile. Notably, frail patients unfit for conventional regimens or maintenance after an induction CT could represent an ideal subgroup of patients for mCT administration.

This hypothesis is warranted to be investigated in future prospective studies conducted in homogeneous contexts. Accordingly, the possible validation of specific drugs and schedules and the identification of molecular predictive are unmet clinical needs which deserve to be addressed. Moreover, considering its immune-modulatory and anti-angiogenic properties, the association of mCT with immune-checkpoint inhibitors (ICIs) could be the starting point of a new line of research.^{25,26,51,52}

AUTHOR CONTRIBUTIONS

Giulia Arrivi: Data curation; writing – original draft; writing – review and editing. **Francesca Spada:** Supervision; visualization. **Samuele Frassoni:** Formal analysis; visualization. **Vincenzo Bagnardi:** Formal analysis; visualization. **Alice Laffi:** Visualization. **Manila Rubino:** Visualization. **Lorenzo Gervaso:** Visualization. **Nicola Fazio:** Conceptualization; supervision; writing – original draft; writing – review and editing.

ACKNOWLEDGMENTS

Open access funding provided by BIBLIOSAN.

CONFLICT OF INTEREST

Nicola Fazio: Personal financial interests: Advisory board, public speaking: Novartis, Ipsen, Pfizer, Merck Serono, Advanced Accelerator Applications, MSD, Sanofi- Aventis, Wren Laboratories Europe. Institutional financial interests: Clinical trials (P.I., Steering committee): Novartis, Ipsen, Merck Serono, MSD, Pharmacyclics, Incyte, Halozyme, Roche, Astellas, Pfizer, FivePrime, BeiGene. Giulia Arrivi: Declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/jne.13189>.

DATA AVAILABILITY STATEMENT

The present study has been authorized by the IEO Institutional Review Board and by the Data Protection Officer on 02/04/2020 and notified to the Regulatory Office on 08/05/2020 (reference number UID 2311).;Metronomic treatment is conventionally used in our institution, and all patients signed an informed consent for chemotherapy at the first oncological visit. No additional informed consent for scientific research purpose was required, as ours was a retrospective study of collecting patient's clinical information.;For further information, please refer to the Corresponding Author.

ORCID

Giulia Arrivi  <https://orcid.org/0000-0003-0541-415X>

Nicola Fazio  <https://orcid.org/0000-0001-6869-0704>

REFERENCES

- Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;76(2):182-188.
- Mross K, Steinbild S. Metronomic anti-cancer therapy – an ongoing treatment option for advanced cancer patients. *J Canc Res Therapeut*. 2012;1:32. doi:10.7243/2049-7962-1-32.
- Gatenby RA, Silva AS, Gillies RJ, Frieden BR. Adaptive therapy. *Cancer Res*. 2009;69(11):4894-4903.
- Browder T, Butterfield CE, Kråling BM, et al. Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. *Cancer Res*. 2000;60(7):1878-1886.
- Li SC, Lee KL, Luo J. Control dominating subclones for managing cancer progression and posttreatment recurrence by subclonal switchboard signal: implication for new therapies. *Stem Cells Dev*. 2012;21(4):503-506.
- Pasquier E, Kavallaris M, André N. Metronomic chemotherapy: new rationale for new directions. *Nat Rev Clin Oncol*. 2010;7(8):455-465.
- Emmenegger U, Francia G, Shaked Y, Kerbel RS. Metronomic chemotherapy: principles and lessons learned from applications in the treatment of metastatic prostate cancer. *Recent Results Cancer Res*. 2010;180:165-183.
- Folkens C, Man S, Xu P, Shaked Y, Hicklin DJ, Kerbel RS. Anticancer therapies combining antiangiogenic and tumor cell cytotoxic effects reduce the tumor stem-like cell fraction in glioma xenograft tumors. *Cancer Res*. 2007;67(8):3560-3564.
- Martin-Padura I, Marighetti P, Agliano A, et al. Residual dormant cancer stem-cell foci are responsible for tumor relapse after antiangiogenic metronomic therapy in hepatocellular carcinoma xenografts. *Lab Invest*. 2012;92(7):952-966.
- Bocci G, Nicolaou KC, Kerbel RS. Protracted low-dose effects on human endothelial cell proliferation and survival in vitro reveal a selective antiangiogenic window for various chemotherapeutic drugs. *Cancer Res*. 2002;62(23):6938-6943.
- Hida K, Akiyama K, Ohga N, Maishi N, Hida Y. Tumour endothelial cells acquire drug resistance in a tumour microenvironment. *J Biochem*. 2013;153(3):243-249.
- Kerbel RS. Inhibition of tumor angiogenesis as a strategy to circumvent acquired resistance to anti-cancer therapeutic agents. *Bioessays*. 1991;13(1):31-36.
- Pasquier E, Tuset MP, Street J, et al. Concentration- and schedule-dependent effects of chemotherapy on the angiogenic potential and drug sensitivity of vascular endothelial cells. *Angiogenesis*. 2013;16(2):373-386.
- Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. *Nature*. 2011;473(7347):298-307.
- Scoazec JY. Angiogenesis in neuroendocrine tumors: therapeutic applications. *Neuroendocrinology*. 2013;97(1):45-56.
- Teulé A, Casanovas O. Relevance of angiogenesis in neuroendocrine tumors. *Target Oncol*. 2012;7(2):93-98.
- Raymond E, Faivre S, Ruzniewski P. *Management of Neuroendocrine Tumors of the Pancreas and Digestive Tract*. Springer; 2014.
- Marion-Audibert AM, Barel C, Gouysse G, et al. Low microvessel density is an unfavorable histoprognostic factor in pancreatic endocrine tumors. *Gastroenterology*. 2003;125(4):1094-1104.
- Couvelard A, O'Toole D, Turley H, et al. Microvascular density and hypoxia-inducible factor pathway in pancreatic endocrine tumours: negative correlation of microvascular density and VEGF expression with tumour progression. *Br J Cancer*. 2005;92(1):94-101.
- Takahashi Y, Akishima-Fukasawa Y, Kobayashi N, et al. Prognostic value of tumor architecture, tumor-associated vascular characteristics, and expression of angiogenic molecules in pancreatic endocrine tumors. *Clin Cancer Res*. 2007;13(1):187-196.
- Hao YB, Yi SY, Ruan J, Zhao L, Nan KJ. New insights into metronomic chemotherapy-induced immunoregulation. *Cancer Lett*. 2014;354(2):220-226.
- Tanaka H, Matsushima H, Nishibu A, Clausen BE, Takashima A. Dual therapeutic efficacy of vinblastine as a unique chemotherapeutic agent capable of inducing dendritic cell maturation. *Cancer Res*. 2009;69(17):6987-6994.
- Bongiovanni A, Riva N, Calpona S, et al. Metronomic capecitabine in gastroenteropancreatic neuroendocrine tumors: a suitable regimen and review of the literature. *Onco Targets Ther*. 2014;7:1919-1926. Published 2014 Oct 20.
- Tafuto S, von Arx C, Capozzi M, et al. Safety and activity of metronomic Temozolomide in second-line treatment of advanced neuroendocrine neoplasms. *J Clin Med*. 2019;8(8):1224 Published 2019 Aug 15.
- Koumariou A, Antoniou S, Kanakis G, et al. Combination treatment with metronomic temozolomide, bevacizumab and long-acting octreotide for malignant neuroendocrine tumours. *Endocr Relat Cancer*. 2012;19(1):L1-L4. Published 2012 Jan 9.
- Berruti A, Fazio N, Ferrero A, et al. Bevacizumab plus octreotide and metronomic capecitabine in patients with metastatic well-to-moderately differentiated neuroendocrine tumors: the XELBEVOCT study. *BMC Cancer*. 2014;14:184 Published 2014 Mar 14.
- Brizzi MP, Berruti A, Ferrero A, et al. Continuous 5-fluorouracil infusion plus long acting octreotide in advanced well-differentiated neuroendocrine carcinomas. A phase II trial of the Piemonte oncology network. *BMC Cancer*. 2009;9:388 Published 2009 Nov 3.
- Yao JC, Phan A, Hoff PM, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *J Clin Oncol*. 2008;26(8):1316-1323.
- NCCN. NCCN Guidelines Version 2.2021 Neuroendocrine and Adrenal Tumors. Accessed July 11, 2021. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf
- Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92(3):205-216.
- Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
- Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol*. 2003;13(3):176-181.
- Mueller D, Krug S, Majumder M, Rinke A, Gress TM. Low dose DTIC is effective and safe in pretreated patients with well differentiated

- neuroendocrine tumors. *BMC Cancer*. 2016;16:645 Published 2016 Aug 18.
34. De Divitiis C, von Arx C, Grimaldi AM, et al. Metronomic temozolomide as second line treatment for metastatic poorly differentiated pancreatic neuroendocrine carcinoma. *J Transl Med*. 2016;14(1):113 Published 2016 May 3.
 35. Squadroni M, Di Meglio G, Spada F, et al. Metronomic capecitabine in advanced well or moderately differentiated neuroendocrine carcinomas. *J Clin Oncol*. 2010;28(15_suppl):e13130.
 36. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):514-523.
 37. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors [published correction appears in *N Engl J Med*. 2011 Mar 17;364(11):1082]. *N Engl J Med*. 2011;364(6):501-513.
 38. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2011;378(9808):2005-2012.
 39. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387(10022):968-977.
 40. Cremolini C, Marmorino F, Bergamo F, et al. Phase II randomised study of maintenance treatment with bevacizumab or bevacizumab plus metronomic chemotherapy after first-line induction with FOLFOXIRI plus bevacizumab for metastatic colorectal cancer patients: the MOMA trial. *Eur J Cancer*. 2019;109:175-182.
 41. Romiti A, Onesti CE, Roberto M, et al. Continuous, low-dose capecitabine for patients with recurrent colorectal cancer. *Med Oncol*. 2015;32(3):54.
 42. Schrader J, Henes FO, Blaeker M, et al. Extended cycle streptozotocin/5-FU chemotherapy for maintenance therapy in pancreatic neuroendocrine tumors. *Endocrine*. 2019;65(2):460-467.
 43. Bajetta E, Catena L, Procopio G, et al. Are capecitabine and oxaliplatin (XELOX) suitable treatments for progressing low-grade and high-grade neuroendocrine tumours? *Cancer Chemother Pharmacol*. 2007;59(5):637-642.
 44. Medley L, Morel AN, Farrugia D, et al. Phase II study of single agent capecitabine in the treatment of metastatic non-pancreatic neuroendocrine tumours. *Br J Cancer*. 2011;104(7):1067-1070.
 45. Andreyev HJ, Scott-Mackie P, Cunningham D, et al. Phase II study of continuous infusion fluorouracil and interferon alfa-2b in the palliation of malignant neuroendocrine tumors. *J Clin Oncol*. 1995;13(6):1486-1492.
 46. AIOM. Linee Guida; 2022. Accessed January 12, 2022. https://www.aiom.it/wp-content/uploads/2019/10/2019_Raccomandazioni-analisi-farmacogenetiche.pdf
 47. Del Re M, Cinieri S, Michelucci A, et al. DPYD*6 plays an important role in fluoropyrimidine toxicity in addition to DPYD*2A and c.2846A>T: a comprehensive analysis in 1254 patients. *Pharmacogenomics J*. 2019;19(6):556-563.
 48. Olson RA, Brastianos PK, Palma DA. Prognostic and predictive value of epigenetic silencing of MGMT in patients with high grade gliomas: a systematic review and meta-analysis. *J Neurooncol*. 2011;105(2):325-335.
 49. Trillo Aliaga P, Spada F, Peveri G, et al. Should temozolomide be used on the basis of O6-methylguanine DNA methyltransferase status in patients with advanced neuroendocrine tumors? A systematic review and meta-analysis. *Cancer Treat Rev*. 2021;99:102261.
 50. Kunz PL, Catalano JP, Nimeiri H, et al. A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: a trial of the ECOG-ACRIN cancer research group (E2211). *J Clin Oncol*. 2018;36(15_suppl):4004.
 51. Chen YL, Chang MC, Cheng WF. Metronomic chemotherapy and immunotherapy in cancer treatment. *Cancer Lett*. 2017;400:282-292.
 52. Sarangi SC, Sopory P, Pattnaik SS, Reeta KH. Antibody-drug conjugates, cancer immunotherapy, and metronomic chemotherapy as novel approaches in cancer management. *Indian J Pharmacol*. 2020;52(5):402-413.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Arrivi G, Spada F, Frassoni S, et al. Metronomic chemotherapy in patients with advanced neuroendocrine tumors: A single-center retrospective analysis. *J Neuroendocrinol*. 2022;e13189. doi:[10.1111/jne.13189](https://doi.org/10.1111/jne.13189)