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Efficacy and safety of low-dose metronomic chemotherapy with capecitabine in heavily pretreated patients with metastatic breast cancer

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ABSTRACT

Aim: Registered dose capecitabine monotherapy is active against metastatic breast cancer (MBC), but retrospective analyses indicate that lower doses may be as effective and better tolerated. This study was conducted to assess the safety and efficacy of metronomic capecitabine in heavily pretreated patients with MBC.

Patients and methods: In this phase II study 60 MBC patients received continuous metronomic capecitabine monotherapy (1500 mg once a day). Primary endpoint was clinical benefit rate, secondary end points were clinical benefit rates (CBRs), tumour response rates (RRs), overall survival (OS), time to progression (TTP), duration of response (DOR) and toxicity.

Results: Fifty eight assessable patients received two or more 28-day cycles of metronomic capecitabine. The CBR was 62%. Median DOR was 7 months. Median TTP and OS were 7 and 17 months, respectively. Two partial responses and 7 cases of stable disease were recorded in 13 patients who had previously received capecitabine intermittently (2000 mg/m^2/day on days 1–14 every 21 days) as first- or subsequent-line treatment for MBC. Grade 3–4 adverse events were uncommon; haematologic toxicity was infrequent (5%) and consistently mild.

Conclusion: This regimen of metronomic capecitabine displayed good activity and excellent tolerability in MBC patients, including those who had previously received the drug at standard doses.

1. Introduction

Metastatic breast cancer (MBC) is a highly heterogeneous disease, and decisions regarding its treatment must be driven by multiple considerations, including not only the clinical and biological parameters of the case but also patient preferences.[1] Despite recent advances in our understanding of the biology of MBC and in the development of new types of therapy, the disease remains incurable.[2,3] The goals of treatment are, therefore, palliative – prolonged survival, control of symptoms, improvement or maintenance of quality of life – all of which require a careful balance between treatment efficacy and toxicity.

Capecitabine is an oral fluoropyrimidine carbamate that acts as a 5-fluorouracil (5-FU) prodrug and mimics continuous infusion of 5-FU.[4] It seems to represent an active,

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well-tolerated treatment for MBC,[5] and the oral formulation meets with a high degree of acceptance by both patients and physicians.[6] Several studies have documented the efficacy in MBC of capecitabine monotherapy at the approved dose of 1250 mg/m^2 b.i.d., days 1–14 every 21 days, with overall response rates ranging from 15% to 26%.[7,8] However, dose modifications are often required for the management of adverse events (mainly hand–foot syndrome and diarrhoea), particularly in patients whose cancers have already been heavily treated. The registered monotherapy dose has never been compared with lower doses in a randomised trial, but data from retrospective analyses indicate that dose reduction does not impair efficacy[9] and that lower doses actually have a more favourable therapeutic index in MBC than the standard dosage.[10–12]

Metronomic regimens involve the frequent (daily, or several times a week, or weekly) or continuous administration of chemotherapy agents at low doses, without lengthy drug-free breaks. This approach is known to enhance the antiangiogenic activity of these drugs.[13–15] Protracted exposure to low doses of conventional cytotoxic drugs also offers important advantages in terms of significantly reduced toxicity.[16] Its pharmacokinetic characteristics and low toxicity profile make capecitabine an ideal drug for metronomic administration.[17] In two small randomised trials, continuous use of low-dose capecitabine (650 or 800 mg/m^2 b.i.d. with no drug-free breaks) proved to be just as effective in MBC patients as intermittent use of higher doses (1000 or 1250 mg/m^2 b.i.d. days 1–14 every 21 days).[18,19]

The clinical findings summarised above prompted us to conduct a phase II trial to explore the activity and tolerability of a metronomic capecitabine regimen (1500 mg daily) in heavily pretreated MBC patients.

2. Patients and methods

The protocol for this single-arm, single-centre study was pre-approved by the Institutional Ethics Committee (IEC), and all patients provided IEC-approved informed consent.

2.1. Enrolment

The eligibility criteria for study entry were: histological diagnosis of breast cancer with evidence of progressive metastatic disease; presence of at least 1 measurable lesion (by physical examination and/or imaging studies); previous treatment for MBC with at least one drug regimen (primary and/or adjuvant chemotherapy or endocrine treatment was still allowed, but not considered in the counting of therapy lines for metastatic disease); age >18 years; Eastern Cooperative Oncology Group performance status $\leqslant$3; adequate bone marrow reserve (white blood cell count $\geqslant$3500/μL, neutrophil count $\geqslant$1500/μL, platelet count $\geqslant$100,000/μL, and haemoglobin $\geqslant$9 gr/dL); adequate liver function (total bilirubin $\leqslant$1.5 times the upper limit of normal [ULN] used by our laboratory, alanine aminotransferase and aspartate aminotransferase $\leqslant$3 times the ULN or $\leqslant$5 times the ULN if the patient had liver metastasis); adequate renal function (serum creatinine $\leqslant$2 mg/dL); life expectancy $\geqslant$3 months; absence of a serious medical disorder or active infection that would impair the patient's ability to complete the treatment protocol. Previous chemotherapy had to have been completed at least 4 weeks prior to enrolment in our study. Prior chemotherapy with capecitabine was allowed provided the treatment had been completed or terminated at least 6 months before study entry.

2.2. Treatment protocol and patient assessment

The baseline evaluation included medical history and physical examination, assessment of performance status, body weight and vital signs, complete blood count and differential, measurement of serum creatinine, liver function tests (AST, ALT, alkaline phosphatase). The physical examination and laboratory analyses were repeated every 4 weeks. The tumour assessment was based on computed tomography, magnetic resonance imaging or ultrasonography performed at baseline and at 8-week intervals during follow-up.

All patients received oral capecitabine in a single daily dose of 1500 mg, which was taken $\leqslant$30 min after lunch. Treatment was continuous (i.e. there were no drug-free intervals). To facilitate comparison of results, 28 days of treatment were arbitrarily considered to represent one treatment cycle. The total dose of capecitabine administered during this cycle is 42,000 mg (compared with 35,000 mg/m^2 during a standard 21-day cycle of intermittent therapy). Treatment continued until disease progression or unacceptable toxicity occurred.

2.3. End-points

The primary aim of the study was to assess the activity of the metronomic capecitabine regimen in terms of overall *clinical benefit rates* (CBR), which reflected the proportion of patients with complete responses (CR), partial responses (PR) or prolonged disease stabilization (SD) lasting $\geqslant$24 weeks, as defined by Response Evaluation Criteria in Solid Tumors (RECIST). Secondary end-points included *time to disease progression* (TTP) calculated from the beginning of study treatment to documentation of progressive disease (PD); *overall survival* (OS) measured from the beginning of study treatment to the date of the last follow-up visit or death (any cause); *duration of response* (DOR) calculated from documentation of CR or PR or, when responses consisted in SD, from the beginning of study treatment to documentation of PD; and *toxicity*, which was assessed every 4 weeks according to the National Cancer Institute Common Toxicity Criteria (version 3).

2.4. Statistical analyses

This phase II study was based on the two-step design reported by Simon. We assumed that a response probability of 20% or more would be of interest, and further patient testing would not be pursued if the response rate was less than 20%. The first step provided for the enrolment of 14 patients. If none of these patients responded to the treatment (PR or CR), the study would be terminated and the regimen deemed inactive. If instead one or more responses were observed in

the first 14 patients, 44 additional eligible patients would be enrolled.

Exact 95% confidence intervals (CI) were calculated for CBRs and the overall RR. The Kaplan–Meier method was used to estimate TTP and OS. Patients whose deaths were unrelated to breast cancer or capecitabine therapy were censored in TTP analysis. In the DOR analysis, patients were censored if, at data cut off, they were alive with no evidence of PD or if they had died from causes unrelated to breast cancer or capecitabine treatment.

3. Results

3.1. Patient characteristics

Between October 2006 and July 2010, 60 women with MBC were enrolled in this study. Their baseline characteristics are listed in Table 1. Over half of the cancers were oestrogen receptor- and progesterone receptor-positive, and the vast majority were HER2/neu-negative. Most of the enrolled patients had developed metastases after treatment of stage I or II disease, but in 22 (37%) cases metastatic disease had been present when the cancer was diagnosed. Before enrolment in our study, all 60 patients had already received chemotherapy for MBC, and 15 patients (25%) had been on 3 or more different regimens.

Six patients had HER2/neu positive metastatic disease and received previous treatment with trastuzumab ± chemotherapy ± endocrinetherapy. Four patients received first line trastuzumab plus chemotherapy for HER2/neu positive and once reached the maximum tolerated dose of chemotherapy, they continued trastuzumab plus endocrine therapy until disease progression. Two patients received first line chemotherapy plus trastuzumab.

Adjuvant chemotherapy had been administered to 8 (13%) of the patients, 24 (40%) patients had received adjuvant chemotherapy and endocrine therapy, and 6 patients (10%) had received endocrine therapy alone for early breast cancer. In well over half the cases, the metastatic disease was predominantly non-visceral (involving bone and/or soft tissue), and over 40% of the patients had metastases at three or more sites.

Thirteen (22%) of the 60 patients had already been treated intermittently (every 3 weeks) with capecitabine (2000 mg/m^2 day on days 1–14) plus oral vinorelbine (Navelbine®, 60 mg/m^2 on days 1 and 8). In 12 of these patients (20%), this regimen had been administered as first-line therapy, and the reported results were PD in 3 cases, SD in 7 cases, PR in 1 case and CR in 1 case. In the present study, metronomic capecitabine produced long term SD (⩾24 weeks) in 6 of these 12 cases, PD in 4 others, and PRs in 2. In the thirteenth patient, capecitabine plus vinorelbine had been used as third-line therapy and resulted in SD. The metronomic study regimen represented fifth-line treatment for this patient, and it produced prolonged SD (⩾24 weeks).

Two patients were excluded from the analyses of efficacy and toxicity because at the time of this report they had received less than one 28-day cycle of the treatment (due to late enrolment). The 58 who were assessable had all received at least two 28-day cycles of the study therapy (total no. of cycles delivered: 469; median no. of cycles per patient: 7 [range 2–36]).

Table 1 – Baseline characteristics of the study population.

Enrolled – no. (%)	60 (100)
Assessable– no. (%)	58 (97)
Median age (range) – years	63 (37–82)
Menopause status – no. (%)	
Pre	20 (33)
Post	40 (67)
Median ECOG performance status (range)	1 (0–3)
Metastatic involvement – no. (%)	
Visceral	26 (43)
Non-visceral	34 (57)
No. of metastatic sites – no. (%)	
1	21 (35)
2	13 (22)
⩾3	26 (43)
Hormone receptor status – no. (%)	
ER +/PGR +[a]	39 (66)
ER +/PGR –	8 (12)
ER –/PGR –	13 (22)
HER2/neu status – no. (%)	
Positive [b]	6 (10)
Negative	48 (80)
Unknown	6 (10)
Prior neoadjuvant therapy – no. (%)	
None	54 (90)
CT/HT	1 (2)
CT	5 (8)
Prior adjuvant therapy – no. (%)	
None	22 (37)
CT	8 (13)
HT	6 (10)
CT/HT	24 (40)
Prior therapy for metastatic disease – no. (%)	
CT	17 (28)
CT/HT	37 (62)
CT/HT/trastuzumab	4 (7)
CT/trastuzumab	2 (3)
No. of prior chemotherapy regimens for metastatic disease – no. (%)	
1	
2	33 (55)
⩾3	12 (20)
	15 (25)
No. of prior endocrine therapy regimens for metastatic disease – no. (%)	
1	
⩾2	24 (40)
	14 (23)
Prior capecitabine therapy – no. (%)	13 (22)
Prior trastuzumab therapy – no. (%)	6 (10)

ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; PGR, progesterone receptor; CT, chemotherapy; HT, hormone therapy.

[a] Positive ⩾ 10%.

[b] HER2/neu overexpression reflected by 3+ immunohistochemical labelling or HER2/neu amplification (fluorescence in situ hybridization ratio ⩾2.

Table 2 – Tumour responses.

No. assessable patients – no. (%)[a]	58 (97)
Complete responses – no. (%)	3 (5)
Partial responses – no. (%)	11 (19)
Disease stabilisation – no. (%)	36 (62)
Long-term (>24 weeks) disease stabilisation	22 (38%)
Progressive disease – no. (%)	8 (14)
Overall response rate (%)[b]	24
95% CI	13–35
Clinical benefit rate (%)[c]	62
95% CI	50–74
Median time to progression (range) – months	7 (2–36)
Median duration of response (range) – months	7 (2–32)
Median overall survival (range) – months	17 (1–87)

[a] Two of the 60 patients enrolled had treatment periods <4 weeks and were excluded from efficacy analysis.
[b] Tumour response was assessed according to RECIST criteria.
[c] Clinical benefits included complete and partial responses plus disease stabilisation >24 weeks.

3.2. *Efficacy*

Treatment responses are summarised in Table 2. In the assessable cohort ($n = 58$), there were eight cases (14%) of PD. Three patients had CRs (5%) and 11 had PRs (19%) for an overall RR of 24% (95% CI: 13%–35%). Disease stabilisation was observed in 36 patients (62%) and was long-term (>24 weeks) in 22 (38%). The overall CBR was thus 62% (3 CRs + 11 PRs + 22 SD > 24 weeks) (95% CI: 50–74%). Of the 26 patients with visceral metastases, five experienced PD, three others had PRs, and 18 achieved SD, which lasted >24 weeks in 10 cases. The median overall DOR was 7 months (range 2–32).

Kaplan–Meier curves of time to progression and overall survival are shown in Figs. 1 and 2, respectively. The median TTP was 7 months (range 2–36), and median OS was 17 months (range 1–87). Forty patients (67%) are still alive at the time of this report, and 16 are still receiving metronomic capecitabine.

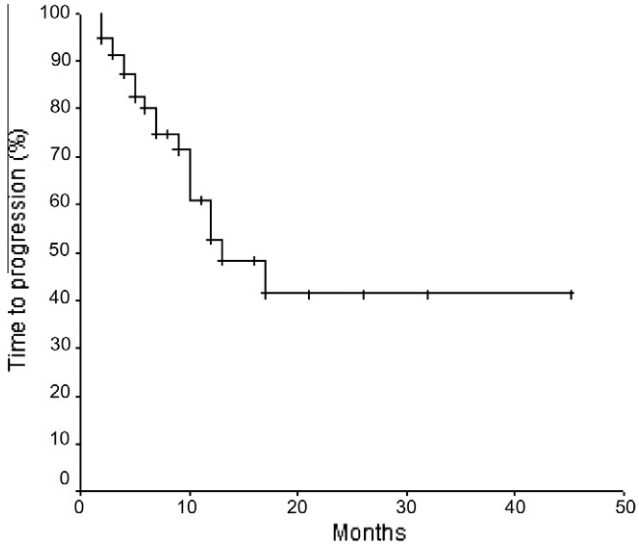

Fig. 1 – Kaplan–Meier curve of time to progression.

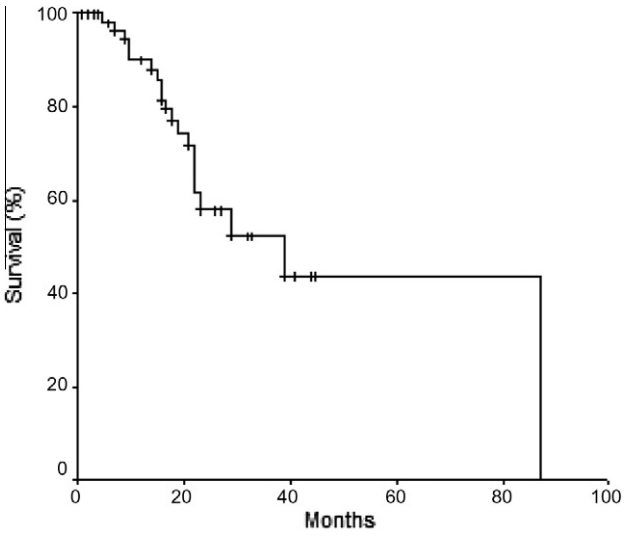

Fig. 2 – Kaplan–Meier curve of overall survival.

3.3. *Safety*

Table 3 shows the main forms of toxicity observed in the 58 assessable patients. On the whole, the treatment was well tolerated. Haematologic toxicity was infrequent and mild. Hand–foot syndrome (10%) and diarrhoea (7%) were the most common adverse effects. There were only three cases of grade 3 toxicity, all involving hand–foot syndrome; it was characterised by skin pain of the feet interfering with walking, but it was rapidly resolved to grade 0–1 with rest and symptomatic treatment (pyridoxine and topical urea/lactic acid-based cream). Dose reduction or interruption of treatment was not required.

Also diarrhoea did not require interruption of treatment or dose adjustments.

4. Discussion

The goals of chemotherapy for metastatic breast cancer are to prolong survival, alleviate or prevent tumour-related symptoms and complications and improve quality of life.[20] The drugs used for this purpose are associated with substantial toxicity that can cause bothersome symptoms, including

Table 3 – Main adverse effects.

Adverse effect	N = 58	
	All grades no. (%)	Grade ⩾ 3 no. (%)
Haematologic – no. (%)		
Leukopenia	1 (2)	–
Thrombocytopenia	2 (3)	–
Non-haematologic – no. (%)		
Diarrhoea	4 (7)	–
Fatigue	2 (3)	–
Anorexia	1 (2)	–
Stomatitis	1 (2)	–
Hand–foot syndrome	6 (10)	3 (5)
Vomiting	1 (2)	–

Table 4 – Reported antitumour activity of metronomic chemotherapy regimens in women with metastatic breast cancer.

Study	Metronomic chemotherapy	No. patients	ORR	CBR	Median TTP
Munzone et al.[13]	Pegylated liposomal doxorubicin	45	18	45	NR
Wong et al.[21]	Cyclophosphamide + methotrexate + prednisone + dalteparin	41	17	24	10
Burstein et al.[22]	Cyclophosphamide + methotrexate	55	10	NR	NR
Colleoni et al.[15]	Cyclophosphamide + methotrexate (arm A)	90	20.9	41.5	NR
	Cyclophosphamide + methotrexate + thalidomide (arm B)	88	11.8	41.5	NR

ORR, objective response rates (%); CBR, clinical benefit rates (%); TTP, time to progression (weeks); NR, not reported.

fatigue, nausea, vomiting, diarrhoea, hair loss, mucositis, neutropenia, and neuropathy. Balancing the benefits and side-effects of chemotherapy is important, particularly when the patient has already been treated with other cytotoxic regimens.

The metronomic capecitabine regimen we tested offers the advantage of palliation without the toxicity associated with standard capecitabine chemotherapy. Furthermore, the administration of capecitabine at the dose of 1500 mg once a day decreases the chance that the patient may forget to take the drug as it could be possible if it is prescribed two or more times a day.

Tolerability was excellent. Severe toxicity was rare and in all cases non-haematological. There was also a low incidence of hand–foot syndrome.

As for efficacy, the overall RR was 24%, and 22 patients experienced SD lasting 24 weeks or more (a reasonable therapeutic end-point in patients with MBC who have already been heavily pretreated), bringing the CBR to 62%. Moreover, the antitumour efficacy of the regimen was unrelated to the number of metastatic sites (three or more in 43% cases) or the type of involvement (predominantly visceral in 43% of our patients). Eighteen of the 26 patients with visceral metastases experienced SD, which were maintained for >24 weeks in 10 cases, and 3 other patients reported PRs.

Thirteen of the 60 patients had been previously treated with intermittent capecitabine (2000 mg/m^2 on days 1–14 every 3 weeks) combined with vinorelbine (60 mg/m^2 on days 1 and 8 every 3 weeks). The median number of cycles per patient was 6 (range 3–14). In most cases, this was first-line therapy, and the results included 1 RC, 1 PR, 7 SDs and 3 PDs, but in one case the regimen had been used as third-line treatment and produced SD. In this subgroup, metronomic capecitabine produced SD in over half the patients and 2 of the 13 had PRs. These findings are consistent with the view that resistance to maximum tolerated doses of a given cytotoxic drug – in this case capecitabine – does not necessarily preclude its later beneficial use in a metronomic regimen.

To our knowledge, this is the first study that examines the safety and efficacy of metronomic capecitabine monotherapy in patients who have already been treated for MBC. As shown in Table 4, however, metronomic regimens of other chemotherapy agents have been tested in this setting with objective RRs of 10–21% and CBRs of 24–45%.

In a recently published phase II trial, Dellapasqua et al.[23] evaluated chemotherapy with capecitabine (500 mg t.i.d.) and cyclophosphamide (50 mg daily) plus bevacizumab (10 mg/kg every two weeks) in patients who had received no more than three previous regimens of chemotherapy for advanced disease. Objective response and SD rates were 46% and 41%, respectively.

In a randomised phase III trial by investigators from the Australian New Zealand Breast Cancer Trials Group, continuous or intermittent administration of capecitabine monotherapy in a first-line setting was also associated with a significant survival benefit as compared with the classic cyclophosphamide, methotrexate and 5-fluorouracil combination (HR 0.72; 95% CI: 0.55–0.94, $P = 0.02$).[18] Unfortunately, this trial was terminated early because of slow accrual, and to date the results have been reported only in abstract form.

Martin et al. conducted a phase II trial comparing continuous versus intermittent capecitabine monotherapy as first- or second-line treatment for MBC. The interim analysis (which comprised 60 patients) demonstrated the non-inferiority of the continuous schedule, which was also somewhat better tolerated than the intermittent regimen.[19]

A phase III study is now underway to evaluate metronomic capecitabine (Xeloda®, Manufacturer; 650 mg/m^2 b.i.d. for 1 year) as adjuvant therapy for operable, triple-negative breast cancer. Disease-free survival will be evaluated in patients randomised to treatment with standard adjuvant chemotherapy alone or standard adjuvant chemotherapy followed by 1 year of metronomic capecitabine therapy.[24]

In conclusion, our findings indicate that metronomic capecitabine is a valid option for pretreated women with metastatic breast cancer. The regimen we tested is characterised by good antitumour activity, no disabling adverse effects, and manageable haematological toxicity. The oral route of administration offers the additional advantages of home treatment, which can reduce stress and improve the quality of life.

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Conflict of interest statement

None declared.

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