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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