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Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer

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Abstract

Treating patients with anthracycline- and taxane-pretreated metastatic breast cancer (MBC) represents a significant challenge to oncologists. The tumour-activated oral fluoropyrimidine, capecitabine, is the only treatment approved for these patients. Our study evaluated the efficacy, safety and impact on quality of life (QOL) of capecitabine in this setting. Patients ($n=126$) with anthracycline- and taxane-pretreated metastatic breast cancer received capecitabine 1250 mg/m^2 twice daily, days 1–14, followed by a 7-day rest period. Median time to progression was 4.9 months (95% Confidence Interval (CI): 4.0–6.4). Thirty-five patients (28%) achieved an objective response (95% CI: 20–36%), including five (4%) complete responses. Median overall survival was 15.2 months (95% CI: 13.5–19.6 months). Capecitabine demonstrated a favourable safety profile, with a low incidence of treatment-related grade 3/4 adverse events. The most common adverse events were hand–foot syndrome and gastrointestinal effects. QOL assessment showed that capecitabine treatment was associated with an increase in mean Global Health Score. Capecitabine is active, well tolerated and improves the QOL of patients with anthracycline- and taxane-pretreated metastatic breast cancer. Based on the consistently high activity demonstrated in clinical trials, capecitabine has become the reference treatment in this setting.

Keywords: Anthracycline; Capecitabine; Efficacy; Fluropyrimidine; Metastatic breast cancer; Oral; Phase II; Quality of life; Safety; Taxane

1. Introduction

Anthracyclines are established as first-line chemotherapy for metastatic breast cancer, while in patients whose disease progresses following anthracycline-based therapy, the taxanes paclitaxel and docetaxel (alone or in combination with capecitabine) are the current 'standard of care'. Recent years have seen a general shift towards the use of more aggressive therapy earlier in the course of breast cancer, including adjuvant anthracyclines in patients with primary, non-metastatic disease [1,2]. Combinations of anthracyclines and taxanes are

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also under evaluation, both as adjuvant/neoadjuvant therapy and as first-line therapy in metastatic disease [3–5]. As a consequence, the number of patients whose disease is resistant or refractory to anthracyclines and taxanes, or who can no longer tolerate these agents, is increasing.

The treatment of anthracycline- and taxane-pretreated patients presents particular challenges for the oncologist. As cure is unlikely at this stage, treatment is primarily palliative. The goal of therapy is therefore to reduce tumour burden and related symptoms and, ultimately, prolong survival, while maintaining quality of life (QOL) by minimising toxicity. The oral fluoropyrimidine, capecitabine, is the only approved treatment for patients with anthracycline- and taxane-pretreated metastatic breast cancer. Capecitabine was rationally designed to generate 5-fluorouracil (5-FU) preferentially in tumour tissue and enable chronic dosing that mimics continuous infusion 5-FU [6]. Following gastrointestinal absorption, capecitabine is metabolised to 5-FU by a three-step enzymatic process, the final step of which is catalysed by the enzyme thymidine phosphorylase. As thymidine phosphorylase activity is significantly higher in tumour compared with normal tissue, 5-FU is generated preferentially in tumour tissue following capecitabine therapy [6,7]. Furthermore, the oral administration of capecitabine is more convenient and enables home-based therapy, which is associated with a significantly improved QOL compared with hospital-based therapy in patients with advanced cancer [8]. Questionnaire-based studies have demonstrated that most patients, given the choice, prefer to receive oral rather than intravenous (i.v.) chemotherapy, provided efficacy is not sacrificed [9,10].

Clinical trials show that capecitabine monotherapy is active and well tolerated in patients with taxane-pretreated metastatic breast cancer [11–15] and a promising first- and second-line therapy for metastatic breast cancer [16,17]. A large, phase III trial has demonstrated that capecitabine in combination with docetaxel results in significantly superior efficacy, including superior time to disease progression (TTP), response rates and overall survival, compared with single-agent docetaxel in patients with anthracycline-pretreated metastatic breast cancer [18]. Capecitabine plus docetaxel is the first cytotoxic combination to improve survival over standard docetaxel and the combination is approved for the treatment of anthracycline-pretreated metastatic breast cancer patients in the United States of America (USA) and Europe.

The approval of capecitabine monotherapy for the treatment of patients with anthracycline- and taxane-pretreated metastatic breast cancer was based on the results of a large, multicentre, phase II trial [11]. In this study, capecitabine achieved an overall response rate of 20% in 163 patients with paclitaxel-pretreated metastatic breast cancer, with disease stabilisation in a further 40% of patients. In addition to favourable response rates, median overall survival was 12.6 months. Importantly, overall survival was similar in patients with disease stabilisation or a tumour response (median 15.0 and 16.6 months, respectively), and much longer than in those with disease progression (median 5.3 months) [12]. These data confirm previous studies showing that disease stabilisation is a meaningful clinical outcome [19]. The safety profile of capecitabine was typical of infused 5-FU, with gastrointestinal side-effects and hand–foot syndrome the most commonly occurring adverse events. Grade 4 adverse events, myelosuppression and alopecia were particularly rare.

Subsequent studies have further demonstrated the high efficacy and favourable safety profile of capecitabine in anthracycline- and taxane-pretreated patients [13–15].

We report here, a phase II study conducted in 17 French centres to evaluate the efficacy and safety of capecitabine in this setting. In addition, this is the first study formally evaluating the impact of oral capecitabine monotherapy on QOL in patients with anthracycline- and taxane-pretreated metastatic breast cancer.

2. Patients and methods

Women aged 18–75 years with histologically-confirmed locally advanced or metastatic breast cancer and at least one measurable metastatic lesion were eligible for the study. Patients were required to have received either two or three prior chemotherapies, including an anthracycline and a taxane, and to have normal haematological, hepatic, renal and cardiological parameters, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and a life expectancy of at least 3 months. A minimum 3-week interval following any prior chemotherapy was required before inclusion in the study. Pretreatment screening assessments were conducted within 15 days prior to treatment start and included full clinical examination, medical history, radiological examination, electrocardiogram (ECG) and evaluation of laboratory parameters. The study was performed according to the Helsinki declaration and written informed consent was obtained from all patients.

2.1. Study design and treatment

This was a single-arm, open-label, multicentre, phase II study conducted between December 1998 and October 2001. The primary endpoint of the study was TTP, or death in patients with no evidence of disease progression. Secondary endpoints included tumour response rate, overall survival, QOL and safety.

Patients received 21-day cycles of oral capecitabine 1250 mg/m^2 twice daily for 14 days followed by a 7-day rest period. In patients experiencing adverse events of grade 2 or higher severity, the standard capecitabine dose modification scheme, described in detail by Blum and colleagues [11], was applied. Treatment was continued for a maximum of 15 cycles or until tumour progression.

2.2. Study assessments

Tumour responses were evaluated every three cycles, based on standard World Health Organisation (WHO) criteria [20]. The best overall response achieved was reported. In responding patients, the response had to be confirmed a minimum of 4 weeks after the response was first observed. TTP was defined as the interval between treatment start and tumour progression, or death in patients with no evidence of disease progression. Duration of response was assessed only in patients achieving an objective response (complete or partial) at cycle 3, and was defined as the interval between this objective response and disease progression or death.

Safety was evaluated in patients who received at least one dose of capecitabine. Adverse events were graded 1–4 according to National Cancer Institute of Canada Common Toxicity Criteria. Hand–foot syndrome (palmar-plantar erythrodysaesthesia) was graded 1–3, as defined in previous capecitabine trials [11,21]. QOL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QOL questionnaire C30 (version 2.0) [22] at screening and subsequent clinic visits (every three cycles), and when going off study. The questionnaire was completed prior to any other assessment at each visit.

2.3. Sample size determination

In a previous study of capecitabine monotherapy in anthracycline and paclitaxel-pretreated metastatic breast cancer, the median TTP was 3 months [11]. Based on this figure and an expected standard error of 5.1 days, 100 patients would be required to determine a 95% Confidence Interval (CI). The planned recruitment figure was therefore 120 patients, to allow for drop-outs and protocol violations.

2.4. Statistical analyses

TTP and overall survival were estimated using the Kaplan–Meier method. Patients withdrawing from the trial or lost to follow-up were censored at the date of drop-out or last review. Clinical cut-off for the study analysis was 22 April 2002. A minimum follow-up of 15 months had been reached for all patients. For QOL, according to the manuals, the 30 questions of the EORTC QLQ-C30 were grouped in Functional Scales and Symptom Scales. The nine scales and the six items were described at cycle (C)3, C6, C9, Cl 2 and Cl 5 using usual descriptive statistics. It was considered that patients failing to complete a questionnaire were more likely to have progressive disease (and poorer QOL), and therefore no attempt was made to replace missing data by bringing forward earlier observations.

3. Results

3.1. Patient demographics

A total of 126 patients were recruited to the study and all received at least one cycle of capecitabine. Of these, only one patient did not have measurable or evaluable disease at the initial assessment. Patient demographics are summarised in Table 1. All but one patient (99%) had previously received at least one prior taxane-containing therapy and 96% had previously received an anthracycline.

3.2. Efficacy

Efficacy was evaluated in the intent-to-treat (ITT) population ($n = 126$). The Kaplan–Meier curve for TTP, the primary endpoint of the study, is shown in Fig. 1. Median TTP was 4.9 months (95% CI: 4.0–6.4).

Table 1
Patient demographics ($n = 126$)

	n	(%)
Median age in years (range)	54 (30–80)	
ECOG performance status[a]		
0	55	(44)
1	61	(49)
2	9	(7)
Previous lines of chemotherapy		
1	4	(3)
2	65	(52)
3	43	(34)
⩾4	14	(11)
Previous chemotherapy agents		
Anthracycline	121	(96)
Taxane	125	(99)
Paclitaxel only	19	(15)
Docetaxel only	99	(79)
Both paclitaxel and docetaxel	7	(6)
5-FU	114	(90)
Sites of metastasis[b]		
Bone	71	(56)
Liver	69	(55)
Lung	33	(26)
Lymph node	29	(23)

ECOG, Eastern Cooperative Oncology Group; 5-FU, 5-fluerouracil.
[a] Data unavailable for one patient.
[b] Sixty-seven per cent of patients had multiple metastatic sites.

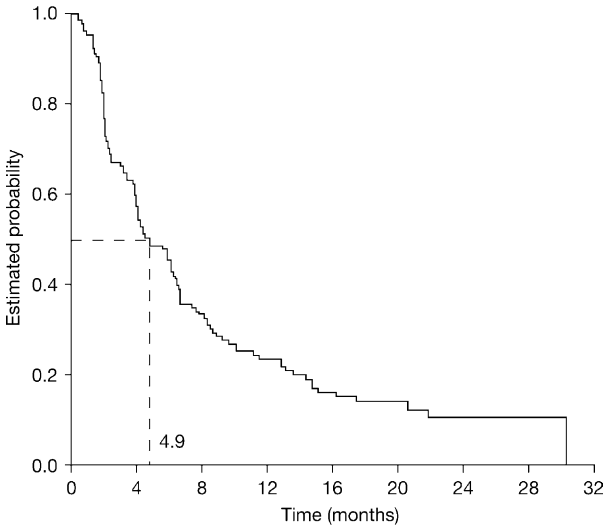

Fig. 1. Time to disease progression (intent-to-treat (ITT) population, $n = 126$).

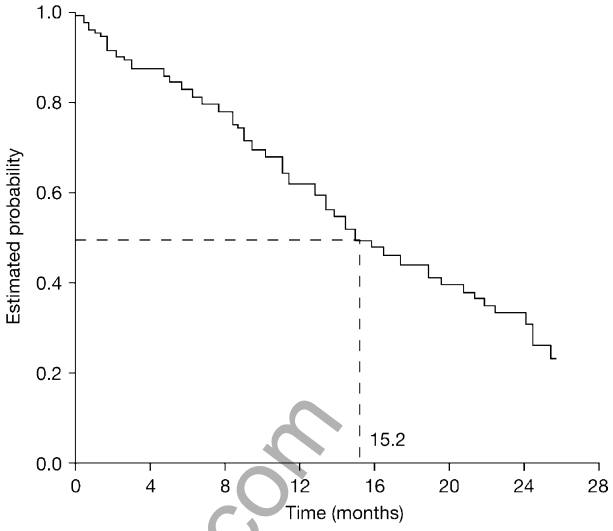

Fig. 2. Overall survival (ITT population, $n = 126$).

Table 2
Tumour response to capecitabine (ITT population, $n = 126$)

	n	(%)
Objective responses[a]	35	(28)
Complete response	5	(4)
Partial response	30	(24)
Stable disease	44	(35)
Disease progression	47	(37)

ITT, intent-to-treat.
[a] Confirmed.

Table 3
Summary of all grade 3/4 laboratory events

Laboratory parameter	Grade 3		Grade 4	
	Patients	(%)	Patients	(%)
Lymphocytopenia	61	(48)	13	(10)
Neutropenia	6	(5)	1	(1)
Thrombocytopenia	0	(0)	2	(2)
Anaemia	1	(1)	2	(2)
Hyperbilirubinaemia	16	(13)	3	(2)
Phosphatase elevation	10	(8)	0	(0)
AST elevation	5	(4)	0	(0)
ALT elevation	2	(2)	0	(0)

AST, aspartate aminotransferase; ACT, alanine aminotransferase.

Objective, confirmed responses occurred in 35 patients (28%; 95% CI: 20–36%), with complete responses in five patients (4%) and partial responses in 30 patients (24%) (Table 2). Disease was stabilised in an additional 44 patients (35%). Among the 24 patients achieving an objective response at cycle 3, median duration of response was 5.9 months (95% CI: 4.5–12.7 months).

Currently, after a minimum follow-up of 15 months, median overall survival is 15.2 months (95% Cl: 13.5–19.6 months) (Fig. 2). To date, 81 deaths have been recorded. Of these, 17 patients died while on study treatment or within 28 days after withdrawal, and the remaining 64 died during the post-trial follow-up. One-year survival was 62.3% (Kaplan–Meier estimate with six patients censored).

3.3. Safety

Patients received a total of 874 cycles of treatment during the study, with a median of six cycles (range 1–15) per patient. Median treatment duration was 4.1 months (range 0.1–13.0 months). The median daily dose administered was 1210 mg/m^2 twice daily (range 715–1396 mg/m^2 twice daily). Dose reduction for adverse events was required by 47 patients (37%). The adverse events most commonly (>5% of patients) leading to dose reduction were hand–foot syndrome (22 patients), neutropenia (10 patients) and diarrhoea (7 patients). The median time to first dose reduction was 1.8 months, corresponding to the third treatment cycle (95% CI: 1.3–2.5 months).

The most common (>20% patients) treatment-related adverse events were hand–foot syndrome (71%), nausea (48%), diarrhoea (48%), asthenia (35%), vomiting (27%), neutropenia (26%), and stomatitis (25%) (Fig. 3). Most treatment-related adverse events were mild to moderate in intensity and the only grade 3/4 adverse events occurring in more than 5% of patients were hand–foot syndrome (21%, grade 3 only), diarrhoea (10%) and neutropenia (14%). There were no treatment-related deaths.

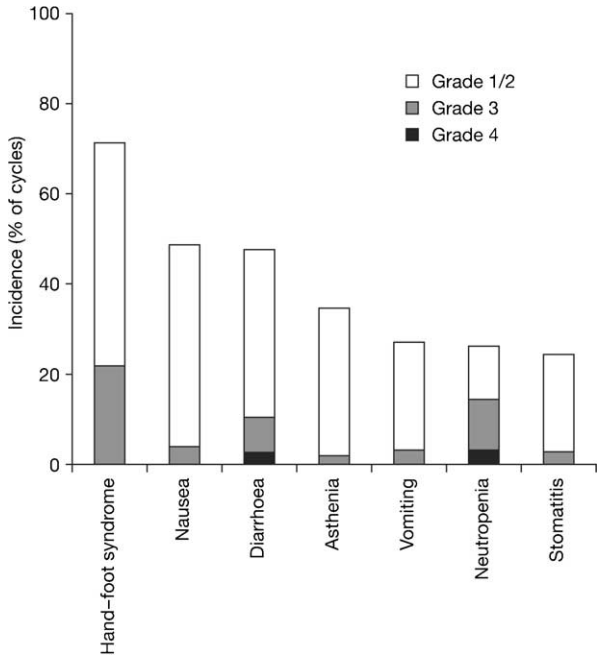

Fig. 3. Most common adverse events (>20% of patients, all grades).

3.4. Laboratory abnormalities

The most common grade 3/4 laboratory abnormalities were lymphocytopenia and hyperbilirubinaemia, which occurred in 59 and 15% of the patients, respectively (Table 3).

Hyperbilirubinaemia was an isolated laboratory abnormality, not associated with grade 3/4 elevations in transaminases or alkaline phosphatase in most patients.

3.5. Quality of life

A total of 119 patients completed the EORTC QLQ-C30 at their first visit, before commencing treatment. At cycles 3 and 6, questionnaires were completed by 78 and 46 patients, respectively. Fig. 4 shows the mean change in QOL scores for Global Health Status over time. In patients who completed a questionnaire, mean Global Health Status increased up to cycle 6, with the increase maintained at subsequent evaluations.

4. Discussion

Prior to the introduction of capecitabine, there was no standard treatment for patients with metastatic breast cancer previously treated with both anthracycline- and taxane-based therapy. In this setting, patients require palliative therapy that offers a good prospect of tumour response and alleviation of tumour-related symptoms as well as prolongation of life, but with minimal toxicity and without substantial adverse impact on QOL.

The current study confirms previous findings that oral capecitabine is a highly effective treatment for patients with heavily pretreated metastatic breast cancer. Capecitabine achieved a median TTP of 4.9 months with an objective response rate of 28% and median overall survival of 15.2 months. These results are impressive considering the poor-prognosis of the patients in this population. More than half the patients had liver metastases and 67% had multiple metastatic sites. The results of this study are consistent with those of previous studies evaluating capecitabine in this setting, which demonstrated objective response rates of 15–26%, and disease control rates of 57–63%, with median TTP and overall survival of approximately 3 and 12 months, respectively [11–15].

The safety profile of capecitabine was also consistent with that observed in previous studies of capecitabine monotherapy [11–17]. Both alopecia and myelosuppression were rare. Most treatment-related adverse events were mild or moderate in intensity and the most frequent adverse event was hand–foot syndrome, a cutaneous condition characteristic of chronic fluoropyrimidine administration. With capecitabine, hand–foot syndrome rarely leads to hospitalisation and, like other capecitabine-related side-effects, is manageable by treatment interruption and dose reduction, if necessary.

The favourable safety profile of capecitabine is due, in part, to the twice-daily oral administration schedule, which offers numerous opportunities to adjust the dose to each patient's individual tolerability. Previous studies show that the capecitabine dose modification scheme is effective in reducing the recurrence of side-effects or the development of more severe adverse events [12,23]. Patients receiving capecitabine should be educated to recognise side-effects and their severity. It is important that patients interrupt treatment upon the development of a moderate or more severe toxicity and, if necessary, contact their physician or nurse for further advice. Importantly, efficacy is maintained in patients requiring capecitabine dose modification. A retrospective analysis of the pivotal phase II trial in paclitaxel-pretreated metastatic breast cancer patients [11] confirmed that the risk of disease progression or death was not increased in patients requiring capecitabine dose modification for adverse events compared with patients who did not require dose modification (Hazard Ratio = 1.02, Wald test $P = 0.935$) [12].

The activity and good tolerability of capecitabine, along with the convenience of an oral, home-based therapy, would be expected to contribute to a significantly improved QOL. The positive impact of capecitabine therapy on mean Global Health Status was evident at the first post-baseline evaluation (after three cycles) and was maintained for the duration of treatment (until cycle 15) in patients who completed QOL

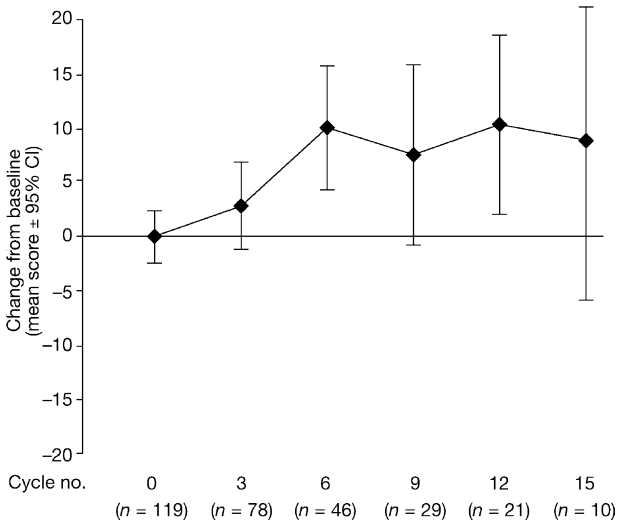

Fig. 4. Mean change in Global Health Status over the treatment period. 95% CI, 95% Confidence Interval.

questionnaires. This is the first study to demonstrate that response to capecitabine treatment is associated with an improved QOL, and extends the findings of Blum and colleagues in Ref. 11, who reported that most patients receiving capecitabine had an improved or stable Clinical Benefit Response score, a composite of pain intensity, analgesic consumption and Karnofsky performance score. In addition, 47% of the 51 patients with significant pain at baseline experienced a durable, $\geqslant 50\%$ decrease in pain intensity in the study by Blum and colleagues.

To date, capecitabine is the only agent to have demonstrated such consistent efficacy in a large population ($n = 730$) of anthracycline- and taxane-pretreated patients treated in multiple trials. A range of chemotherapy agents, including the taxanes, vinorelbine and gemcitabine, have been evaluated in this setting, predominantly in small, single-centre trials that do not allow definitive conclusions about efficacy and safety to be drawn. However, results suggest that an acceptable balance of efficacy and safety has been difficult to achieve in heavily pretreated patients. Paclitaxel is clinically active in docetaxel-pretreated patients, but most patients experienced grade 4 neutropenia [24]. Similar results were reported with docetaxel in paclitaxel-pretreated patients [25]. Attempts to improve the safety profile of vinorelbine by dose reduction led to a loss of antitumour activity [26], and neutropenia was dose-limiting with high-dose vinorelbine in paclitaxel-pretreated patients, despite the co-administration of granulocyte colony-stimulating factor [27]. In a recently reported study, it was concluded that gemcitabine, which failed to achieve any objective responses, is ineffective in patients with anthracycline- and taxane-pretreated metastatic breast cancer [28]. Combination chemotherapy regimens have, in some instances, achieved high response rates of 25–60% [29–33], but it is not clear if these translate into significant improvements in survival. The inconvenience and toxicity associated with the administration of multiple i.v. agents present significant and possibly prohibitive drawbacks to their use in heavily pretreated patients, for whom palliation and maintenance of QOL are the primary goals of treatment. Therefore, capecitabine is the only treatment evaluated in anthracycline- and taxane-pretreated breast cancer that successfully combines meaningful clinical efficacy with a good safety profile.

In conclusion, this study confirms that oral capecitabine is an effective and well-tolerated agent that also improves QOL in patients with anthracycline- and taxane-pretreated metastatic breast cancer. The activity of capecitabine has now been proven across several studies in this setting. Given the clear preference among patients with advanced cancer for oral therapy, capecitabine merits consideration as 'standard therapy' for anthracycline and taxane-pretreated patients.

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