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Clinical experience of capecitabine in metastatic breast cancer

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Abstract

Results from two phase II studies in metastatic breast cancer have shown that the novel, tumour-selective fluoropyrimidine capecitabine provides an effective and well tolerated therapy in patients with metastatic breast cancer failing or resistant to anthracycline and taxane therapy. Response rates of between 20 and 25% have been observed, with median survival of 12.2–12.6 months. In addition, there was an acceptable incidence of adverse events including diarrhoea and hand–foot syndrome, which can be controlled with a dose reduction. Promising results from two further randomised, phase II studies have indicated that capecitabine may also play a role in first- and second-line treatment of metastatic breast cancer. Capecitabine compared favourably with paclitaxel in anthracycline-resistant patients and with intravenous (i.v.) CMF (cyclophosphamide/methotrexate/5-fluorouracil (5-FU)) in post-menopausal women who had received no prior chemotherapy for metastatic disease, with high efficacy and good tolerability. The results of these four phase II studies demonstrate that capecitabine is active and well tolerated in a range of settings for metastatic breast cancer.

Keywords: Capecitabine; Breast cancer; Paclitaxel; Anthracyclines; Fluoropyrimidines

1. Introduction

Breast cancer is the most common cancer among women in Europe and the USA, and approximately 30–40% of all patients treated with curative intent will develop metastatic disease. The average survival time for patients after the diagnosis of metastatic disease is 18–30 months, but this varies widely according to the metastatic site of disease [1], being bleak in patients with visceral disease, for whom the median survival is approximately 6–13 months.

Breast cancer is a highly heterogeneous disease and in patients who are resistant to hormonal therapy, hormone-receptor negative, or in patients with rapidly growing visceral disease, systemic cytotoxic chemotherapy is the treatment of choice [2]. The aims of chemotherapy in this setting are to relieve tumour-related symptoms and maintain the patient's quality of life by inducing remission and maintaining control of the disease. Although chemotherapy can achieve a modest improvement in survival and relief of tumour-related symptoms in many patients, those who have been heavily pretreated for their metastatic disease present a particular problem as they are often symptomatic and have exhausted all standard treatment options. A number of chemotherapeutic approaches have been tested in patients failing anthracycline and/or paclitaxel treatment, but owing to a lack of obvious clinical benefit, no optimal treatment option has been established.

New agents are clearly needed, and the ideal cytotoxic agent in this setting would offer a reasonable prospect of anti-tumour response and a reduction in tumour-related symptoms, improve progression-free and overall survival and maintain patients' performance status with minimal toxicity. Furthermore, enhanced convenience, patient preference for oral therapy and improved patient control over treatment are important considerations in this setting [3,4].

2. Capecitabine as an alternative to continuous infusion 5-fluorouracil

Continuous infusion 5-fluorouracil (5-FU) is effective in metastatic breast cancer, but this treatment is labour intensive, cumbersome and inconvenient for the patient. In addition, continuous infusion 5-FU can lead to

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catheter-related complications in 20–40% of patients [5]. Continuous infusion 5-FU is associated with a response rate of 12% in women with metastatic breast cancer pretreated with paclitaxel and anthracyclines [6]. Major toxicities include mucositis and hand–foot syndrome, as well as problems related to central venous access. Clearly, there is a need for an oral agent that is capable of mimicking continuous infusion 5-FU, but with improved convenience and tolerability for patients.

Capecitabine is a novel, enzymatically-activated fluoropyrimidine carbamate that is converted to 5-FU preferentially in tumour tissue. In addition, as capecitabine is an oral compound, chronic daily dosing is possible, therefore conveniently mimicking the effects of continuous infusion 5-FU therapy. Capecitabine is converted to 5-FU via a triple enzymatic pathway that exploits the higher concentrations of the enzyme thymidine phosphorylase present at the tumour site compared with normal tissue. A number of phase II trials have been conducted with capecitabine in metastatic breast cancer patients pretreated with paclitaxel, docetaxel and/or anthracyclines, and also as first-line treatment versus intravenous (i.v.) CMF (cyclophosphamide/methotrexate/5-FU).

3. Capecitabine in patients pretreated with taxanes

Two phase II studies have shown that capecitabine is effective in advanced/metastatic breast cancer patients whose disease has progressed during or following taxane (paclitaxel and/or docetaxel) therapy. Patients in these studies had already received at least two cytotoxic chemotherapy regimens with at least one including a taxane. The dosing schedule for capecitabine was 1250 mg/m^2 twice daily, administered for 14 days followed by a 7-day rest period (intermittent schedule). Capecitabine was taken within 30 min of breakfast and dinner, with water, and doses were adjusted based on toxicity. Patients were allowed to continue therapy until disease progression or unacceptable toxicity.

3.1. Paclitaxel-pretreated patients

The first open-label, multicentre, phase II study involved 163 heavily pretreated metastatic breast cancer patients who had failed or were refractory to paclitaxel [7]. All patients entered a 1-week run-in period during which they were assessed for adequate pain control, and those with no pain or stable pain were entered into the study. Inclusion criteria included a Karnofsky Performance Status (KPS) of at least 70% and prior treatment with at least two, but not more than three prior chemotherapeutic regimens, one of which must have included paclitaxel as treatment for metastatic disease. The primary objective of the study was to demonstrate a response rate with capecitabine in the order of 20%. Other objectives included evaluation of safety and tolerability of capecitabine, determination of the duration of response and overall survival, and evaluation of clinical benefit. This was assessed using a Clinical Benefit Response (CBR) scoring system, a composite profile of the patient's pain intensity, analgesic consumption and performance status. The definitions of positive CBR are shown in Table 1.

Of the 163 patients enrolled, 162 received capecitabine and were included in the analysis. A total of 135 patients presented with measurable disease and 27 had evaluable disease. The mean age of patients was 55.8 years (range 26–78 years) with a mean KPS of 86.2% (range 70–100%). All patients had received prior paclitaxel, 91% had received prior anthracyclines and 82% had received prior bolus 5-FU (as part of CMF or cyclophosphamide/doxorubicin/5-FU (CAF) regimens). The mean number of prior chemotherapeutic agents was 4.7 and the mean number of prior chemotherapeutic

Table 1
Definition of positive Clinical Benefit Response [7]

Pain intensity	$\geqslant$50% reduction in patients with baseline pain $\geqslant$20 mm using the daily Memorial Pain Assessment Card
Analgesic consumption	$\geqslant$50% reduction in patients with baseline analgesic consumption $\geqslant$70 mg morphine equivalents/week
Karnofsky Performance Status	Improvement of $\geqslant$20 points

Table 2
Capecitabine phase II trial in metastatic breast cancer patients pretreated with paclitaxel

	Overall (n = 162)	Measurable disease (n = 135)	Evaluable disease (n = 27)
Objective response rate (%)	20	20	19
Complete response (%)	2	2	0
Partial response (%)	18	18	19
Stable disease (%)	43	40	60
Progressive disease (%)	31	34	14
Incomplete data (%)	6	6	7

Reproduced with permission from Blum and colleagues [7].

regimens was 2.5. In addition, 75% of the patients had more than two metastatic sites at baseline.

Capecitabine demonstrated high antitumour activity in this heavily pretreated patient population. The overall response rate with capecitabine was 20%, with a further 43% of the patients achieving disease stabilisation (Table 2). Additionally, in a retrospectively-defined subgroup of 42 patients with breast cancer resistant to both anthracyclines and paclitaxel the response rate was 29%. The median survival for the entire population was 12.6 months, with a median survival of 12.8 months in the subgroup of patients who achieved disease stabilisation (Fig. 1). The median survival in patients achieving a tumour response had not been reached at the time of clinical cut-off. CBR data were available for 147 patients, 29 (20%) of whom had an improved score following treatment. A further 45 patients (31%) had a stable CBR score. Of 51 patients with considerable tumour-related pain at baseline, 47% achieved a durable reduction in pain intensity of more than 50%, thereby demonstrating the palliative effect of capecitabine treatment.

Capecitabine treatment was well tolerated with the most frequently reported adverse events being cutaneous effects (hand–foot syndrome), gastrointestinal effects (diarrhoea, nausea and vomiting) and fatigue. The majority of these events were graded as mild to moderate in intensity. Of note, alopecia was rarely observed. Moreover, in some patients with alopecia at baseline, hair regrowth was observed during capecitabine therapy. The only grade 3/4 adverse events occurring in more than 5% of patients were diarrhoea (14%), hand–foot syndrome (10%) and fatigue (7%), all of which were manageable with dose interruption and/or adjustment. Myelosuppression was rare, with grade 3/4 toxicity in the white blood cell count observed in 2.5% of patients, haemoglobin in 1.2% of patients and platelets in 3.1% of patients. Grade 4 events occurred in only 4% of patients. There were no treatment-related deaths during the study.

3.2. Capecitabine in taxane-refractory patients

A confirmatory phase II trial of the intermittent capecitabine schedule included 75 metastatic breast cancer patients who had received two to three prior chemotherapy regimens and were resistant to or had failed treatment with docetaxel and/or paclitaxel [8]. The primary objective of the study was evaluation of the overall response rate, with secondary objectives including time to disease progression, overall survival, duration of response and assessment of safety.

Of the 75 patients enrolled, 74 received capecitabine treatment. All patients had received prior chemotherapy with either paclitaxel or docetaxel, and 8 patients (11%) had received treatment with both of these agents. The patients included in the study were all heavily pretreated: the majority had received at least three prior chemotherapeutic regimens and 85% had received four or more cytotoxic agents.

The overall response rate with capecitabine was 25%. Partial responses were confirmed in 17 of 69 (25%) patients with measurable disease, with a further 30% of patients achieving disease stabilisation. Similar response rates were seen in the paclitaxel- and docetaxel-pretreated patients (27 and 20%, respectively). The median duration of response was 8.3 months, median time to disease progression was 3.2 months and the median survival was 12.2 months.

As in the previous trial, treatment with capecitabine was well tolerated; the most common treatment-related adverse events were hand–foot syndrome, diarrhoea, nausea, vomiting and stomatitis. Of note, capecitabine was associated with a low incidence of myelosuppression, neurological toxicity and alopecia. Adverse events were easily managed by individual dose titration.

4. Capecitabine as first- and second-line treatment

Two additional open-label, randomised, phase II studies of capecitabine in patients with metastatic breast cancer have also been conducted, and have indicated that capecitabine is an active therapy in the first- and second-line settings.

4.1. Capecitabine versus paclitaxel

In the first study, 43 patients with anthracycline-resistant metastatic breast cancer were randomised to treatment with either capecitabine (1250 mg/m^2 twice daily, intermittent or continuous regimen) or paclitaxel (175 mg/m^2 i.v. on day 1 every 3 weeks) [9]. Of the 43 patients enrolled, two received continuous capecitabine,

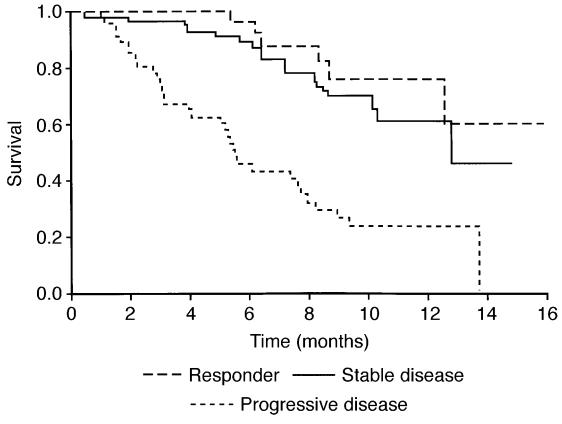

Fig. 1. Capecitabine in paclitaxel-failing breast cancer: survival time, subgroup analysis. Reproduced with permission, Blum JL, *et al.* Multicenter phase II study of capecitabine in paclitaxel refractory metastatic breast cancer. *J Clin Oncol* 1999, **17**(2), 485–493.

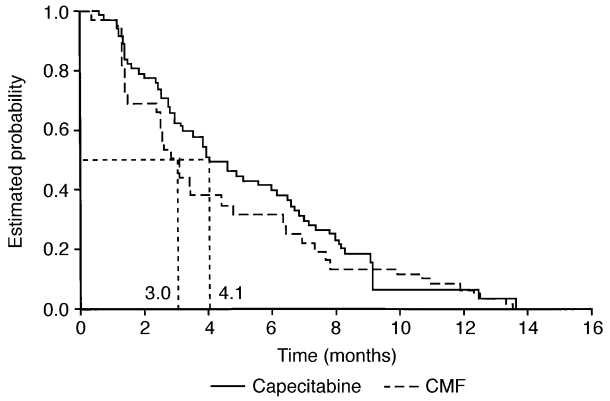

Fig. 2. Capecitabine versus cyclophosphamide/methotrexate/5-FU (CMF): time to disease progression.

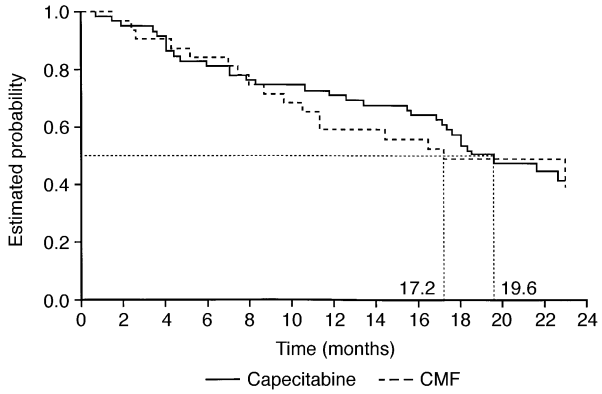

Fig. 3. Capecitabine versus cyclophosphamide/methotrexate/5-FU (CMF): overall survival.

22 received intermittent capecitabine, and 19 received paclitaxel. The continuous regimen capecitabine arm was closed after enrolment of only 2 patients because the intermittent regimen was selected for further development following completion of a randomised, phase II trial in colorectal cancer. The median age of the patients was 52.0 years in both the intermittent capecitabine group and the paclitaxel group. Median KPS scores were 82.5 and 80.0%, respectively.

The response rates were 36 and 26% in the intermittent capecitabine and paclitaxel arms, respectively. Owing to the small sample size, the 95% Confidence Intervals (CIs) were overlapping. 3 patients (14%) in the intermittent capecitabine arm experienced a complete response compared with none in the paclitaxel arm. The median time to progression was comparable in the intermittent capecitabine (3.0 months) and paclitaxel groups (3.1 months). Overall survival was also similar between the two groups, with median survivals of 7.6 months with intermittent capecitabine and 9.4 months with paclitaxel.

In terms of safety, the side-effects of intermittent capecitabine were similar to those reported previously; gastrointestinal adverse events (vomiting and diarrhoea) and hand–foot syndrome were more common with capecitabine. In comparison, alopecia, paraesthesia and neutropenia were more common with paclitaxel. There were substantially more grade 3 and 4 adverse events reported with paclitaxel treatment than with intermittent capecitabine (grade 3: 58% versus 23%, respectively; grade 4: 11% versus 5%, respectively), driven mainly by the high incidence of grade 3 alopecia in the paclitaxel arm.

4.2. Capecitabine versus CMF

In another phase II study, 95 women aged $\geqslant 55$ years were randomised (2:1) to first-line treatment with either oral capecitabine monotherapy (intermittent schedule) or i.v. CMF polychemotherapy (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-FU 600 mg/m^2 given every 21–28 days) [10]. Patients had received no prior cytotoxic chemotherapy for their metastatic breast cancer.

Of the 95 patients enrolled, 93 received treatment (61 with capecitabine and 32 with CMF). The majority of patients had received previous treatment for their breast cancer: 90% of the capecitabine group and 80% of the CMF group had received prior treatment with anti-oestrogens. The response rate with capecitabine was 30% compared with 16% in the CMF arm (not statistically significant due to the small sample size), including a 5% complete response rate with capecitabine. There were no complete responses in the CMF group. Partial responses were observed in 25% of capecitabine- and 16% of CMF-treated patients. The median times to disease progression were 4.1 and 3.0 months with capecitabine and CMF, respectively (Fig. 2). Median survival durations similar in the capecitabine- and CMF-treated patients were 19.6 and 17.2 months, respectively (Fig. 3).

The majority of patients in both treatment groups experienced at least one adverse event during the study, but most were graded by the investigator as mild or moderate in intensity. Clinical grade 3 adverse events were more common with capecitabine and the incidence of grade 4 events was similar in the two groups. Neutropenia was more common in the CMF group and diarrhoea and hand–foot syndrome were more common with capecitabine. The toxicities associated with capecitabine were adequately managed with temporary treatment interruption and/or dose modification leading to continued treatment in women who were benefiting from the drug.

5. Conclusions

Previously, no acceptable standard therapy was available for patients with metastatic breast cancer that

had been pretreated with anthracyclines and taxanes. However, the two phase II studies of capecitabine in heavily pretreated metastatic breast cancer demonstrate that capecitabine is an active and well tolerated agent in this setting. In addition, capecitabine resulted in an improvement in tumour-related symptoms and demonstrated an acceptable safety profile. The side-effects of capecitabine treatment can be controlled and ameliorated with treatment interruption and dose reduction where necessary. Therefore, capecitabine provides an effective and tolerable therapy for patients who previously had no proven treatment options.

The promising results from two randomised, phase II studies have indicated that capecitabine may also play a role in first- and second-line treatment of metastatic breast cancer. Capecitabine demonstrated antitumour activity similar to paclitaxel in anthracycline-resistant patients and to i.v. CMF in previously untreated postmenopausal women, demonstrating significant efficacy and acceptable tolerability.

Oral capecitabine is a convenient treatment option, which avoids the risk of complications associated with central i.v. drug administration and provides patients with a degree of independence, potentially improving quality of life. In light of the results of phase II trials in heavily pretreated metastatic breast cancer, capecitabine has received regulatory approval in more than 35 countries worldwide, including the USA, and is the only registered treatment for patients in whom anthracycline and taxane treatment has failed.

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