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Capecitabine named-patient programme for patients with advanced breast cancer: the UK experience

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Abstract

Following the encouraging results achieved with the oral fluoropyrimidine capecitabine in clinical trials, a named patient programme was initiated in the UK, through which patients with advanced breast cancer were prescribed capecitabine monotherapy. In this programme, patients were treated with the standard dose of oral capecitabine (1250 mg/m^2 twice daily on days 1–14 of a 21-day treatment cycle). Efficacy and safety data were collected and analysed from 102 patients receiving outpatient treatment with capecitabine. All patients had previously received chemotherapy and for the majority (75%) this was in the metastatic setting. In total, 482 treatment cycles were administered, with a median of 4.5 treatment cycles (range 1–22) per patient. Tumour responses were observed in 20 patients (20%), with an additional 47 patients (46%) achieving disease stabilisation. The median time to disease progression was 4.1 months and median overall survival was 7.7 months. The most common treatment-related adverse events were palmar-plantar erythrodysaesthesia (PPE) (36%) and gastrointestinal toxicities (diarrhoea (33%) and nausea (24%)). Dose reductions due to adverse events were required in 33% of patients, but capecitabine was administered without a dose reduction for 90% of cycles. The results achieved with capecitabine in this named-patient programme confirm that, under 'real practice' conditions, capecitabine is active and well tolerated in patients with advanced breast cancer.

Keywords: Capecitabine; Fluoropyrimidine; Breast cancer; Named-patient programme

1. Introduction

An increasing number of patients are presenting with anthracycline- and taxoid-pretreated metastatic breast cancer due to the use of these highly active agents earlier in the disease course, including as adjuvant therapy. Until recently, there have been no established treatment options for such patients. However, the oral fluoropyrimidine capecitabine (Xeloda®; F. Hoffmann-La Roche, Basel, Switzerland) has considerable activity in this setting, and is the only treatment registered in more than 80 countries, including the USA and the European Union, for patients with anthracycline- and taxane-pretreated metastatic breast cancer. Capecitabine is also approved in combination with docetaxel for the treatment of patients with anthracycline-pretreated metastatic breast cancer.

Capecitabine is a rationally designed, tumour-activated, oral fluoropyrimidine that mimics continuous infusion 5-fluorouracil (5-FU). It is converted to 5-FU preferentially in tumours through exploitation of the high intratumoral concentrations of the enzyme thymidine phosphorylase [1,2]. Capecitabine is a promising and well-tolerated first- and second-line monotherapy for women with metastatic breast cancer [3]. Capecitabine has

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shown consistently high efficacy in patients who have taxane-pretreated metastatic breast cancer ($n = 500$), achieving objective response rates of 18–29% and a survival duration of approximately 1 year [4–7]. The regulatory approval of capecitabine plus docetaxel for the treatment of patients with anthracycline-pretreated metastatic breast cancer was based on the results of a phase III trial showing that this combination achieves significantly superior tumour response rate, time to disease progression and overall survival compared with standard docetaxel monotherapy [8]. Indeed, capecitabine/docetaxel is the only cytotoxic combination demonstrating a significant survival benefit over docetaxel monotherapy in this patient population.

In all clinical trials, capecitabine monotherapy has demonstrated a favourable safety profile with a low incidence of severe adverse events, particularly myelosuppression, stomatitis and alopecia. The side-effect most commonly associated with capecitabine is palmar-plantar erythrodysaesthesia (PPE (hand–foot syndrome)), a cutaneous condition which is characteristic of infused 5-FU. With capecitabine, PPE occurs predominantly at only mild to moderate intensity. As capecitabine is administered as a tablet twice daily for 14 days, side-effects including PPE can be readily managed by immediate treatment interruption and, if necessary, dose reduction to each individual's tolerable dose [9].

In the UK, capecitabine was prescribed to patients with advanced breast cancer in a named-patient programme from August 1998 until February 2001. We have collected and analysed data from these patients to evaluate the efficacy and safety of capecitabine in the clinical setting.

2. Patients and methods

2.1. Treatment

All patients received the standard dose of oral capecitabine 1250 mg/m^2 twice daily, administered on days 1–14, followed by a 7-day rest period. To facilitate the management of toxicities, the standard schedule for capecitabine dose modification, which includes both treatment interruption and dose reduction, was implemented in the event of toxicities of moderate or more severe intensity [4,9]. Additionally, the start of a new treatment cycle was delayed until treatment-related adverse events resolved to at least mild intensity.

2.2. Patient assessment

Tumours were evaluated by the investigator during treatment using standard clinical and/or radiological methods and the best response achieved by each patient was recorded. Safety was assessed in all patients receiving capecitabine. Adverse events were graded based on their severity: grade 1 (mild), grade 2 (moderate), grade 3 (severe), or grade 4 (life threatening), according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) (version 2.0). PPE was graded 1–3 according to a scale used in the clinical trials of capecitabine [4]. The incidence of treatment interruption and dose reduction was also recorded for all patients.

3. Results

3.1. Patient characteristics

Data were collected from all 102 patients with advanced breast cancer who received outpatient treatment with oral capecitabine at 21 centres in the UK named-patient programme. The baseline characteristics of the patients are shown in Table 1. The majority of patients were Caucasian and had grade 2/3 tumours (61%). A significant proportion (24%) had poor performance status Eastern Cooperative Oncology Group (ECOG) 2 or 3). All patients had at least one metastatic site, with visceral disease present in two-thirds of patients. They had all received prior chemotherapy. Three-quarters were pretreated in the metastatic setting (average number of regimens: 1.3; range: 0–3), approximately two-thirds had received prior anthracycline therapy and one-quarter had been previously exposed to taxoids, of whom almost all had also received an anthracycline (Table 2).

Table 1
Baseline characteristics of patients ($n = 102$)

	Number of patients
Median age (years)	53 (range 30–95)
Male/female	3/99
Caucasian	100
ECOG performance status	
0/1	61
2/3	24
Unknown	17
No. of metastatic sites	
1–3	96
$\geqslant 4$	6
Metastatic sites	
Liver	37
Lung	23
Lymph nodes	62
Bone	45
Oestrogen receptor status	
Positive/negative	40/22
Unknown	40

ECOG, Eastern Cooperative Oncology Group.

Table 2
Prior treatment history of patients ($n = 102$)

Treatment	Number of patients
Chemotherapy setting	
Neoadjuvant	21
Adjuvant	50
Metastatic	76
Chemotherapeutic agents	
Anthracyclines[a]	62
Taxoids[a]	26
Infused 5-FU	7
Hormone therapy setting	
Adjuvant	61
Metastatic	54
Prior surgery	89
Prior radiotherapy	102

5-FU, 5-fluorouracil.
[a] 22 patients had received both anthracyclines and taxoids.

Table 3
Antitumour activity

Best response	Number of patients (%; 95% confidence interval)
Overall	20 (20; 12–27)
Complete	3 (3; 0–6)
Partial	17 (17; 9–24)
Stable disease	47 (46; 36–56)
Progressive disease	31 (30; 21–39)
Unknown	4 (4; 0–8)

3.2. Efficacy

Among 102 patients treated, 20% responded and disease was stabilised in an additional 47 patients (46%) (Table 3). A retrospective subpopulation analysis confirmed that capecitabine was active in patients pretreated in the metastatic setting ($n = 76$; response rate: 18%) and in those pretreated with an anthracycline ($n = 62$; response rate: 16%) or with both a taxoid and an anthracycline ($n = 22$; response rate: 14%). The rate of disease stabilisation was also consistently high in these patient subgroups (49, 52 and 41%, respectively). Notably, objective responses were achieved in 4 of the 7 patients who had previously received treatment with 50-fluorouracil (5-FU) given by continuous infusion.

To date, 88 patients have experienced disease progression, with a median duration of response of 6.9 months and median time to disease progression of 4.1 months (Fig. 1). Median overall survival was 7.7 months (Fig. 1).

3.3. Safety

In total, 482 treatment cycles were administered, with each patient receiving a median of 4.5 cycles (range 1–22).

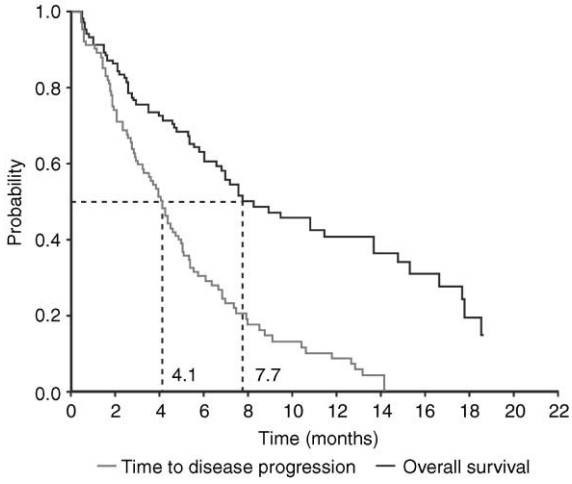

Fig. 1. Time to disease progression and overall survival.

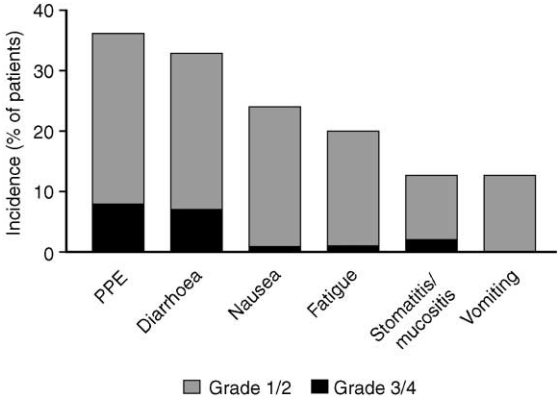

Fig. 2. Most common (>10% of patients) treatment-related adverse events.

The most common (occurring in at least 20% of patients) treatment-related adverse events were PPE (36%) and gastrointestinal side-effects (diarrhoea (33%) and nausea (24%)) (Fig. 2). The majority of adverse events were mild to moderate in intensity.

Treatment-related haematological adverse events were rare and occurred at grade 3/4 intensity in only 4 patients. Grade 3/4 neutropenia occurred in 3 patients (3%) and grade 3 thrombocytopenia occurred in 1 patient (1%). There were no grade 3/4 alterations in laboratory parameters, and hyperbilirubinaemia occurred in only 1 patient.

Dose reductions due to adverse events were required by 33% of patients and the adverse events most commonly leading to a capecitabine dose modification (delay, interruption or reduction) were PPE (20 patients), diarrhoea (19 patients) and stomatitis/mucositis (8 patients). The median dose intensity (planned versus administered) was 100%. Capecitabine was administered without a dose reduction in 90% of cycles.

4. Discussion

The most important finding of this study is that the efficacy and safety of capecitabine in patients treated in the UK named-patient programme support the results of the clinical trials evaluating capecitabine monotherapy in patients with metastatic breast cancer. Unlike prospective clinical trials, which have strict eligibility criteria and require systematic monitoring of tumour responses, the UK named-patient programme reflects 'real practice' conditions. Among the patients treated in the programme, a significant proportion had poor performance status (at least 24% with ECOG performance status 2/3), the majority had grade 2/3 tumours and approximately one-quarter had previously received taxoid and anthracycline therapy. In contrast, the study population in the pivotal capecitabine regulatory trial consisted of a homogeneous group of heavily pretreated patients with advanced/metastatic breast cancer who had experienced disease progression during or following paclitaxel treatment. All patients ($n = 162$) had a Karnofsky Performance status of at least 70% (median 90%) and had been treated with at least two, but no more than three, prior chemotherapy regimens (including paclitaxel in the metastatic setting) [4]. Reassuringly, a similar overall response rate (20%) was achieved in the UK named-patient programme as in this clinical trial, confirming that capecitabine is highly active in heavily pretreated patients. The response rate is also consistent with two other regulatory trials, which showed response rates of 18 and 26% in patients with anthracycline- and taxoid-pretreated metastatic breast cancer [5,6]. In contrast, with some agents, response rates in compassionate-use programmes are considerably lower than in clinical trials. For example, response rates of 34–58% were achieved with second-line docetaxel in clinical trials [10], whereas the response rate was 23% in a compassionate-use programme involving a large number of patients ($n = 825$) [11].

Interestingly, capecitabine produced tumour responses in 4 of 7 patients who had previously received treatment with continuous-infusion 5-FU. In addition, capecitabine was associated with a consistently high rate of disease stabilisation in the overall patient population (46%), as well as in patient subgroups who were pretreated in the metastatic setting (49%) and those who had received prior anthracyclines (52%) or both an anthracycline and a taxoid (41%). Disease stabilisation has been shown to be a clinically meaningful outcome in patients receiving endocrine therapy for advanced breast cancer [12]. Similarly, the pivotal phase II trial evaluating capecitabine in anthracycline- and paclitaxel-pretreated patients demonstrated that median survival was similar in patients with stable disease and those with confirmed responses [4]. With a well-tolerated, oral treatment this is a benefit for many patients. The median time to disease progression in the capecitabine named-patient programme compares favourably with that achieved in clinical trials evaluating capecitabine as first-, second- or third-line therapy (4.1 versus 3.0–4.1 months) in patients with metastatic breast cancer [3–5]. Overall survival was more favourable in the pivotal registration trial [4]. However, in this 'real practice' setting a substantial number of patients had poor performance status and prognosis.

As in clinical trials, capecitabine demonstrated a favourable and manageable safety profile in the current study, although it has to be recognised that in a named-patient programme, minor toxicities may be less accurately documented than in formal clinical trials. The majority of treatment-related adverse events were mild to moderate in intensity and manageable with treatment interruption and, if necessary, dose reduction. The most common treatment-related side effects were PPE and diarrhoea. However, these adverse events occurred only very rarely at grade 3/4 intensity (in 8 and 6% of patients, respectively). Myelosuppression was particularly rare and alopecia was not observed. The excellent tolerability of capecitabine is reflected by the high median dose intensity administered (100%) and the fact that capecitabine was given without dose reduction in 90% of cycles. As a chronically administered oral agent, any side-effects due to capecitabine can be readily managed by treatment interruption and dose reduction, when necessary [9]. But as with any cytotoxic agent administered in the outpatient setting, patient education and follow-up are important for the effective management of side-effects. With capecitabine, patients should be educated to recognise side-effects and their severity, to interrupt treatment upon the development of a moderate or more severe toxicity and to contact their physician or nurse for further advice. In our experience, patients cope well with capecitabine. They are able to identify significant side-effects early, allowing prompt action to prevent the development of more serious toxicity.

The results achieved in this named-patient programme confirm that, under 'real practice' conditions, capecitabine is active and well tolerated in patients with advanced breast cancer. Capecitabine, as a powerful oral therapy, enables home-based therapy that allows patients greater freedom and avoids the inconvenience and discomfort associated with intravenous (i.v.) administration. Given its high single-agent activity, with apparent lack of cross-resistance with anthracyclines and taxanes, and favourable safety profile, oral capecitabine is potentially an ideal agent for use in the adjuvant setting. Several trials evaluating capecitabine as adjuvant therapy for primary breast cancer are ongoing or in the planning stages.

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