ORIGINAL ARTICLE

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Oral Capecitabine in Anthracycline- and Taxane-Pretreated Advanced/Metastatic Breast Cancer

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An open-label, non-randomized, compassionate-use study was carried out to investigate the effects of oral capecitabine at a dose of 1 250 mg/m^2 twice daily on days 1 to 14 every 21 days in anthracycline- and taxane-pretreated advanced/metastatic breast cancer patients. Forty-eight patients were enrolled from April 2000 to December 2001. Twenty-four patients (50%) had metastases to the liver, 18 to bone, 13 to lung, 10 to regional lymph nodes, 8 to pleura, 7 to the thoracic wall, 5 to skin, 3 to the mediastinum, 1 to breast and 1 had metastasis to the abdomen. Thirty-three patients (69%) had metastases to more than one site. Median age of the patients was 55 years (range 35–74). Three patients had an ECOG performance status (PS) of 0, 32 PS 1 and 13 PS 2, respectively. Fourteen patients (29%; 95% CI 16 to 42%) obtained a partial response (PR) while 16 (33%) had stable disease (SD) as the best response, of whom 6 had stabilization for more than 24 weeks. This gives a clinical benefit (PR+SD > 24 weeks) of 42% (95% CI 28 to 56). Dose reduction was necessary in 29% of the patients. Median dose reduction was 25%. Grades 2 and 3 hand-foot syndrome (PPE) was observed in 17 patients (36%). Eleven patients experienced grades 2 and 3 gastrointestinal toxicity, and haematological toxicity grade 3 was observed in 3 patients (6%). Median time to progression was 107 days (CI 95% 85 to 129), and median overall survival was 281 days (CI 95% 164 to 398). Third-line, oral capecitabine in anthracycline- and taxane-pretreated metastatic breast cancer appears to be effective and has an acceptable toxicity profile.

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Capecitabine, a rationally designed oral fluoropyrimidine carbamate, is enzymatically converted to 5-fluorouracil (5-FU) by thymidine phosphorylase (TP) (1). TP is found at higher concentrations in tumours than in normal tissues (2). Its TP activation and its mechanism of action make capecitabine different from anthracyclines and taxanes that constitute the most effective single cytostatic agents in the treatment of advanced and metastatic breast cancer. Anthracyclines, and even taxanes (paclitaxel and docetaxel), are increasingly used world-wide as adjuvant therapy after breast cancer. There is therefore a need for new substances that can be used in the treatment of metastatic disease.

Capecitabine has been shown to be effective and to have high tolerability in breast cancer patients pretreated with anthracyclines and taxanes (3–7).

The purpose of this compassionate-use, phase II trial was to further evaluate the efficacy and safety of capecitabine at a dose of 1 250 mg/m^2 twice daily for 14 days followed by a one-week rest.

MATERIAL AND METHODS

An open label, non-randomized, compassionate-use study of oral capecitabine was performed. From April 2000 until December 2001 48 patients entered this study. Capecitabine was given orally 1 250 mg/m^2 twice daily, on days 1 to 14 every 21 days. Drug dosage were adjusted at any time during the study on the basis of grade 2, or greater, related adverse events as defined by the National Cancer Institute of Canada (NCIC) common toxicity criteria, version 1.0, as described by Blum et al. (3). Treatment continued until progression, prohibitive toxicity or on the patient's request to stop treatment.

Inclusion criteria

Women with histologically or cytologically confirmed diagnoses of advanced or metastatic breast cancer who had failed both an anthracycline-containing regimen and paclitaxel or docetaxel were eligible for enrolment. A pre-study evaluation included a complete history and medical

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examination, full blood count, platelet count, serum chemistries, ECG (optional), bone scan, tumour measurements and radiographic, computed tomography (CT) scan or magnetic resonance imaging (MRI) for tumour assessment.

The patients had to have bidimensionally measurable disease. Patients were required to be ≥ 18 and ≤ 75 years of age, to be ambulatory and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 (Karnofsky performance index $\geq 60\%$), have adequate bone marrow, renal and liver functions (absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, serum creatinine and bilirubin < 1.5 times the upper limits of normal (ULN) and aspartate aminotransferase and alanine aminotransferase < 3 times the ULN) and to provide written informed consent. Participants of childbearing age were required to deliver a negative pre-study pregnancy test and had to practice appropriate contraception while taking part in the study. A life expectancy of ≥ 3 months was required.

Exclusion criteria

Exclusion criteria, in addition to those mentioned above, included other malignant disease, rapidly progressing visceral involvement (liver, lymphatic, lung), history of seizures, disorders of the central nervous system including brain metastases, psychiatric disability thought to be clinically significant and previous unexpected reaction to fluoropyrimidine therapy (with or without documented DPD deficiency) or known hypersensitivity to 5-FU. Patients with dementia, altered mental status or psychosis could not be included. Patients with significant cardiac disease (symptomatic ventricular arrhythmias, congestive heart failure, myocardial infarction within 12 months of study entry) and patients with lack of physical integrity of the upper gastrointestinal (GI) tract or known malabsorption syndrome were also excluded.

Response and toxicity assessment

Tumour measurements for response assessment were obtained every 9 weeks and all responses had to be confirmed by a second measurement after an additional 4 weeks. Patients had to have completed at least three courses (each course consisting of 14 days on capecitabine and 7 days off) of chemotherapy to be considered assessable for response, but patients who developed symptoms of progressive disease before completing the three courses were considered as non-responders. Complete response (CR) was defined as the disappearance of all clinical and radiographic evidence of disease determined on two observations at least 4 weeks apart. Partial response (PR) was defined as a decrease of 50% or more in the sum of the products of the biperpendicular diameters of measurable lesions. Stable disease (SD) was defined as a less than 50% decrease and less than 25% increase in the sum of the products of the biperpendicular diameters of measurable lesions and no appearance of new lesions. Progressive disease (PD) was defined as a greater than 25% increase in the sum of the products of the biperpendicular diameters of measurable lesions or the appearance of new lesions.

Statistical methods

The primary endpoint was time to progression (TTP). Secondary endpoints were response rate, overall survival and toxicity. TTP and overall survival were calculated from the day of study entry until the day of documented progression or death, respectively. Duration of response was calculated from the day the response was first recorded until the day of progression. Patients who died without documented progression were censored on the day of death or last follow-up. Patients who survived were censored on the day they were last known to be alive. TTP, overall survival and duration of response were estimated using the Kaplan–Meier method.

The Regional Ethics Committee, East Norway Health Region, authorized the study. Patients were informed that non-participation in the study would not in any way jeopardize their medical treatment.

RESULTS

A total of 48 patients were enrolled into the study. All patients were assessable for response and toxicity. Patient demographic and clinical characteristics are given in the Table 1.

The median age of patients included in the study was 55 years (range 35–74). Out of 48 patients, 24 (50%) had metastases to the liver, 18 to the bone, 13 to the lung, 10 to regional lymph nodes, 8 to the pleura, 7 to the thoracic wall, 5 to the skin, 3 to the mediastinum, 1 to the breast, and 1 to the abdomen. Thirty-three patients had metastases to more than one site. Three patients had an ECOG performance status (PS) of 0, 32 PS 1 and 13 PS 2, respectively.

Effect of treatment

Fourteen patients (29%; 95% CI 16 to 42) obtained a PR while 18 (37%) did not respond to the treatment. Sixteen patients (33%) had SD as the best response. This gives a disease control rate (PR + SD) of 62%. Six of those achieving SD had stabilization for more than 24 weeks. This gives a clinical benefit (PR + SD > 24 weeks) of 41% (95% CI 27 to 55%). Median TTP was 107 days (CI 95% 85 to 129%) (Fig. 1), duration of response 134 days (range 23–534 days) and median overall survival was 281 days (CI 95%

Table 1

Patient characteristics

Characteristic	
Number of patients enrolled	48
Median age (range; years)	55 (35–74)
ECOG performance status	
0	3
1	32
2	13
Median time since primary diagnosis	1 520 (176–7 543) days
Mean time since primary diagnosis	1 776 (±1 414) days
Number of metastatic sites	
1	15
2+	33
Metastatic sites involved	
Liver	24
Lung/pleura	21
Skin/thoracic wall	12
Bone	18
Lymph nodes	10
Mediastinum	3
Abdomen	1
Breast	1
TNM status at time of primary diagnosis	
T1	13
T2	18
T3	7
T4	5
Tx	5
N0	16
N1	27
Nx	5
M0	44
M1	4
Hormone receptor (ER and/or PgR) status of primary tumour	
Positive	28
Negative	20
HER2/neu status	
Positive	3
Negative	13
Unknown	32
Adjuvant chemotherapy	
None	13
CMF	22
Anthracycline containing regimens	4
Neoadjuvant chemotherapy	3
Other cyclophosphamide containing regimens	2
Not applicable due to metastatic disease at diagnosis	4
Adjuvant endocrine therapy	
Yes	19
No	25
Not applicable due to metastatic disease at diagnosis	4
Endocrine therapy for metastatic disease	
Yes	17
No	31

164 to 398%) (Fig. 2). In 4 out of 14 responders the response lasted for more than 300 days.

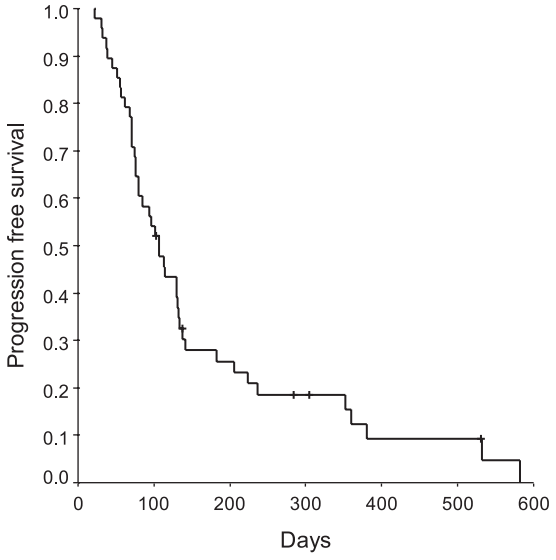

Fig. 1. Kaplan–Meier analysis of time to progression. Median time to progression, 107 days.

Toxicity

Dose reduction was necessary in 29% of patients. Median dose reduction was 25%. Grades 2 and 3 hand-foot syndrome (PPE) was observed in 17 patients (35%). Eleven patients experienced grades 2 and 3 GI toxicity. Haematological toxicity grade 3 was observed in 3 patients (6%) but no other grade 3 or 4 toxicities were observed.

DISCUSSION

Anthracyclines (doxorubicin or epirubicin) are essential parts of first-line chemotherapy regimens for metastatic breast cancer. Anthracyclines are combined with taxanes in

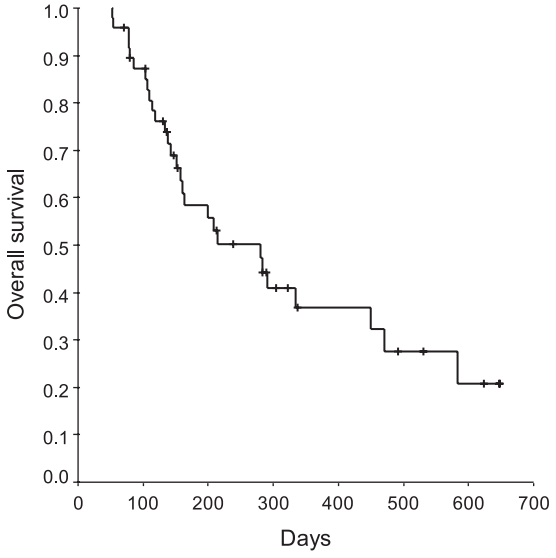

Fig. 2. Kaplan–Meier analysis of overall survival. Median overall survival, 281 days.

many regimens. If this were not so, taxanes would be the main agents of second-line chemotherapy after anthracycline failure. Anthracyclines are also an essential part of most adjuvant regimens in breast cancer and the use of taxanes in this setting is increasing.

Relapses occurring within a few months after adjuvant chemotherapy containing anthracyclines or taxanes, or treatment failure after using these drugs in the advanced and metastatic setting clearly introduces a strong need for new treatment options.

The goals of palliative treatment are to reduce tumour burden, to improve or maintain performance status and to increase TTP and possibly prolong overall survival. Reducing toxicity and improving convenience and control for patients are also important aspects of palliative chemotherapy.

Oral capecitabine monotherapy is well suited for administration in the palliative setting. Patients' preference for oral versus intravenous chemotherapy has been demonstrated in two trials (8, 9). The quality of life is significantly reduced in patients receiving chemotherapy in hospitals versus home. Eighty-nine percent of patients prefer oral therapy but more than 70% are unwilling to sacrifice efficacy to retain their original preference (8).

Capecitabine monotherapy has been evaluated in taxane (docetaxel or paclitaxel) pretreated metastatic breast cancer in a number of studies elsewhere (3–6). The US pivotal study by Blum et al. (3) recruited 163 patients of whom 162 received capecitabine and were included in the final analysis. All patients were either paclitaxel resistant or had failed paclitaxel treatment. Ninety-one percent were pretreated with anthracycline. The estimated median time to progression was 93 days, median duration of response 241 days and median overall survival 384 days. Confirmatory studies from US and France (4), Germany (5), France (6) and Mexico (7) accruing 75, 136, 126 and 32 patients, respectively, gave comparable results. The overall response rate has varied from 15 to 44%, disease control rate from 57 to 63%, median time to progression from 3.0 to 4.6 months and the median survival from 10.4 to 15.2 months (3–7).

In our study using capecitabine after both anthracyclines and taxanes we have confirmed the results from these previous studies. The overall response rate (PR) was 29%. The disease control rate (PR + SD) was 62%. The median TTP was 107 days, duration of response 134 days, ranging from 23 days to 534, and overall survival 281 days.

With respect to toxicity, this study is comparable with the pivotal study (3). Grades 2 and 3 PPE occurred in 35% compared with 42% of patients in the pivotal study. Eleven patients (23%) experienced grades 2 and 3 GI toxicity compared with 33%. Haematological toxicity grade 3 was seen in 3 patients (6%) compared with 5% in the pivotal study.

The treatment results from using capecitabine monotherapy in anthracycline and taxane pretreated metastatic breast cancer are impressively consistent. Capecitabine seems to compare favourably with other monoagent third-line therapies used to treat metastatic breast cancer.

Capecitabine provides an effective, well-tolerated and convenient therapy for patients with heavily pretreated metastatic breast cancer for whom previously there were no established treatment options. Taking the drug orally gives the patients new opportunities to plan their daily life activities and reduces the number of visits to the hospital.

Capecitabine is achieving high activity and has a favourable toxicity profile.

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