Anti-Cancer Drugs 2002, **13,** pp. 405–410

Clinical report

Capecitabine in patients with breast cancer relapsing after high-dose chemotherapy plus autologous peripheral stem cell transplantation—a phase II study

A Jakob,[1] C Bokemeyer,[1] S Knop,[1] M Schupp,[1] F Mayer[1] and L Kanz[1]
[1]Department of Hematology/Oncology, University Hospital Tübingen, Otfried-Mueller-Strasse 10, 72076 Tübingen, Germany.

Capecitabine, a tumor-selective, oral fluoropyrimidine, has demonstrated significant antitumor activity in patients with metastatic breast cancer. In this open-label monocenter phase II study the efficacy and safety of capecitabine in patients with metastatic breast cancer who relapsed after high-dose chemotherapy was examined. Female patients 18-65 years of age, with a histologically confirmed diagnosis of metastatic breast cancer, who relapsed after high-dose chemotherapy (adjuvant and/or metastatic) followed by autologous peripheral blood stem cell transplantation (PBSCT) and who had been treated in their course of the disease with an anthracycline and/or an anthracycline/taxane containing regimen were included into this clinical study. Capecitabine was applied as the first salvage chemotherapy at relapse after high-dose chemotherapy (1250 mg/m^2 b.i.d. p.o. for 14 days followed by 7 days rest period). Responding patients or those with stable disease after two treatment cycles were offered to continue treatment until tumor progression. Response rate, time to disease progression, survival, toxicity and quality of life were assessed. Fourteen patients between 35 and 60 years (median 45.5 years) entered this study and received a median number of 5 cycles (range 1–19) of capecitabine. All patients were evaluable for response. All patients had been pretreated with 1–2 cycles of high-dose chemotherapy plus PBSCT. Furthermore, 13 patients had additionally received local radiotherapy. On average, the patients showed metastatic disease in two organ sites (range 1–4 sites). One patient obtained a complete response and five patients a partial response, accounting for a response rate of 42.9% [95% confidence interval (17.7%; 71.1%)]. All responses were already achieved at the first observation time point 6 weeks after treatment initiation. Two further patients obtained stable disease for at least 12 weeks. At the time of final analysis all patients have progressed. Median time to progression was 2.8 months (range 0.4–13.3 months). No median survival time was reached (range 3.9–36.5 months, at the time of reporting eight patients were alive and six patients had died). Two patients developed grade III granulocytopenia. Five patients developed grade III hand–foot syndrome. One patient had the combination of nausea, fever and diarrhea grade III. All adverse events were considered manageable. We conclude that capecitabine as single-agent oral chemotherapy is active and well tolerated in heavily pretreated patients with breast cancer. It can be safely used in patients who have been intensively pretreated by myelotoxic chemotherapy or who have even relapsed after high-dose chemotherapy with PBSCT. [© 2002 Lippincott Williams & Wilkins.]

Key words: Anthracycline resistance, breast cancer, capecitabine, oral chemotherapy, peripheral blood stem cell transplantation, taxane resistance.

Introduction

High-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (PBSCT) has been used both in the adjuvant as well as in the metastatic setting in patients with breast cancer in order to prolong survival and/or to increase the cure rates in these patients. However, if relapse occurs, there is no established therapeutic option. In this situation it is important to keep in mind that the aim of further treatment is to improve quality of life (QoL) and to relieve tumor-related symptoms, since there is no proof that therapy will prolong survival. At present, individualized therapy is offered to the patients. Special concern must be given to the post-transplant condition, since cytostatic agents with dominant hematopoetic side effects may be difficult to use in this setting.

Capecitabine (Xeloda®; Hoffmann-La Roche, Basle, Switzerland) was developed as an orally active drug to mimic continuous infusion and to deliver

This study was in part presented at the Annual Meeting of the American Society of Clinical Oncology (ASCO) in San Francisco, May 2001.

Correspondence to C Bokemeyer, Department of Hematology/Oncology, University Hospital Tübingen, Otfried-Mueller-Strasse 10, 72076 Tübingen, Germany.
Tel: (+49) 7071 2987121; Fax: (+49) 7071 293675;
E-mail: carsten.bokemeyer@med.uni-tuebingen.de

5-fluorouracil (5-FU) preferentially intratumoral. After gastrointestinal absorption, capecitabine is hydrolyzed in the liver by carboxylesterase to 5′-deoxy-5-fluorocytidine, which is subsequently deaminated at its pyrimidine ring by cytidine deaminase. The last enzymatic step, the activation of 5-deoxy-5-fluorouridine to 5-FU, is catalyzed by the enzyme thymidine phosphorylase which is predominantly found in tumor tissue.[1–3]

Capecitabine has demonstrated activity in 5-FU-sensitive solid tumors such as colon cancer and breast cancer.[4–6] Efficacy has also been shown in paclitaxel pretreated breast cancer patients;[7] however, there was no information previously available about the efficacy of this drug in patients relapsing after high-dose chemotherapy. It was thus the primary objective of this pilot study to assess the response rate to capecitabine in a heavily pretreated breast cancer patient population. Further objectives were to assess the QoL and tolerability of treatment, especially the hematological toxicity, in this patient population.

Patients and methods

The study was performed according to the Declaration of Helsinki, the German Drug Law (AMG), and ICH-GCP at the Division of Hematology and Oncology of the Department of Internal Medicine at Tübingen University. The Ethics Committee of the University of Tübingen approved the study. All patients gave written informed consent before enrolment into the study. In order to avoid treating an unnecessarily large number of patients with a potentially ineffective treatment, a two-stage design for phase II trials by Gehan[8] was employed. The minimum response rate of clinical interest in this patient population was defined at 20% and 14 patients were planned to enter the trial.

Patients were eligible for the study by the following criteria: age between 18 and 65, female, histologically confirmed diagnosis of breast cancer, bidimensionally measurable or evaluable metastatic lesions, relapse after treatment with high-dose chemotherapy for breast cancer (adjuvant or metastatic) including induction treatment with an anthracycline and/or a taxane followed by autologous PBSCT, Karnofsky performance status of 60–100%,[9] life expectancy of at least 3 months, adequate renal and hepatic function. Exclusion criteria were: abnormal hematologic values (absolute neutrophil count $<1.5\times10^9$/l, platelet count $<75\times10^9$/l, Hb <9 g/dl); impaired hepatic or renal function (bilirubin $>2.0\times$ upper normal limit, transaminases or alkaline phosphatase $>2.5\times$ upper normal limit or $>5\times$ upper normal limit in case of liver or bone metastases, serum creatinine $>1.5\times$ upper normal limit); clinically significant cardiac disease; known hypersensitivity to 5-FU; previous continuous (duration for more than 48 h) infusional 5-FU therapy; hypercalcemia (serum calcium >11.5 mg/dl); serious uncontrolled intercurrent infections; patients known to be positive for either hepatitis B surface antigen, hepatitis C antibodies or human immunodeficiency virus type 1 antibodies; previous cytotoxic chemotherapy within the last 4 weeks prior to treatment start; initiation of bisphosphonate treatment or hormonal treatment within 3 weeks prior to treatment start; pregnancy or lactating women.

Baseline evaluations included: patient history, physical examination, laboratory evaluations (hematology, clinical chemistry, tumor markers, urine analysis, pregnancy test in women not amenorrheic in the previous 12 months), tumor staging with measurement of all target lesions, as well as a QoL assessment (EORTC QLQ C 30). Laboratory tests were repeated in 3-weekly intervals. The EORTC QLQ C 30 questionnaire was completed before each second treatment course (6-weekly intervals). Target lesions were followed by the same diagnostic method in intervals of 6 weeks.

Treatment

Capecitabine was supplied by Roche as film-coated unscored tablets in strengths of 150 and 500 mg. Patients received a total daily dose of 2500 mg/m^2 b.i.d. (two separate doses 12 h apart) capecitabine orally for 14 days followed by 7 days rest. The medication was to be taken at approximately the same time each day within 30 min after the patient had ingested a meal (breakfast, dinner) with approximately 200 ml water. Patients did not receive any vitamin B_6 supplements to prevent hand–foot syndrome. Patients responding or those with stable disease at the end of two treatment cycles were allowed to continue treatment until disease progression. The dose of capecitabine was not to be changed throughout the study unless due to adverse events, in which case treatment interruptions and dose modification schedules were handled according to the manufacturer's recommendations. No dose reduction or interruption was planned for anemia, since this was successfully controlled by transfusions.

Statistical analysis

The clinical data was transcribed on case record forms by the investigators and study nurses at the site. The study was monitored by clinical research associates of Hoffmann-La Roche (Grenzach) and BZT (Munich). The data in the case record forms was source data verified. Tumor assessment was based on the WHO criteria for response.[10] Side effects were graded according to the NCIC Common Toxicity Criteria Grading System (May 1991 revision). The statistical analysis was performed using SAS (SAS Institute, Cary, NC). Time to progression was calculated from first treatment until disease progression or death. Time to response was calculated from first treatment until first documentation of response. Duration of response was calculated from first documentation of response until disease progression. Survival was calculated from the start of treatment to the date of death or the last date the patient was known to be alive. The actuarial probability of survival was estimated by the Kaplan–Meier method.

Results

Between September 1998 and July 2000, 14 patients entered the study. All patients were female Caucasians and evaluable for efficacy and toxicity. Patient details are listed in Table 1. Age ranged from 35 to 60 years (mean 45.9 years, median 45.5 years). All patients were pretreated with high-dose chemotherapy followed by autologous PBSCT. Eight patients had received three cycles of AT induction therapy (cumulative doses: adriamycin 150 mg/m^2, docetaxel 225 mg/m^2) followed by one cycle of high-dose VIC chemotherapy (etoposide 1500 mg/m^2, ifosfamide 12 g/m^2, carboplatin 1500 mg/m^2) and a second (tandem) cycle of high-dose chemotherapy (thiotepa 800 mg/m^2, cyclophosphamide 6000 mg/m^2). Six patients received two cycles of VIPE induction therapy (cumulative doses: cisplatin 100 mg/m^2, etoposide 1000 mg/m^2, ifosfamide 8 g/m^2 and epirubicin 100 mg/m^2) followed by one cycle of high-dose VIC therapy. Furthermore, 13 patients received local radiotherapy. The median interval between last dose of high-dose chemotherapy and initiation of capecitabine therapy was 21 months (range 8–78 months). The localization of metastases at relapse is displayed in Table 1. On average the patients had metastatic disease at two organ sites (range 1–4 sites). Furthermore, most patients had multiple metastases. Patients received a median of 5 cycles of capecitabine therapy (range 1–19 cycles).

Table 1. Patient characteristics

	No. of patients (%)
Patients enrolled	14
Age (years)	
median	45.5
range	35–60
Height (cm)	
median	164.5
range	157–173
Weight (kg)	
median	67
range	53–83
Previous treatment	
chemotherapy	14 (100)
high-dose chemotherapy (single cycle) with PBSCT	6 (43)
high-dose chemotherapy (two cycles, tandem) with PBSCT	8 (57)
radiotherapy	13 (93)
second radiotherapy	5 (36)
hormone therapy	14 (100)
surgical resection	14 (100)
biophosphonate therapy	5 (36)
immunotherapy	1 (7)
other therapies	4 (29)
Localization of metastases	
bone	9 (64)
liver	9 (64)
lung	2 (14)
lymph nodes	4 (29)
pleural	2 (14)
skin	3 (21)
mediastinal mass	1 (7)

One patient obtained a complete response and five patients a partial response [overall response rate 42.9%, 95% confidence interval (17.7%; 71.1%)]. All responses were observed at the first observation according to the study protocol: 6 weeks after initiation of treatment and confirmed 4 weeks later. Median duration of response was 7.2 months (range 0.7–12.0). Two further patients obtained stable disease for at least 12 weeks.

Time to progression calculated with the Kaplan–Meier method is displayed in Figure 1. During the course of the study all patients became progressive, therefore there are no censored observations. Median time to progression was 2.8 months (range 0.4–13.3 months). The median survival time according to Kaplan–Meier was not reached (range 3.9–36.5 months, at the time of reporting eight patients were alive and six patients had died, Figure 1). The shortest observation period of the patients still alive is 14.4 months, thus it can be expected that the median survival will be at least 14.4 months.

The study confirmed the favorable toxicity profile of capecitabine. In total, 105 drug related events

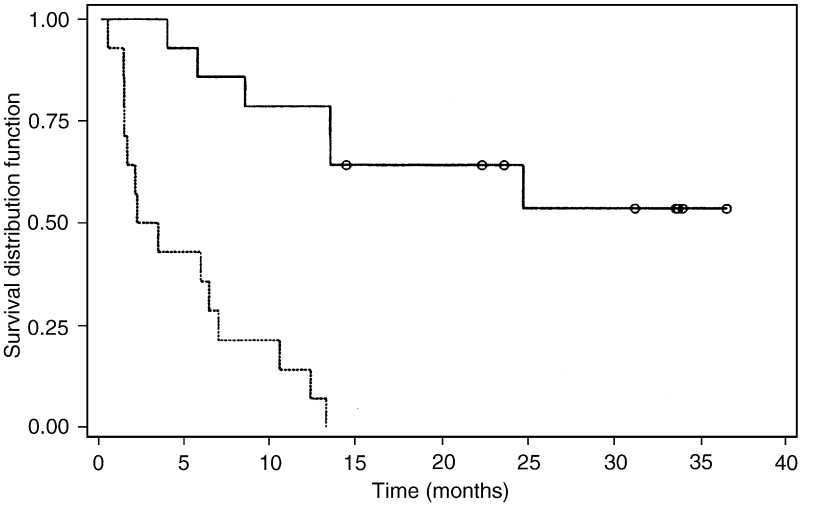

Figure 1. Progression-free (median 2.8 months, n=14) and overall survival (no median reached) calculated according to Kaplan–Meier. Solid line: variable=overall survival; open circles: censored variable=overall survival; dotted line: variable=progression.

were reported, but only 13% were classified as severe (grade III). Hand–foot syndrome was reported most frequently (40 entries in seven patients) followed by nausea (21 entries in nine patients) and mucositis (eight entries in five patients). Seven of these patients suffered from severe drug-related side effects: five patients of hand–foot syndrome, one of dizziness, and one patient of diarrhea, nausea and fever. All adverse events were well manageable.

Hematological side effects are displayed in Table 2. Two patients had grade 3 leukopenia. One of these patients had neutropenic fever with a leukocyte count of 1100/μl and was successfully treated with antibiotics. Treatment with capecitabine was interrupted and then continued at a 50% reduced dose according to the dose modification guidelines. Five further patients experienced grade 2 leukopenia once during the course of the treatment. The effects on thrombocytes and hemoglobin were minimal, and did not cause any clinical problems. There has been no termination of therapy due to toxicity.

Twelve of the 14 patients were evaluable for QoL assessment; six patients (50%) showed improvement of the QoL score of at least 20% and one further patient of more than 10%. Thus the total number of patients obtaining at least a 10% increase in their QoL score was 7 (58.3%).

Table 2. Hematologic toxicity according to NCIC CTC grading system (N=14)

	Grade I	Grade II	Grade III
Anemia	8 (57%)	3 (21%)	–
Leukopenia	2 (14%)	5 (36%)	2 (14%)
Thrombocytopenia	4 (29%)	1 (7%)	–

Discussion

Breast cancer is the most common malignancy among women in the industrialized world. Unlike other areas in oncology, survival time has not significantly improved in recent decades. One approach aiming at the improvement of survival of high-risk breast cancer patients has used aggressive combination chemotherapy based on the most active drugs, particularly alkylating agents, given at high doses. This treatment is followed by autologous PBSCT due to its myelotoxicity. A considerable number of patients will relapse despite this dose-intensive approach and the therapeutic options for these patients are limited, since they may have a decreased bone marrow reserve and the tumor may have become resistant to the most active drugs against breast cancer. The aim of the therapy in this situation is clearly palliative with considerations on the QoL, since the chances to obtain prolonged survival are minimal.

Treatment of patients failing high-dose chemotherapy plus PBSCT has been a clinical dilemma and no standard recommendations exist. The achievement of significant antitumor activity appears difficult due to the decreased hematopoetic reserve which does not allow the use of myelosuppressive agents, and due to the pretreatment of patients with anthracyclines/taxanes and alkylating agents.

Objective response rates in anthracycline-pretreated breast cancer patients to cisplatin, mitomycin C, mitoxantrone, etoposide and vinca alkaloids are less than 15%, and for combination regimens less than 30%.[11] Furthermore, most responses are of short duration. 5-FU has been shown to possess activity in anthracycline-pretreated patients. With 5-FU monotherapy or in combination with other drugs overall remission rates of approximately 25–30% have been obtained (for review, see Wilke *et al.*[12]). In 1996, Wilke *et al.*[12] reported a phase I/II study of 24-h continuous infusion 5-FU and folinic acid in pretreated breast cancer patients. Treatment was given on an outpatient basis once weekly for 6 weeks followed by a 2-week rest period. Thirty-two patients received 500 mg/m^2 of folinic acid as a 2-h infusion followed by a 24-h infusion of 2.1 g/m^2 5-FU. Thirteen of the 32 patients have responded, resulting in a 41% objective response rate. Median time to progression in responding patients was 11 months.

The response rate to capecitabine of 43% in our study with this heavily pretreated patient population with extensive metastatic disease appears very promising. Two further patients (14%) obtained stable disease, thus the majority of the patients (57%) had a clear benefit from treatment. The response rate in this trial is in line with the results obtained with high-dose continuous infusion (c.i.) 5-FU. However, high-dose c.i. 5-FU therapy puts some burden on the patients, since the patient has to endure a central catheter and an infusion pump. Capecitabine, on the other hand, is an oral treatment facilitating a true outpatient therapy without these restraints.

The results of this study are in line with the findings of Sundaram *et al.*,[13] who recently reported the results of a small pilot trial on eight breast cancer patients relapsing after high-dose chemotherapy and autologous stem cell support. Both the tolerability and the efficacy results of that study appear to be comparable to our results.[13] The median survival in our study is at least 14.4 months and thus in the same range as in the study by Blum *et al.*,[7] who reported 12.8 months for patients receiving capecitabine after failure of anthracycline therapy and taxanes. This finding indicates that treatment with capecitabine in this group of patients may positively influence survival, although neither our nor the other study by Blum *et al.* was controlled for the type of subsequent further treatment.

Our study also confirmed the overall low toxicity profile of capecitabine. All adverse events were easily manageable. Taking into account the heavy myelotoxic pretreatment of these patients, the effects of capecitabine on leukocyte counts are moderate and with one exception did not cause any clinical problem. The effects on thrombocytes and hemoglobin were minimal. As expected from the clinical results the QoL evaluation showed an increase in QoL scores in the majority of patients.

In conclusion, capecitabine appears to be a very reasonable option for salvage therapy in heavily pretreated breast cancer patients even at relapse after high-dose chemotherapy. Oral capecitabine can provide effective palliation even in patients with extensive disease and is still well tolerated. Additionally, oral treatment with capecitabine in this palliative setting does avoid a significant amount of hospitalization or outpatient treatment time.

References

1. Ishikawa T, Sekiguchi F, Fukase Y, Sawada N, Ishitsuka H. Positive correlation between the efficacy of capecitabine and doxifluridine and the ratio of thymidine phosphorylase to dihydropyrimidine dehydrogenase activities in tumors in human cancer xenografts. *Cancer Res* 1998; **58**: 685–90.
2. Jones A, Harris AL. New developments in angiogenesis: a major mechanism for tumor growth and target for therapy. *Cancer J Sci Am* 1998; **4**: 209–17.
3. Miwa M, Ura M, Nishida M, *et al*. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. *Eur J Cancer* 1998; **34**: 1274–81.
4. Hoff PM, Ansari R, Batist G, *et al*. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol* 2001; **19**: 2282–92.
5. Blum JL. The role of capecitabine, an oral, enzymatically activated fluoropyrimidine, in the treatment of metastatic breast cancer. *Oncologist* 2001; **6**: 56–64.
6. Leonard RC. Oral fluoropyrimidines among the new drugs for patients with metastatic breast cancer. *Br J Cancer* 2001; **84**: 1437–42.
7. Blum JL, Jones SE, Buzdar AU, *et al*. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1999; **17**: 485–93.
8. Gehan EA. The determination of the number of patients required in a follow-up trial of a new chemotherapeutic agent. *J Chron Dis* 1961; **13**: 346–53.
9. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma, with particular reference to bronchogenic carcinoma. *Cancer* 1948; **1**: 634–56.

10. *WHO handbook for reporting results of cancer treatment*. Geneva: World Health Organization 1979.
11. Henderson IC. Chemotherapy for advanced disease In: Harris JR, Hellman S, Henderson IC, eds. *Breast diseases*. Philadelphia, PA: Lippincott 1987: 428–9.
12. Wilke H, Klaassen U, Achterrath W, *et al*. Phase I/II study of a weekly 24-hour infusion of 5-fluorouracil plus high dose folinic acid (HD-5FU/FA) in intensively treated patients with metastatic breast cancer. *Ann Oncol* 1996; **7**: 55–8.
13. Sundaram S, Lancaster A, Silva J, Corringham S, Law P, Ball ED, Bashey A. Oral capecitabine is an active and well tolerated primary palliative treatment in patients with metastatic breast cancer who progress after high-dose chemotherapy and autologous stem cell support. *Proc Am Soc Clin Oncol* 2000; **19**: 58a (abstr 223).

(Received 8 January 2001; accepted 21 January 2002)