Preoperative chemotherapy with epidoxorubicin, docetaxel and capecitabine plus pegfilgrastim in patients with primary breast cancer

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The objective of this pilot trial was to evaluate the safety and activity profile of epidoxorubicin, docetaxel and oral capecitabine plus pegfilgrastim (TEX + P) as preoperative first-line treatment for patients with breast cancer. Eleven consecutive patients were enrolled in this prospective clinical pilot trial. Preoperative treatment consisted of epidoxorubicin [75 mg/m^2 body surface area (BSA)] and docetaxel (75 mg/m^2 BSA) administered sequentially on day 1 in combination with oral capecitabine 2000 mg/m^2 daily divided into two doses on days 1–14 of each 3-week treatment cycle. Pegfilgrastim 6 mg fixed dose was administered s.c. on day 2 of every treatment cycle. Patients received a total of 58 cycles (median 6 cycles, range 1–6) of this therapeutic regimen. Outpatient TEX + P was well tolerated. No WHO grade IV toxicity was observed. A pathological major response to this preoperative therapy regimen could be demonstrated in eight of nine evaluable patients leading to breast-conserving surgery in seven of nine evaluable patients. We conclude that outpatient TEX + P is safe in the neoadjuvant treatment of patients with primary breast cancer. Thus, this regimen can be considered for further clinical trials. *Anti-Cancer Drugs* 16:441–445 © 2005 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2005, **16**:441–445

Keywords: breast cancer, capecitabine, epidoxorubicin, docetaxel, neoadjuvant, pegfilgrastim

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Received 23 October 2004 **Revised form accepted** 29 December 2004

Introduction

The early use of chemotherapy in the preoperative treatment setting of breast cancer can potentially avoid resistance and can possibly kill or inhibit clinically undetectable micrometastases to prevent or delay the development of metastatic disease. Preoperative therapy can also lead to a reduction in tumor size and can therefore raise the rate of breast-conserving surgery [1,2]. A pathological complete response (pCR) after preoperative chemotherapy might be a surrogate marker for longer overall survival, but the rates of pCR with current treatment regimens are still rather low.

To date, anthracyclines and taxanes are the most active drugs in the treatment of advanced breast cancer, and a combination of these is considered to produce the highest response rates in the neoadjuvant as well as in the palliative treatment setting [2,3].

Capecitabine is an orally administered fluoropyrimidine carbamate activated by a three-step enzymatic conversion to the cytotoxic agent 5-fluorouracil. In the last step thymidine phosphorylase (TP) mediates the activation of capecitabine. TP is highly active in tumor tissue compared with corresponding normal tissue [4]. Therefore, the antitumor activity of capecitabine is enhanced by upregulation of TP activity and preclinical studies have demonstrated synergy when capecitabine is combined with therapies, including taxanes, that upregulate TP [5]. Currently, capecitabine monotherapy is an important treatment option for patients with metastatic breast cancer who have exhausted all treatment options. A randomized phase III trial has demonstrated that capecitabine combined with docetaxel results in significantly superior tumor response rates, time to progression or death and overall survival compared with docetaxel monotherapy in patients with anthracycline pre-treated advanced breast cancer [6].

Venturini *et al.* [7,8] demonstrated high antitumor activity in patients with advanced breast cancer by adding capecitabine to standard chemotherapy including epidoxorubicin and docetaxel.

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As a consequence of these data, we have initiated this prospective clinical evaluation to determine the toxicity and the efficacy of combined chemotherapy with outpatient epidoxorubicin, docetaxel and oral capecitabine plus pegfilgrastim (TEX + P) in the neoadjuvant treatment of patients with primary breast cancer.

Patients and methods

Patients

Eleven consecutive patients with histological proven breast cancer were accrued to this prospective clinical phase II evaluation between January and December 2003. Patients received a preoperative combination therapy consisting of TEX + P.

Criteria for inclusion were as follows. Histologic proof of invasive breast cancer, age 18–70 years, Karnofsky performance status $> 80\%$, absence of distant disease, adequate hematologic parameters (WBC $\geq 3500/\mu l$, hemoglobin level > 9 g/dl and platelet count $\geq 100\,000/\mu l$), and adequate hepatic (serum bilirubin < 1.5 mg/dl, transaminases $< 2 \times$ upper limit of normal) and renal (serum creatinine < 1.5 mg/dl) function.

Drug administration

Treatment was administered on an outpatient setting. Preoperative chemotherapy consisted of 30-min i.v. short infusion epidoxorubicin (Farmorubicin; Pfizer, New York, NY) 75 mg/m body surface area (BSA) followed by a 1-h infusion of docetaxel (Taxotere; Aventis, Strasbourg, France) 75 mg/m BSA administered sequentially on day 1 of each 3-week treatment cycle in combination with oral capecitabine (Xeloda; Hoffman-La Roche, Nutley, NJ) 2000 mg/m^2 daily divided into two doses on days 1–14 of each 3-week treatment cycle. Concomitant medication consisted of dexamethasone to prevent peripheral fluid retention and anaphylactic reactions [9], and ondansetron as prophylactic antiemetic therapy. To prevent leukocytopenia or febrile neutropenia, treatment regimen were accompanied with s.c. administration of pegfilgrastim, a pegylated granulocyte colony stimulating factor (G-CSF; Neulasta; Amgen, Thousand Oaks, CA) 6 mg fixed dose on day 2 of every treatment cycle.

Treatment assessment

Baseline evaluations included a complete medical history, physical examination, complete blood count with differential, platelet count and blood chemistry. Pathological diagnosis of invasive breast cancer, hormone receptor status and HER2 status was performed in all patients by core biopsy prior to their preoperative treatment. All patients were defined as hormone receptor-positive if either estrogen receptor or progesterone receptor turned out to be positive and as negative if both receptors were judged negative. HER2 receptor was judged positive if either HER2 turned out to be immunohistochemistry (IHC; HercepTest; Dako Cytomation, Carpenteria, CA) + + + positive or fluorescence *in situ* hybridization (FISH) positive, in case of a + + positive IHC. Hormone receptor and HER2 status were assessed from the final surgical specimen after preoperative therapy. Due to possible cardiotoxic effects of this anthracycline-containing regimen, patients were required to have a normal baseline electrocardiogram and produce an echocardiography [left ventricular ejection fraction (LVEF) $> 50\%$] prior to chemotherapy. The LVEF was monitored twice during treatment (begin and end of treatment). In order to exclude metastatic locations a computed tomography of the chest and abdomen and a bone scan were required. X-ray studies of selected osseous segments were performed when clinically indicated. Tumor size was determined by mammography, sonography or magnetic resonance imaging (MRI). The most suitable radiological method was chosen to monitor the tumor site. Patients were scheduled to receive 6 therapy cycles, and were restaged after 2, 4 and 6 cycles with mammography, sonography or MRI.

Therapy response was evaluated using the following criteria. Complete response (CR) was defined as the disappearance of all measurable disease. Partial response (PR) was a 50% or greater decrease in tumor size. Stable disease (SD) was less than 50% decrease and less than 25% increase without the appearance of new lesions. Progressive disease (PD) was a more than 25% increase in tumor size or the appearance of new lesions. A pathological CR (pCR) was defined as the absence of invasive tumor in the final surgical specimen after completion of the neoadjuvant therapy.

Dose modifications

Data were analyzed as of 13 July 2004. Toxicity was evaluated according to the WHO criteria. Dose-limiting hematological toxicity was defined as grade IV neutropenia or thrombocytopenia, lasting for 1 week or longer, or fever (single oral temperature above 38.5°C or three temperatures of above 38.5°C within 24 h) lasting more than 2 days. This resulted in a reduction of all drugs by 25% in the next and subsequent cycles. If there was further symptomatic grade IV hematological toxicity, there was a further dose reduction to 50% of the starting dose.

For all grade III non-hematological toxicities, the dose of respective drug was reduced by 25%. For example, for hand–foot syndrome or diarrhea, capecitabine dose was reduced by 25%. If grade III stomatitis occurred despite this dose reduction, then both epidoxorubicin and docetaxel were reduced, also by 25%, on the next course of treatment. However, for grade III peripheral polyneuropathy, a 25% dose reduction of docetaxel was performed.

Results

Eleven consecutive patients (median age 56 years, range 33–67; premenopausal:postmenopausal: 4:7) suffering from biopsy-proven invasive breast cancer were included in this prospective clinical evaluation. If conventional criteria for breast-conserving surgery had been applied, all included patients would have been treated with modified radical mastectomy. Nine patients presented with a tumor greater than 2 cm; the remaining two suffered from a disadvantageous tumor/breast relation ($n = 1$) and a central tumor site ($n = 1$) [T4: $n = 5$ (46%), T3: $n = 4$ (36%), T2: $n = 2$ (18%)]. The clinical lymph node status was negative in five (46%) patients and positive in six (54%) patients. The pre-therapeutic HER2 status was positive in three (27%) patients and negative in eight (73%) patients, and the pre-therapeutic hormone receptor status was positive in seven (64%) patients and negative in four (36%) patients.

All patients were evaluable for toxicity and 10 patients for clinical response, because in one patient the application of capecitabine after 1 cycle was not suitable for compliance reasons. This patient continued preoperative chemotherapy receiving epidoxorubicin and docetaxel plus pegfilgrastim on day 1 every 21 days. One patient was lost to follow-up after 3 cycles of therapy and therefore this patient was not evaluable for pathological response. Table 1 lists the characteristics of the 11 included patients.

Toxicities

TEX + P was well tolerated and all patients completed therapy on an outpatient basis. Eleven patients received a total of 58 cycles (median 6 cycles, range 1–6). All documented toxicities of the 58 cycles are shown in Table 2.

No WHO grade IV toxicity was observed. The most frequent and important toxic effect were anemia, diarrhea and hand–foot syndrome. WHO grade III hematological toxicities consisted of anemia (2%) in one patient. WHO grade III non-hematological toxicities consisted of diarrhea (3%) and hand–foot syndrome (3%).

These WHO grade III toxicities led to a dose reduction of capecitabine of 25% in the next and subsequent cycles in four patients. In all these patients the treatment-related toxicities resolved after dose reduction. Hand–foot syndrome WHO grade III resolved after dose reduction within 6 weeks.

Renal impairment, cardiac toxicity or allergic reactions were not observed in any of our patients. No toxicity-related deaths occurred.

Response data

In the neoadjuvant treatment, 10 out of 11 patients were evaluable for clinical response and nine out of 11 patients for pathological response. In one patient the application of capecitabine after 1 cycle was not suitable for

Table 2 Toxicity of preoperative TEX ($n = 57$ cycles) in 11 patients with primary breast cancer

	WHO grade [*n* (%)]			
	I	II	III	IV
Leukocytopenia	3 (5)	–	–	–
Thrombocytopenia	1 (2)	–	–	–
Anemia	21 (37)	3 (5)	1 (2)	–
Nausea/vomiting	3 (5)	–	–	–
Stomatitis	2 (4)	2 (4)	–	–
Hand–foot syndrome	2 (4)	5 (9)	2 (4)	–
Fever	1 (2%)	1 (2)	–	–
Infection	–	–	–	–
Diarrhea	4 (7)	1 (2)	2 (4)	–
PNP	–	–	–	–
Pulmonary toxicity	–	–	–	–
Cardiac toxicity	–	–	–	–
Nail toxicity	–	–	–	–
Edema	–	–	–	–
Allergic reaction	–	–	–	–
Alopecia	–	–	49 (86)	–

Table 1 Patient characteristics

Patients	Age	Pre-/post-menopausal	HR[a]	HER2[b]	Therapeutic		Dose reduction (%)			Cycle	Pathological response	QUAD/MRM[c]
					T	N	E	T	C			
1	67	post	–	–	T4	N1	–	–	–	1[d]	–	–
2	57	post	+	–	T2	N0	–	–	25	6	PR	QUAD
3	57	post	+	–	T2	N0	–	–	–	6	PR	QUAD
4	48	pre	–	–	T3	N0	–	–	–	6	pCR	QUAD
5	57	post	–	–	T3	N1	–	–	–	6	PR	QUAD
6	35	pre	+	–	T4	N1	–	–	25	6	SD	MRM
7	52	post	+	–	T4	N0	–	–	–	6	PR	MRM
8	63	post	+	+	T4	N1	–	–	25	6	PR	QUAD
9	33	pre	+	+	T3	N1	–	–	–	6	pCR	QUAD
10	56	post	+	+	T3	N0	–	–	25	6	PR	QUAD
11	41	pre	–	–	T4	N1	–	–	–	3[e]	–	–

[a]HR: hormone receptor status.
[b]HER2 status. Positive: IHC + + + or FISH positive.
[c]QUAD: quadrantectomy with axillary node dissection; MRM: modified radical mastectomy.
[d]The application of capecitabine was not suitable for compliance reasons.
[e]Patient was lost to follow-up after 3 cycles of therapy.

compliance reasons and was only evaluable for toxicities. Another patient was lost to follow-up after achieving a clinical PR after 3 cycles. This PR was counted as best possible clinical response. In all nine patients therapy was stopped after 6 cycles of TEX + P according to the trial plan. Clinically, a major response was observed in eight of nine patients [CR (0 patients) + PR (eight patients)] and one patient presented with clinically SD. Pathologically, a major response (pCR + PR) was observed in eight out of nine patients, with two patients experiencing a pCR (pT0: two patients, pDCIS: zero patients) of the invasive tumor and in six out of nine patients showing a PR. Only one of nine patients presented SD only. Breast-conserving surgery was possible in seven of nine patients.

None of the patients progressed during therapy and all patients are to date alive without evidence of disease.

Discussion

Reviewing the literature it can be found that combination chemotherapy regimen containing anthracyclines and taxanes are currently the most active drugs in the treatment of advanced breast cancer [2,3,10,11]. This combination of anthracyclines and taxanes leads to an overall response rate of 55–88% with a CR rate of 5–20% in the palliative setting and of 70–88% with a pCR rate of 10–20% in the neoadjuvant setting, respectively [2,3,10,11]. The Austrian Breast and Colorectal Cancer Study Group (ABCSG) demonstrated that doubling the number of cycles in the neoadjuvant setting by applying 6 versus 3 cycles of docetaxel and epidoxorubicin results in significantly higher rates for pCR (18.6 versus 7.7%) and negative axillary nodal status (56.6 versus 42.8%) with no excess of side-effects [12].

Capecitabine, as a well-tolerated, highly effective and convenient alternative to parenteral 5-fluorouracil, plays an important role in the treatment of patients with advanced breast cancer who have exhausted all treatment options. In particular, the low incidence of myelosuppression with capecitabine makes it an attractive agent for incorporation into combination regimens with myelosuppressive drugs such as anthracyclines and taxanes. The principal dose-limiting toxicity of capecitabine is hand–foot syndrome and diarrhea. Capecitabine, in combination with docetaxel, provides a significant survival benefit (by a median of 3 months) as well as significantly increased tumor response rate and time to disease progression compared with docetaxel monotherapy [6].

Adding capecitabine to the standard chemotherapy including epidoxorubicin and docetaxel, Venturini *et al.* [7,8] could demonstrate high antitumor activity. In a phase I trial [7] applying standard epidoxorubicin 75 mg/m^2 and docetaxel 75 mg/m^2 in combination with capecitabine 765–1060 mg/m^2 on day 1–14 every 3 weeks, in patients suffering from stage III and IV breast cancer, an objective response was observed in 95% of evaluable patients, including one CR. In the subsequent phase II trial [8] standard epidoxorubicin and docetaxel plus capecitabine 1000 mg/m^2 resulted in an objective response rate of 82% with 21% CR. Subgroup analysis revealed in patients with stage III disease an objective response of 79% with CR in 29% and among patients with stage IV disease 67 and 12%, respectively.

Our results are the first evaluation of TEX + P in the neoadjuvant setting. Our data confirm the effectiveness of adding capecitabine to a highly active chemotherapy regimen in patients with locally advanced breast cancer without unacceptable toxicities. The pathological responses in eight of nine patients reaching a pCR in two patients leading to a breast-conserving surgical procedure in seven of nine patients with advanced breast cancer are comparable to the Venturini data in patients with advanced disease.

TEX proved to be safe and well tolerated. All patients were able to complete this therapy on an outpatient basis. Side-effects were generally manageable with appropriate dose modification in combination with supportive care, comprising both pharmacologic and non-pharmagologic interventions. No WHO grade IV toxicity was observed. The incidence of WHO grade III toxicities was generally low in this trial. WHO grade III hematological toxicity only consisted of anemia in one patient. Venturini *et al.* [8] documented febrile neutropenia in 16% of patients with no standard G-CSF application. Comparing hematological WHO grade II/IV toxicities with those of the Venturini data in advanced disease [7,8] applying the same cytostatic regimen, our low incidence is most probably based on the prophylactic application of pegylated G-CSF. WHO grade III non-hematological toxicities consisted of diarrhea and hand–foot syndrome. In addition, the majority of patients received the full planned dose intensity until best possible response was achieved, with dose modification to 75% of the planned dose occurring in four patients. Cardiac events were not observed in any of our patients.

In conclusion, the combination chemotherapy of epidoxorubicin 75 mg/m^2, docetaxel 75 mg/m^2 and capecitabine 1000 mg/m^2 plus pegfilgrastim 6 mg fixed dose has been shown to be well tolerated and active in the neoadjuvant setting in patients with primary breast cancer. Thereby, all patients have been able to undergo the therapy on an entirely outpatient basis leading to an obtained and improved quality of life. This first preoperative pilot trial results support further evaluation of this triple combination in phase II/III studies in patients with advanced breast cancer. Meanwhile, based on the Venturini data [7,8] sets and the results of this pilot trial, the ABCSG

has set up a clinical phase III prospective randomized evaluation of 6 cycles of epidoxorubicin and docetaxel versus 6 cycles of TEX + P in patients with primary breast cancer.

References

1 Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, *et al.* Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 1997; **15**: 2483–2493.

2 Wenzel C, Locker GJ, Schmidinger M, Rudas M, Taucher S, Gnant MF, *et al.* Combined analysis of two phase II trials in patients with primary and advanced breast cancer with epidoxorubicin and docetaxel + granulocyte colony stimulating factor. *Anticancer Drugs* 2002; **13**:67–74.

3 Sparano JA, O'Neill A, Schaefer PL, Falkson CI, Wood WC. Phase II trial of doxorubicin and docetaxel plus granulocyte colony-stimulating factor in metastatic breast cancer: Eastern Cooperative Oncology Group Study E1196. *J Clin Oncol* 2000; **18**:2369–2377.

4 Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, *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**:1274–1281.

5 Sawada N, Ishikawa T, Fukase Y, Nishida M, Yoshikubo T, Ishitsuka H. Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by taxol/taxotere in human cancer xenografts. *Clin Cancer Res*; **4**:1013–1019.

6 O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, *et al.* Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002; **20**:2812–2823.

7 Venturini M, Del Mastro L, Garrone O, Angiolini C, Merlano M, Bergaglio M, *et al.* Phase I, dose-finding study of capecitabine in combination with docetaxel and epirubicin as first-line chemotherapy for advanced breast cancer. *Ann Oncol* 2002; **13**:546–552.

8 Venturini M, Durando A, Garrone O, Colozza MA, Contu A, Stevani I, *et al.* Capecitabine in combination with docetaxel and epirubicin in patients with previously untreated, advanced breast cancer. *Cancer* 2003; **97**: 1174–1180.

9 Dieras V, Chevallier B, Kerbrat P, Krakowski I, Roche H, Misset JL, *et al.* A multicentre phase II study of docetaxel 75 mg/m^2 as first-line chemotherapy for patients with advanced breast cancer: report of the Clinical Screening Group of the EORTC. *Br J Cancer* 1996; **74**:650–656.

10 De Matteis A, Nuzzo F, D'Aiuto G, Labonia V, Landi G, Rossi E, *et al.* Docetaxel plus epidoxorubicin as neoadjuvant treatment in patients with large operable or locally advanced carcinoma of the breast: a single-center, phase II study. *Cancer* 2002; **94**:895–901.

11 Milla-Santos A, Milla L, Rallo L, Solano V. High-dose epirubicin plus docetaxel at standard dose with lenograstim support as first-line therapy in advanced breast cancer. *Am J Clin Oncol* 2001; **24**: 138–142.

12 Steger GG, Kubista E, Hausmaninger H, Gnant M, Tausch C, Lang H and the Austrian Breast and Colorectal Cancer Study Group. 6 vs. 3 cycles of epidoxorubicin/docetaxel + G-CSF in operable breast cancer: results of ABCSG-14. *Proc Am Soc Clin Oncol* 2004; **22**:14S (abstr 553).