Oxaliplatin and 5-fluorouracil for heavily pretreated metastatic breast cancer: a preliminary phase II study

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Oxaliplatin shows *in vitro* and *in vivo* synergism with 5-fluorouracil (5-FU). In this study we evaluate the clinical efficacy of oxaliplatin and 5-FU in heavily pretreated metastatic breast cancer. Eligible patients had to be pretreated with both anthracyclines and taxanes. Pretreatment with capecitabine was recommended but not mandatory. Chemotherapy: oxaliplatin 85 mg/m^2/2 h day 1, folinic acid 400 mg/m^2/2 h day 1, 5-FU 400 mg/m^2 i.v. push day 1, 5-FU 2400 mg/m^2 continuous infusion/48 h day 1, q2w. Fourteen patients were included: one male and 13 females; age: median 53 years (38–62); ECOG 0: three patients, 1: nine patients, 2: two patients; all patients were pretreated with anthracyclines and taxanes, capecitabine: nine patients, vinorelbine: six patients, trastuzumab: four patients, hormonal therapy: 12 patients; lines of prior palliative chemotherapy: 0: one patient, 1: three patients, 2: one patient, 3: three patients, 4: four patients, 5: two patients. Results: median number of cycles: 8 (range 1–17). Toxicity (14 patients evaluable; no. of patients with Common Toxicity Criteria grade 3/4): asthenia: 2/–, paraesthesia 3/–, leuko/neutropenia: 1/2, no neutropenic fever, other (alopecia, skin): 2/–. Response (12 patients evaluable, all with bidimensionally measurable disease): complete remission: no patients, partial remission: four patients (33%, all confirmed), stable disease: five patients, progressive disease: three patients. We conclude that despite the small number of patients, the combination of 5-FU and oxaliplatin shows promising efficacy in this heavily pretreated population. *Anti-Cancer Drugs* 14:549–553 © 2003 Lippincott Williams & Wilkins.

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Introduction

There is no standard chemotherapy regime for breast cancer patients who progressed after anthracyclines and taxanes. Capecitabine, an oral prodrug of 5-fluorouracil (5-FU), is one of the best-investigated chemotherapeutics for this situation. In two studies with 131 and 162 heavily pretreated patients, capecitabine induced response rates of 18–20% and disease stabilization in 43–48% [1,2]. Vinorelbine and trastuzumab (Herceptin®) also show promising efficacy in anthracycline and taxane pretreated patients [3,4].

As taxane/anthracycline combinations both in first-line metastatic and in large adjuvant programs are used increasingly, there is more need for new chemotherapeutic options after failure of anthracyclines and taxanes. Oxaliplatin and 5-FU is an option for this setting.

5-FU, administered as single agent via continuous infusion, results in response rates of 29–41% [5,6]. Oxaliplatin, a diaminocyclohexane platinum, has recently been approved in Europe for use in colorectal cancer patients in combination with 5-FU. Oxaliplatin forms intrastrand DNA adducts, which differ from those of cisplatin or carboplatin in their repair capability, thus accounting for its activity in cisplatin-resistant cell lines and cancer patients [7].

Oxaliplatin has shown efficacy in doxorubicin-resistant breast cancer cell lines [8] in a breast cancer mouse model [9] and response rates of 21% as single agent in a small phase II study in metastatic breast cancer [10]. In colorectal cancer studies [11,12] and in breast cancer cell lines [8], oxaliplatin has shown relevant synergism with 5-FU. Two recently published phase II trials with the combination of oxaliplatin and 5-FU showed promising efficacy with tumor remission in 27–34% of patients [13,14]. A subgroup of these patients was resistant to anthracyclines and taxanes. None was reported to be pretreated with capecitabine. These results encourage confirmatory trials.

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We conducted a phase II study in metastatic breast cancer patients who were all pretreated with anthracyclines and taxanes. Additional pretreatment with capecitabine was recommended according to the current protocol, but not mandatory. We used a bimonthly regime combining 5-FU bolus and protracted infusion with oxaliplatin established in the therapy of colorectal cancer [15,16]. The rationale of this regime is based on the different mechanisms of inducing cytotoxic effects of a 5-FU bolus (inhibition of RNA synthesis) and a 5-FU protracted infusion (inhibition of thymidylate synthase) [17], and the synergism of 5-FU and oxaliplatin. This regime has a known and well manageable toxicity profile, and can be given in an outpatient setting, even with oxaliplatin doses of 100 mg/m^2 [16]. To reduce the risk of developing cumulative neurotoxicity and hematotoxicity in taxane-pretreated breast cancer patients, we modified the FOLFOX 6 regime [16] by reducing the dose of oxaliplatin to 85 mg/m^2, which also is the approved dose for colorectal cancer in Germany.

Patients and methods

Patient population

The study was approved by the ethics committee of the Charité, Humboldt University Berlin. To be eligible, the patient had to meet the following inclusion criteria: signed informed consent, age 18–80 years, Karnofsky index 60–100%, histologically confirmed metastatic breast cancer with progressive disease at study entry, bidimensionally measurable or evaluable manifestations, life expectancy >3 months. The patient had to be pretreated with anthracyclines and with taxanes in the adjuvant or metastatic setting. Excluded were patients who were pregnant, breast feeding or without adequate contraception, pretreated with oxaliplatin, with inadequate function of bone marrow or kidney, with preexisting paraesthesias CTC grade 2 or above, or with uncontrolled severe concurrent disease. Chemotherapy within the last 3 weeks prior to study entry or concurrent hormonal therapy were not allowed.

Treatment

This was a multicenter phase II trial in which patients received oxaliplatin 85 mg/m^2 over 2 h in 5% glucose, day 1, simultaneously to folinic acid 400 mg/m^2 over 2 h via a second venous access, followed by 5-FU bolus 400 mg/m^2 in 3 min as i.v. push, followed by 5-FU protracted infusion 2400 mg/m^2 over 48 h via a portable perfusion pump. Therapy was repeated every 14 days. Granulocyte colony stimulating factor was not administered routinely. Chemotherapy was delayed until normalization of toxicity if on the day of the planned administration one of the following criteria was met: diarrhea $\geq$ CTC grade 1, mucositis $\geq$ CTC grade 1, neutropenia $\geq$ CTC grade 2, thrombocytopenia <100/nl and other toxicity $>$ CTC grade 2. If at any time during the therapy any CTC grade 3 or 4 toxicity occurred (except alopecia) the dose of oxaliplatin and/or 5-FU bolus and/or 5-FU protracted infusion was reduced by 25%. In case of persistent paraesthesias or any development of painful paraesthesias, oxaliplatin was reduced by 25% or stopped when toxicity persisted. Full blood count was assessed weekly, toxicity bimonthly and tumor assessment was performed every 6 weeks, after every 3 cycles of chemotherapy.

Results

Patient characteristics

Between June 2000 and March 2002, 14 patients were included (13 females and one male). The median age was 53 years (range 28–62). Further patient characteristics are listed in Table 1. All patients were pretreated with anthracyclines and taxanes. Twelve of 14 patients had been pretreated with hormonal therapy, nine of 14 patients with capecitabine and six of 14 patients with vinorelbine. Tumor-related symptoms were present in 13 of 14 patients.

Safety

A median of 8 cycles of chemotherapy per patient was administered (range 1–17, total number of cycles 105).

Table 1 Patient characteristics

Characteristic	No. of patients ($N=14$)	%
ECOC PS		
0	3	21
1	9	64
2	2	14
Grade		
2	5	36
3	7	50
unknown	2	14
ER or PR positive	13	93
Her $-2 \geq 2+$	4	29
No. of organs involved		
1	3	21
2	5	26
3	3	21
≥ 4	3	21
Metastatic sites		
liver	10	71
bone	8	57
lung	6	43
pleura effusion	4	29
lymph node	3	21
lymphangiosis carcinomatosa lung	3	21
skin	1	7
Prior therapy		
anthracyclines	14	100
taxanes	14	100
hormonal therapy	12	86
capecitabine	9	64
vinorelbine	6	43
Herceptin	4	29
No. of lines of previous palliative chemotherapy		
0	1	7
1	3	21
2	1	7
3	3	21
≥ 4	7	50
median	3	
range	0–5	

Table 2 CTC Toxicity

	No. of patients ($N=14$) (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	2 (14)	4 (29)	–	–
Vomiting	1 (7)	3 (21)	–	–
Diarrhea	2 (14)	2 (14)	–	–
Asthenia	2 (14)	6 (43)	2 (14)	–
Stomatitis	4 (29)	2 (14)	–	–
Hand–foot syndrome	4 (29)	1 (7)	–	–
Paraesthesia	3 (21)	3 (21)	3 (21)	–
Leuko- or neutropenia	1 (8)	2 (15)	1 (8)	2 (15)
Thrombopenia	1 (8)	2 (15)	–	–
Anemia	2 (15)	2 (15)	–	–
Other[a]	2 (14)	2 (14)	2 (14)	–

[a]Other: conjunctivitis grade 1, dermatitis grade 1, constipation grade 2, thrombosis grade 2, alopecia grade 3, skin toxicity (worsening of a preexisting leg ulcer) grade 3; 13 patients were evaluable for hematologic toxicity.

Table 3 Efficacy of chemotherapy

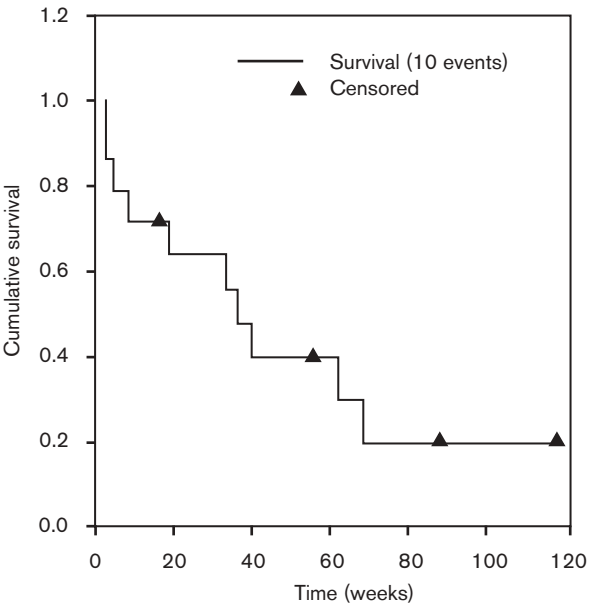
	No. of patients	%
CR	–	–
PR	4	33
SD	5	42
PD	3	25

All 14 patients were evaluable for toxicity. The chemotherapy was well tolerated with only asthenia, paraesthesia, leukopenia and skin toxicity accounting for some grade 3/4 toxicity. There was no episode of neutropenic fever. Chemotherapy had to be delayed due to toxicity at least once in six of 14 patients during their course of therapy. Dose reduction was necessary in four of 14 patients. Toxicity data are shown in Table 2.

Efficacy

Twelve patients were evaluable for response. Two patients were not evaluable for efficacy: one patient withdrew consent after the first cycle of chemotherapy, in another patient therapy was stopped after 2 cycles due to a pre-existing leg ulcer which worsened under chemotherapy. Tumor measurements were not performed in this patient. All evaluable patients had bidimensionally measurable disease. Response was assessed according to WHO criteria by the investigator together with an independent radiologist using computed tomography scans, chest-X-rays or ultrasonography as objective imaging techniques. All responses were confirmed with a second assessment at least 4 weeks later. In no patient was a complete remission (CR) of all tumor sites observed. As best response, partial remission (PR) was documented in four patients, stable disease (SD) in five patients and progressive disease (PD) in three patients (see Table 3). The median time to tumor progression was 22 weeks (range 3–52 weeks). The median duration of response was 33 weeks (range 32–52 weeks) (calculated for PR from study entry to PD). The median survival from the start of study medication was 37 weeks (range 4–118 + weeks), calculated for all 14 patients. Three deaths occurred within the first 6 weeks after start of chemotherapy, all due to tumor progression. Four patients were alive at their last follow-up. See Figure 1.

Fig. 1



Survival.

Discussion

The study was initiated at a time when no data on the efficacy of oxaliplatin and 5-FU in breast cancer were available. The development of this regime was motivated by the need for new therapeutic options in patients with metastatic breast cancer: The most active agents, anthracyclines and taxanes, are increasingly used in the adjuvant setting or as combination regimen in the first-line palliative situation. Capecitabine could be shown to be a valid therapeutic option after failure of taxanes and anthracyclines [1], but even this compound is going to be integrated into primary or adjuvant treatment (replacement studies of NSABP B27 and BCIRG 005). Vinorelbine is another possible therapy after failure of anthracyclines and taxanes. Many breast cancer patients, heavily pretreated with these kinds of therapies, are still in good general condition and ask for further therapy. The combination of oxaliplatin and 5-FU might therefore be a therapeutic option for this patient population.

Fourteen patients were included in this study. The study was initially planned to include 40 patients in a Minimax design [18] with an interim analysis after 22 patients (P0 = 10%, P1 = 25%, $\propto$-error = 5%,

power = 80%). In the interim analysis three of 22 patients must have responded for the study to be continued. With four patients of the initial 14 patients in the study showing a confirmed PR, the criteria for the interim analysis were already met. The study was stopped due to slow accrual. One reason for slow accrual might be the necessity for an i.v. port system to administer 5-FU as continuous infusion, which might be helped by replacing 5-FU with capecitabine in future trials.

Four of 12 patients evaluable for response showed a PR of their disease, which was confirmed with a tumor assessment at least 4 weeks later. The duration of response ranged from 32 to 52 weeks. Two of the patients responding with PR were both pretreated with two lines of hormonal therapy, anthracyclines, taxanes and capecitabine, and one with additional trastuzumab and the other with additional vinorelbine. In another five patients, who all had tumor progression at study entry, the disease was stabilized with a median time to tumor progression of 23 weeks for the entire study population. The therapy was well tolerated with no unexpected toxicities.

Ongoing trials in breast cancer investigate oxaliplatin in combination with 5-FU [19] or in combination with 5-FU and vinorelbine [20]. Efficacy is reported but the proportion of patients pretreated with anthracyclines and taxanes is small. In an ongoing phase II/III trial the combination of oxaliplatin/5-FU is compared to vinorelbine/5-FU, efficacy results are awaited [21].

In a study by Zelek *et al.* [13], a combination therapy of 5-FU and oxaliplatin was investigated in anthracycline- and taxane-pretreated patients. A response rate of 27% could be demonstrated using a regime consisting of oxaliplatin 130 mg/m^2 day 1 and 5-FU 1 g/m^2 day 1–4, continuous infusion, q3w. All patients were pretreated with anthracyclines and taxanes, as in our study. Pectasides *et al.* [14] investigated oxaliplatin and 5-FU using the FOLFOX 4 regime (oxaliplatin 85 mg/m^2/2 h day 1, leucovorin 200 mg/m^2/2 h, bolus 5-FU 400 mg/m^2 and 5-FU 600 mg/m^2/22 h day 1 and 2) [15]. An overall response rate of 34% was reported; 60% of the patients had been pretreated with both anthracyclines and taxanes. The response rate of 33% seen with our bimonthly regime lies in the same range as in those two trials. Our study confirms the efficacy of oxaliplatin/5-FU in anthracycline- and taxane-pretreated breast cancer. However, none of the patients published so far was reported to have been pretreated with capecitabine. Sixty-four percent of our patients were pretreated with anthracyclines, taxanes and with capecitabine, including two of the four responding patients. The tumor response of two patients under a 5-FU/oxaliplatin combination despite pretreatment with an oral fluoropyrimidine might be due to the synergism of oxaliplatin and 5-FU.

Of the 5-FU/oxaliplatin regimens investigated in breast cancer, our modified FOLFOX 6 regime is probably the easiest one to administer in view of days on chemotherapy [13] or required outpatient visits per cycle [14].

Despite the small number of patients, our study confirms the efficacy of oxaliplatin and 5-FU in heavily pretreated metastatic breast cancer. In future studies this combination might be replaced by oxaliplatin and capecitabine which would be more convenient for the patient.

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