Salvage Chemotherapy with Oxaliplatin and Capecitabine for Breast Cancer Patients Pretreated with Anthracyclines and Taxanes

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Abstract. *There is no standard treatment for breast cancer patients whose tumors have been exposed both to anthracyclines and taxanes. Oxaliplatin shows synergism with 5-fluorouracil (5-FU) and capecitabine is an oral prodrug of 5-FU with known efficacy in pretreated patients. This phase II trial studied the efficacy and toxicity of the oxaliplatin-capecitabine combination as salvage treatment in breast cancer patients pretreated with anthracyclines and taxanes. Patients received oxaliplatin 80 mg/m^2 on day 1 followed by oral capecitabine 1800 mg/m^2 divided in two doses for 7 days every two weeks for a maximum of twelve courses or until disease progression. Twenty-eight patients were evaluable for efficacy and toxicity. Objective responses (all partial) were documented in 9 patients [32%; 95% confidence interval (CI): 13-51.2%]. Responses were documented at all metastatic sites. The median response duration was 5 months (range 3-9), median time to progression was 4.5 months (range 2-10) and median overall survival was 10 months (range 2-18). Myelotoxicity was minimal with grade 3 thrombocytopenia as the main toxicity. Hand-foot syndrome was well tolerated. The present regimen was well tolerated with a rather moderate effectiveness but very significant for this group of patients. Further studies where the combination could be compared with single agent capecitabine are warranted.*

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Metastatic breast cancer remains an incurable disease and although several advances in its management have been made in recent years, there is no significant prolongation of survival and the treatment remains palliative (1). Anthracyclines, alone or in combination, have been extensively used either in the adjuvant setting or as first-line treatment for advanced disease. Although the effectiveness of the anthracycline-containing regimen in metastatic breast cancer is significant, yielding response rates up to 80% (2, 3), the results of second-line chemotherapy in patients treated initially with an anthracyline-containing regimen are poor, with responses ranging between 10 to 35% depending on the level of resistance to anthracyclines (4, 5). Tumor resistance is expressed either as primary resistance to first-line treatment or as early relapse after adjuvant treatment or as early tumor recurrence after an initial response (4, 5).

The introduction of new chemotherapeutic agents with an innovative mechanism of action, potentially non-cross resistant to antracyclines, offers an opportunity for a second tumor response and, eventually, for life prolongation. Paclitaxel is a highly active new agent with response rates of 56-62% as first-line treatment in breast cancer (6, 7) and with encouraging response rates of 22-35% in tumors refractory to anthracylines (8, 9). Docetaxel, another taxane, was found to be superior to doxorubicin (10). Doxorubicin exhibited the highest reported response rate for any single agent administered as first-line treatment. This has been reported for anthracycline pre-treated patients and for patients with visceral disease (11, 12). The combination of taxanes and anthracyclines has gained acceptance in advanced breast cancer with response rates and time to disease progressions higher than those previously reported (13, 14). The use of taxane anthracyclines in sequential administration, or in combinations, both in the adjuvant setting and for metastatic disease, has created the need for new agents in the group of patients with progressive disease who have

exhausted the taxane and anthracycline therapeutic options. The optimal treatment for those patients is to be found among the new agents (15-20).

Oxaliplatin, a diaminocyclohexane platinum, forms intrastrand DNA adducts different from those of other platinum compound, and this explains its activity in cisplatin-resistant cell lines (21). In colorectal and breast cancer cell lines, oxaliplatin has shown relevant synergism with 5-fluorouracil (5-FU) (22). In several studies in breast cancer patients, oxaliplatin in combination with 5-FU slowed promising efficacy, with objective response rates of 27-35% (23-25). Capecitabine, a prodrug of 5-FU converted to the active drug 5-FU by thymidine phosphorylase which has been found to be 3 to 10 times higher in various solid tumors compared to normal tissue. The localization of the enzyme to the liver and tumor cells allows for targeted intratumoral release of 5-FU with less systemic toxicity compared with *i.v.* 5-FU (26-27). Capecitabine in pretreated breast cancer patients with anthracyclines had a better therapeutic profile compared to paclitaxel (28). In addition, response rates of 15-29% have been reported when the agent was administered in metastatic disease to patients pretreated with anthracyclines and taxanes (16, 28-30). Tolerability has been favorable, with the major adverse effects being gastrointestinal toxicity or hand-foot syndrome. Capecitabine is approved by the FDA for patients progressing on taxanes and or anthracyclines or when an anthracycline is contraindicated (31).

In the present study, oxaliplatin was combined with capecitabine for the treatment of breast cancer patients who were pretreated and progressed after anthracycline and taxane-containing regimens. The addition of oxaliplatin to capecitabine was decided with the hope of achieving a higher response rate, relying on the well-known synergism between the two agents.

Patients and Methods

Patient population. Patients were required to have histologically confirmed adenocarcinoma of the breast, with manifestations of locoregional or metastatic measurable disease; lesions had to be located outside of a previously irradiated field, unless definite evidence of progression of the in-field lesion could be verified (at least 3 months after prior radiotherapy). Eligibility criteria included: patients with primary tumors considered resistant (tumors non-responding to or progressing after first-line anthracycline and or taxane treatment) or: tumors recurring within 3 to 6 months after an objective response to anthracycline and or taxane, aged 18-75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2; hematological parameters and blood chemistry indicating normal organ function (absolute neutrophil count $\geq 1.5\times10^9$/l; platelet count $\geq 100\times10^9$/l; hemoglobin ≥10 g/dl); normal total serum bilirubin aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤2.5 times the upper limit of normal value (ULN), alkaline phosphatase ≤6×ULN; and normal renal function. Normal baseline left ventricular ejection fraction (LVEF) was required. Exclusion criteria included: prior treatment with platinum compounds or capecitabine; previous cumulative dose of doxorubicin ≥600 mg/m^2 or epirubicin ≥720 mg/m^2 during adjuvant plus systemic treatment; history of bone irradiation encompassing >25% of bone marrow; history of prior malignancies, excluding excised carcinoma *in situ* of the cervix and non-melanoma skin cancer; known central nervous system metastases; pregnancy. The Ethics and Scientific Committees of the center approved the study, and informed consent was obligatory.

Treatment plan. Treatment was given on an outpatient basis and comprised 80 mg/m^2 oxaliplatin given in 500 ml normal saline over 2 hours. Anti-emetic treatment was given before chemotherapy and consisted of dexamethasone (8 mg) plus ondansetron (24 mg) given as *i.v.* bolus. Oxaliplatin followed by 7 days, capecitabine at 1, 800 mg/m^2/day was given every 2 weeks for a maximum of 12 cycles, unless there was evidence of disease progression, unacceptable toxicity or patient refusal. After 8 cycles, patients with an objective response or with stable disease continued treatment until disease progression or prohibitive toxicity or for 2 cycles after achieving complete response, whichever occurred first.

Dose modifications. The prerequisites for dose modifications were set as follows: i) any episode of grade 4 neutropenia of longer than 7 days' duration, ii) any episode of febrile grade 3 or higher neutropenia, iii) any episode of grade 4 thrombocytopenia requiring platelet transfusions, iv) any nonhematological grade 3 or 4 toxicity excluding nausea and vomiting. The following guidelines were applied with respect to dose reductions for toxicity: i) for neutropenia, meeting the aforementioned criteria, oxaliplatin, and capecitabine doses were reduced by 20% in subsequent cycles, and if toxicity reappeared after a total of 40% reduction from the starting dose in consecutive cycles treatment was withdrawn; however, the patient would be evaluable for toxicity and response; ii) for thrombocytopenia, reduction of oxaliplatin by 20% was applied in addition to capecitabine dose reduction as specified for neutropenia; iii) for grade 3 or higher mucositis, the dose of capecitabine was reduced by 20% in subsequent cycles; iv) for neuropathy grade 3 or higher, treatment was interrupted; v) for renal toxicity grade 3 or higher toxicity (serum creatinine elevations, >3 × normal) treatment was withheld until recovery (serum creatinine, <1.8 mg/dl). Where blood counts had not recovered to ANC ≥1.500/μl and platelet count ≥100,000/μl on the day of therapy, treatment was withheld until recovery, and after a maximum delay of 2 weeks, no further therapy was administered in cases in which counts did not return to normal.

Patient evaluation. Baseline evaluations included: patient history, physical examination, chest X-rays, complete blood count with differential and platelet count, standard blood chemistry and ECG. Computed tomography (CT) scans of the chest, abdomen, pelvis brain and whole body bone scintigraphy were performed at study entry. Complete blood counts with differential and platelet counts were performed twice weekly or daily in case of grade 3/4 neutropenia, thrombocytopenia or febrile neutropenia until hematological recovery; blood chemistry and physical examination were performed every 3 weeks. Patients were evaluated before each cycle for lesions assessable by physical examination. All patients were evaluated by the appropriate imaging studies indicative of the measurable target lesions every 2 chemotherapy cycles.

Tumor evaluation and criteria for response. Tumor response was assessed after every 2 cycles using the World Health Organization (WHO) response criteria (32). An independent radiologist reviewed

all tumor responses. Response duration was calculated from the day on which at least a 50% reduction in tumor volume was documented until the first documentation of progressive disease. Time to tumor progression (TTP) was calculated from the first day of drug administration to the first documentation of tumor progression. Overall survival was measured from the date of first drug administration to death. Patients without progression who died during the study were considered treatment failures.

Monitoring for toxicity. Toxicity evaluations were graded according to National Cancer Institute (NCI) common toxicity criteria (32). Hematological and clinical chemistry parameters were measured at baseline and then at least weekly throughout treatment. Liver function was monitored at each cycle.

Statistical methods. The primary objective of the study was the overall response rate. All analyses were based on the intent to treat population. Confidence intervals (CI) for response rates were calculated according to the method described by Simon (33). Simon's two-stage mini-max design was used to allow for early termination of the trial in the event of a poor response rate. An optimized two-stage plan for accrual was used at a first-stage design with 16 patients. It was calculated that, with an anticipated response rate (RR) of approximately 30% (minimum level of activity to be of interest), the sample size required for having confidence limits of ±8% would be 32 patients. The survival distributions for response duration, TTP and overall survival were estimated using the Kaplan-Meier method. Dose intensity was expressed in mg/m^2/week.

Results

Patient characteristics. From June 2003 to September 2006, 28 patients were enrolled and their characteristics are listed in Table I. The majority of the patients had visceral metastases, with 80% manifesting more than two metastatic sites. Half of them in the past had received two chemotherapy regimens for advanced disease, 32% had received three and 18% four different treatments. All the patients had been exposed to antrhracyclines and taxanes. A total of 258 courses were administered, with a median of 6 courses per patient (range 4-12).

Response and survival data. All 28 patients were assessable for response and toxicity. The efficacy of the regimen is presented in Table II. Responses were observed in all sites of disease such as the liver (30%), lung (20%), pleura (29%) and cutaneous (25%) (Table III). On an intention-to-treat analysis, 9 (32%) patients (95% CI, 13-51.2%) achieved a partial response, 10 (36%) patients had stable disease, while 9 (32%) progressed during treatment. The median duration of the response was 5 months (range 3-9), the median time to progression was 4.5 months (range 2-10), the median survival was 10 months (range 2-18) and the median duration of stable disease was 4 months (range 2-6).

Table I. *Patient characteristics.*

	Number of patients (%)
Eligible patients	28
Age (years)	
Median	56
Range	39-66
Performance status (ECOG)	
0	7 (25)
1	13 (47)
2	8 (28)
Estrogen receptor status	
Positive	18 (65)
Negative	8 (28)
Unknown	2 (7)
Menopausal status	
Premenopausal	8 (28)
Postmenopausal	15 (54)
Perimenopausal	5 (18)
Sites of disease	
Liver	20 (72)
Lung	10 (36)
Pleura	7 (25)
Bone	17 (60)
Lymph nodes	7 (25)
Cutaneous	4 (15)
Number of organs involved	
1	6 (21)
2	12 (43)
3	6 (21)
≥4	4 (15)
Number of previous chemotherapeutic regimen	
2	14 (50)
3	9 (32)
4	5 (18)
Prior anthracyclines	28 (100)
Prior taxanes	28 (100)
Hormonal therapy	20 (86)
Radiotherapy	
Adjuvant	22 (79)
Palliative	7 (25)

Compliance with treatment. A total of 16 treatment cycles (6%) were delayed for 3-14 days (median 7 days), mainly as a result of patient choice due to difficulties in traveling from district areas (10 cycles) and 6 cycles due to low platelet count on the day of treatment. The delivered dose intensity was 85% of the planned dose for the two agents due to delays and dose reductions.

Toxicities. Hematological and nonhematological toxicities encountered in the present study were evaluated in all patients and cycles and are presented in Tables IV and V, respectively. Grade 3 toxicities included neutropenia in 10% of patients. Grade 3 thrombocytopenia developed in 5% . No renal toxicity was observed. Peripheral neuropathy, mainly caused by oxaliplatin, was common, but not severe.

Table II. *Clinical response to treatment.*

	No. patients	Percentage of all patients (n=28)
Complete response	-	-
Partial response	9	32% (95% CI 11%-33%)
Stable disease	10	36%
Progressive disease	9	32%
Responses according to prior chemotherapies		
Anthracycline-resistant	9/28	32%
Taxane-resistant	9/28	32%

Table III. *Response by site of disease.*

Site	No. patients	Percentage of all patients (n=28)
Liver	6/20	30%
Lung	2/10	20%
Pleura	2/7	29%
Bones	1/17	6%
Lymph nodes	1/7	14%
Cutaneous	1/4	25%

Table IV. *Hematological toxicities (NCI-CTC grade).*

	NCI-CTC grade (% of patients, all cycles)			
Toxicity	1	2	3	4
Leukopenia	40	15	10	-
Neutropenia	35	15	5	-
Thrombocytopenia	30	20	5	-
Anemia	20	10	5	-

NCI, National Cancer Institute; CTC, common toxicity criteria.

Table V. *Nonhematological toxicities (NCI-CTC grade).*

	NCI-CTC grade (% of patients, all cycles)			
Toxicity	1	2	3	4
Nausea vomiting	65	10		
Mucositis	30	20	5	
Peripheral neuropathy	30	10		
Hand-foot syndrome	20	10		
Alopecia		100		
Renal	4			

NCI, National Cancer Institute; CTC, common toxicity criteria.

Discussion

The present study was initiated by the increased need for effective second-line therapeutic choices for patients with advanced breast cancer in whom taxane and anthracycline-based chemotherapies have failed.

The application of the two aforementioned drugs for the treatment of breast cancer patients in the adjuvant or neoadjuvant treatment and subsequently for advanced disease upon recurrence rends a great percentage of patients with resistant tumors. In these cases, salvage chemotherapy with an easily administered nontoxic regimen needs to be established. The two agents used in the present study are active in breast cancer, have a synergistic activity and a favorable toxicity profile (21-27).

The achieved RR (32%) in the present study is only moderate but is significant for this group of patients with extensive metastatic disease and tumors practically resistant to anthracyclines and taxanes. The RR, TTP and median survival do not different from those reported by other investigators that have used the combination of oxaliplatin with 5-FU plus folinic acid for the same type of patients (23-25). In prior studies, the dose of oxaliplatin was from 85 mg/m^2 administered every two weeks or every three works (34), escalated to 130 mg/m^2 with the addition of vinorelbine in the most recent study resulting in a 34.8% response rate, with an estimated 18.8 month overall survival (35).

Alternative regimens in breast cancer patients with tumors resistant to anthracyclines and taxanes have been used in the past with moderate results. Combinations of vinorelbine, either with cisplatin or with 5-FU have been tested in such patients, yielding response rate 47% and 27% respectively (19, 35). In addition, oral vinorelbine with capecitabine achieved a response rate of 41%, but without further information on time-related parameters (36). The results of single agent capecitabine also seem to be moderate, with a response rate of 9-28% and overall survival between 9.4 and 15.2 months (16, 17, 29, 31).

As for toxicity, the regimen applied in the present study is to be considered relatively atoxic because of its mild myelotoxicity and its moderate gastrointestinal side-effects due to oral capecitabine. It is interesting to note that granulocyte colony-stimulating factor (GCSF) was used only for 4 patients at the completion of their treatment. Thrombocytopenia was also moderate but was the cause of delay of treatment and the reason for decreasing the dosage of oxaliplatin in 6 patients. Neurotoxicity, as expected, was related to the cumulative dose of oxaliplatin and was experienced mostly by those patients responding to treatment that had received the highest total dose of the drug. However, neurotoxicity was not a major problem, particularly in this group of patients that had already some

degree of neurotoxicity due to prior taxane administration. The degree of neurotoxicity reported in other studies was also nonsignificant, with grade 2 and 3 in 18% and 12% respectively in the study of Pectacides *et al*. (25), and 25% and 8% respectively in the study of Zelek *et al*. (24). In this latter report, grade 3 neurotoxicity developed in patients that received a median total dose of oxaliplatin of 1,666 mg/m^2 (range 769 to 1,513 mg/m^2) as a result of to nine treatment cycles (24).

In conclusion, the regimen used in the present study is active in patients with tumors resistant both to anthracyclines and taxanes, it is easy to administer and it has a very safe toxicity profile. These are qualifications for a palliative treatment. Since the two major drugs (anthracyclines and taxanes) have entered into the treatment of both early and advanced disease, it seems that in the future, the number of patients requiring salvage regimen is going to increase. Due to its synergistic effect, the oxaliplatin-capecitabine combination might became an alternative regimen now that capecitabine is used in first-line treatment as a partner of docetaxel.

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