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Capecitabine and oxaliplatin in combination as first or second-line therapy for metastatic breast cancer: A Wisconsin Oncology Network trial

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Abstract

Purpose—Several cytotoxic chemotherapy regimens are active against metastatic breast cancer; however, benefits are modest and overall prognosis remains limited. For anthracycline and taxane-pretreated metastatic breast cancer, there remains a relative paucity of therapies with significant activity. This Phase II study evaluated the combination of capecitabine and oxaliplatin (XELOX) among patients with metastatic breast cancer being treated in the first or second-line setting.

Methods—Patients received oxaliplatin 85 mg/m^2 on days 1 and 15, and capecitabine 1500 mg/m^2 twice daily on days 1-7 and 15-21 of a 28 day cycle. Patients were treated until progression or intolerable toxicity. The primary objective was to estimate the objective response rate by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria with tumor assessments every 8 weeks.

Results—10 patients were treated of which 3 had received prior neurotoxic therapy in the metastatic setting. There were no confirmed complete responses, 5 patients had partial response, 4 patients had stable disease for at least 24 weeks, and one patient was unevaluable. Median time to progression (TTP) was 10.4 months (95% lower confidence bound [LCB]: 5.75 months), median progression free survival (PFS) was 14.2 months (95% LCB: 6.14 months), and median overall survival (OS) was 19 months (95% LCB: 12.8 months). Multiple patients experienced pain

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syndromes and unusual neuropathies. Other common toxicities included fatigue, diarrhea, and nausea.

Conclusions—XELOX is a promising regimen for anthracycline-pretreated metastatic breast cancer although careful patient selection is indicated and alternate dosing schedules should be explored to minimize neurologic morbidity.

Keywords

XELOX; neuropathy; capecitabine; oxaliplatin; breast cancer; metastatic

Introduction

Breast cancer remains the most common cancer diagnosis in women and the second leading cause of cancer death in women, with an estimate of 39,520 deaths among women in the United States in 2011 [1]. The overall prognosis with metastatic disease is poor, despite the existence of multiple cytotoxic chemotherapy agents with activity in breast cancer. Doxorubicin, capecitabine, docetaxel, paclitaxel, gemcitabine, and vinorelbine have response rates (RR) in metastatic breast cancer (MBC) ranging from 20-42% and time to progression of 4.2-8.1 months [2-6]. Given the overall poor prognosis associated with MBC, there is need for development of new therapies with improved response rates and tolerable side effects.

Platinum agents work by inducing DNA damage and among this family, cisplatin and carboplatin have demonstrated high activity as first-line treatment of breast cancer, yet have very little activity in anthracycline-pretreated breast cancer patients [7]. Oxaliplatin is a diaminocyclohexane platinum that could potentially overcome this difficulty. DNA damage induced by oxaliplatin is more cytotoxic than damage caused by other platinum analogues, partly due to its activity in mismatch repair-deficient cells [8,9]. Oxaliplatin demonstrates activity in cisplatin–resistant cell lines and a different preclinical spectrum of activity compared with other platinum compounds [8,9]. Additionally, small studies have demonstrated activity for oxaliplatin in heavily pretreated MBC, including those resistant to anthracyclines and taxanes. In a phase 1 study reported by Caussanel *et al*, an objective response was observed in two of 12 patients with pretreated breast cancer [10]. Additionally, Delpeuch *et al* evaluated off-label use of oxaliplatin in patients with metastatic breast cancer. Among 15 evaluable patients, one patient achieved a complete response while another had a partial response [11].

Capecitabine is a fluoropyrimidine carbamate that is preferentially converted to 5-FU by the enzyme thymidine phosphorylase (TP), present in higher levels in tumor cells compared to normal cells [8]. Capecitabine has single agent activity against metastatic breast cancer, including anthracycline and taxane-resistant disease, with response rates ranging from 20% to 40% [12,3,13]. Activity of the combination of capecitabine and oxaliplatin (XELOX) in breast cancer has already been evaluated in a single institution study. Polyzos *et al* reported a phase 2 trial involving 28 evaluable patients. 50% had received 2 lines of therapy for metastatic disease while the remaining patients had received more than 2 regimens. There were partial responses in 9 patients. Median response duration was 5 months, median time to progression was 4.5 months, and median overall survival was 10 months. Major complications included thrombocytopenia and hand-foot syndrome [14].

We report results of a multicenter single arm phase 2 study of the same combination in metastatic breast cancer, to assess the response rate in the first or second-line setting. Our study was conducted within the Wisconsin Oncology Network (WON).

Patients and Methods

Inclusion/exclusion criteria

Eligible women had histologically confirmed metastatic breast cancer, treated with ≤ 1 prior cytotoxic regimens for metastatic disease. Additional criteria included measurable or evaluable disease, performance status (PS) ≤ 2 and adequate organ reserve (absolute neutrophil count (ANC) > 1,500/mL, hemoglobin ≥ 10 g/dL, platelet count > 100,000/mL, estimated creatinine clearance > 50 mL/min, total bilirubin < 1.5 times the upper limit of normal (ULN), aminotransaminases < 2.5 times the ULN or < 5 times the ULN in the case of liver metastasis). Patients were also required to have a life expectancy ≥ 3 months and be at least four weeks from prior cytotoxic treatment (six weeks in the case of prior mitomycin C or nitrosoureas) or 24 hours from prior endocrine treatment.

Previous 5-FU in the adjuvant setting was permitted (≥ 6 months prior), but not prior capecitabine or oxaliplatin. Exclusion criteria included current pregnancy or breastfeeding status, symptomatic or progressing brain metastatic disease, other malignancy within the preceding five years, severe allergic reaction to 5-fluorouracil, intestinal malabsorption, surgery within four weeks, preexisting uncontrolled coagulopathy, or peripheral neuropathy ≥ grade 1. The Institutional Review Board of the University of Wisconsin approved the study protocol prior to its implementation. All patients provided written informed consent prior to enrollment.

Assessments

Baseline laboratory and imaging studies were performed within two and four weeks prior to enrollment, respectively. Subsequent laboratory studies, history and physical examinations were performed on day 1 of each cycle. A complete blood count was drawn prior to each oxaliplatin infusion. Measurable disease was imagedand graded using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [15] every two cycles (8 weeks). Patients were followed every 6 months for up to 3 years following study registration.

Therapy

Each 28-day cycle of therapy consisted of oxaliplatin 85 mg/m^2 on days 1 and 15, and capecitabine 1500 mg/m^2 twice daily on days 1 to 7 and 15 to 21. Oxaliplatin was administered as an intravenous infusion over 2 hours. Capecitabine was administered as an oral dose beginning on the evening of day 1 and 15. This schedule was chosen to maximize the doses of oxaliplatin and capecitabine. Scheitauer *et al* [16] showed that a dose intensive regimen of oxaliplatin 85 mg/m^2 on day 1 and capecitabine 3500 mg/m^2/d on days 1 through 7 every 14 days had equivalent toxicities compared with dosing of both agents on a 21-day cycle. However, while 3500 mg/m^2/day of capecitabine resulted in an improved time to progression, it was associated with a higher incidence of grade three diarrhea and myelotoxicity. This resulted in dose delays and dose reductions in 26% of patients. We opted to use a 21-day cycle and employed a slightly lower dose of capecitabine (3000 mg/m^2/day) in an attempt to avoid dose delays and reductions.

Dose Modifications/Delays

Treatment was discontinued in cases of disease progression, significant toxicity and/or withdrawal of consent. Therapy could only be resumed when the requirements for starting both oxaliplatin and capecitabine were met. If toxicity required a delay or interruption in therapy for more than 3 weeks, the patient was withdrawn from the study. Dose modifications were made for oxaliplatin in cases for peripheral neuropathy, skin toxicity, and laryngopharyngeal dysesthesia; for capecitabine in cases of cardiac toxicity and palmar-plantar erythrodysesthesia; and for both drugs in cases of stomatitis, nausea, vomiting,

diarrhea, and hematologic toxicity. Toxicity could be graded as due solely to one of the drugs. In such cases, the dose of the other drug was not modified. If oxaliplatin was discontinued, patients were withdrawn from the study and treated with single-agent capecitabine off-study. Doses were reduced by 25% for the first occurrence, 50% for the second occurrence, and treatment was discontinued at the third occurrence. Persistent grade 2 symptoms interfering with quality of life (e.g. nausea) could lead to dose reduction at the discretion of the treating physician.

Recombinant hematopoietic growth factor administration was allowed for prophylaxis against neutropenia, and treatment of anemia was also allowed if deemed medically appropriate. Prophylactic use of hematopoietic growth factors was not allowed in cycle 1. Appropriate antiemetics were administered per standard practice.

Statistical Plan

This phase 2 study was designed using an admissible design [5], testing the null hypothesis that the true objective RR is at most 30% at a one-sided level 0.1 against the alternative hypothesis that it is at least 50% with 0.85 power. We planned an initial enrollment of 17 patients, and subsequent accrual of 17 more patients if six or more responses were observed in the initial cohort. The regimen would be considered worthy of further study if 13 or more confirmed responses were observed, with acceptable toxicity. The primary objective was to estimate the objective response rate (RR). Disease response was monitored every second cycle in accordance with RECIST. Standard criteria were used for assessments of efficacy and toxicity, and all treated patients were included in the calculations. Secondary objectives included safety, tolerability and time to progression. Safety and tolerability were evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events V3.0 (NCI CTCAE v.3.0) [17]. Objective response was summarized with proportion and a 95% confidence interval, while time to progression, progression-free and overall survival were analyzed using the Kaplan-Meier method.

Results

Patient characteristics

Between May 2005 and November 2006, a total of 11 patients were enrolled into this study from two sites (8 from UW Hospitals and Clinics and 3 from Oconomowoc Memorial Hospital) in the Wisconsin Oncology Network (WON). Of those 11 patients, 1 patient had worsened performance status soon after enrollment and was not treated on the protocol and thus not included in the analysis, while another withdrew before day 15 of cycle 1. A total of 9 patients were evaluable for response. Trial enrollment was terminated prematurely due to concerns regarding the degree and cumulative nature of toxicities, particularly painful neuropathies. Data analysis is current as of August 2008. Baseline characteristics are summarized in Table 1. Due to concerns over neurotoxicity, we also retrospectively tracked the number of prior neuropathy-inducing regimens. A total of 10 patients, including one patient unevaluable for response, were included in the analysis with follow-up until March 2010.

Clinical response

A median of 4 cycles per patient was delivered (range <1 to 16). Eight patients received more than one cycle. All evaluable patients (n=9) received at least one dose of oxaliplatin and capecitabine. One patient (patient 11) withdrew before day 15 because of multiple side effects, none of which met the criteria for dose reduction. Of the 9 evaluable patients, 8 were evaluated for response using the Response Evaluation Criteria in Solid Tumors (RECIST). However, patient 11 had advanced cutaneous disease and a sustained disease response was

documented on clinic progress notes. As a result, the patient was included in calculation of response rates.

There were no confirmed complete responses; patient 11 is described as having complete resolution of all skin lesions. However, no imaging or photography is available to confirm this. Despite having received only 1 cycle, patient 11 did not have any evidence of disease progression for several months, and later received further doses of capecitabine at a reduced dose with further disease control. Four other patients had partial responses (PR) through 6, 12, 15 and 16 cycles. Four patients had stable disease (SD) through 2, 4, 4, and 6 cycles. The overall RR was 50% with a 95% confidence interval (CI) of (18.7%, 81.3%). Clinical benefit rate (CR, PR, and stable disease lasting six months or more) was 60% with a 95% CI of (26%, 88%). Response data is summarized in Table 2. With follow-up until March 2010, median time to progression was 10.4 months with a 95% lower confidence bound (LCB) of 5.75 months; median progression free survival (PFS) 14.2 months with a 95% LCB of 6.14 months; and median overall survival was 19.0 months with a 95% LCB of 12.8 months.

Overall toxicities

The most common toxicities were neuropathy, fatigue, diarrhea, and nausea. Six patients experienced grade 3 or 4 toxicities (see Table 2). Five patients (50%) required dose reductions for both capecitabine and oxaliplatin by cycle 3. Multiple patients experienced pain syndromes and unusual neuropathies and in total, 8 out of 9 evaluable patients developed some degree of peripheral neuropathy. Out of all 10 patients started on protocol treatment, 2 (1 evaluable) were unwilling to continue on study past cycle 1 as a result. For the single evaluable patient who withdrew after cycle 1, toxicities were of grade 1 and 2, and did not meet pre-specified criteria for drug discontinuation or dose modification. Toxicities are summarized in Table 3.

Discussion

There has been growing interest in the use of platinum agents for the treatment of breast cancer particularly triple negative and BRCA 1 and 2-associated breast cancer. Consistent with the report by Polyzos *et al*[14], we have demonstrated promising clinical activity of the combination of capecitabine and oxaliplatin in heavily-treated metastatic breast cancer. Since single agent capecitabine has response rates (RR) of 21- 37% [3,4], the addition of oxaliplatin appears to enhance activity although comparison across different studies has inherent limitations. In our study, all 9 evaluable patients demonstrated some clinical benefit and 5 patients had partial responses (56%). Although our study is limited by a small sample size, response rates do compare favorably with rates for other active combination regimens in this population such as 43% for ixabepilone and capecitabine [18].

The trial closed prematurely as a result of concerns about a greater than expected degree of sensory neuropathy when compared to clinical experience with the combination in colorectal cancer. In one phase II trial, the XELOX regimen was associated with a 16% rate of neuropathy [19] and in another study a randomized phase II design revealed a 12% rate of neuropathy with a 3-weekly standard XELOX regimen compared to a 16% rate with an intensified twice-weekly regimen of oxaliplatin 85mg/m2 on day 1 and capecitabine 3500mg/m2/day from day 1 to 7 [16]. In yet another study, an intensification of oxaliplatin delivery involved administration of oxaliplatin 100mg/m2 on day 1 and capecitabine 2000mg/m2/day from day 1 to 11 in a 2-week cycle. Grade 3 neuropathy was seen in 24% of patients [20]. All the aforementioned studies involved patients with colorectal cancer who are therefore less likely to have received prior neuropathy-causing agents. A study in advanced gastric cancer further illustrates that XELOX may be more tolerable among patients who have not previously received potentially neurotoxic agents. Xiang *et al* recently

reported results of a study among 45 patients who received oxaliplatin 130 mg/m2 on day 1 and capecitabine 850 mg/m2 twice daily on days 1-14 of a 3-week cycle in the first line setting. The incidence of peripheral neuropathy was 2.2% [21]. Among our study population, 3 out of 9 received prior taxane or vinorelbine. Several patients experienced pain syndromes and were unwilling to continue on study suggesting a particularly painful component in the sensory neuropathies although there were no cases of grade 3 or 4 neuropathy. Our findings were in contrast to the study by Polyzos *et al* which reported neuropathy rates of 30% (grade 1) and 10% (grade 2) among taxane-exposed breast cancer patients but used a different dosing regimen of oxaliplatin 80mg/m^2 on day 1 and capecitabine 1800mg/m^2/day from day 1 to 7 every 2 weeks. Neuropathy was common but mild and there were no cases of premature treatment discontinuation as a result of neurologic toxicity [14].

In summary, to our knowledge, this is one of only 2 studies of capecitabine in combination with oxaliplatin for pretreated metastatic breast cancer. Our study provides another piece of evidence in support of the combination of capecitabine and oxaliplatin for metastatic breast cancer. Our dosing regimen was poorly tolerated implying that alternate regimens should be explored such as a 2-week regimen with reduced doses of both drugs. Careful patient selection is essential and may include exclusion of individuals with prior receipt of neurotoxic agents in the metastatic setting. Additionally, pharmacogenetic studies using candidate gene approaches have revealed a possible association between polymorphisms in the glutathione S-transferase (GST) genes and predisposition to oxaliplatin-induced neuropathy[22,23]. In the future, such biomarkers hold promise in allowing a priori identification of patients at heightened risk of oxaliplatin-induced neuropathy thereby facilitating personalized treatment decision making.

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References

1. DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics, 2011. CA Cancer J Clin. 2011; 61(6):409–418.10.3322/caac.20134 [PubMed: 21969133]
2. Pectasides D, Pectasides M, Farmakis D, Bountouroglou N, Nikolaou M, Koumpou M, Mylonakis N, Kosmas C. Oxaliplatin plus high-dose leucovorin and 5-fluorouracil in pretreated advanced breast cancer: a phase II study. Ann Oncol. 2003; 14(4):537–542. [PubMed: 12649097]
3. Oshaughnessy JA, Blum J, Moiseyenko V, Jones SE, Miles D, Bell D, Rosso R, Mauriac L, Osterwalder B, Burger HU, Laws S. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. Ann Oncol. 2001; 12(9): 1247–1254. [PubMed: 11697835]
4. Bajetta E, Procopio G, Celio L, Gattinoni L, Della Torre S, Mariani L, Catena L, Ricotta R, Longarini R, Zilembo N, Buzzoni R. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. J Clin Oncol. 2005; 23(10):2155–2161.10.1200/JCO.2005.02.167 [PubMed: 15710946]
5. Jung SH, Lee T, Kim K, George SL. Admissible two-stage designs for phase II cancer clinical trials. Stat Med. 2004; 23(4):561–569.10.1002/sim.1600 [PubMed: 14755389]
6. Zamora, P AdMM.; Calvo, L.; Jara, C.; Virizuela, JA.; Yubero, A.; Chacon, JI.; Mira, J.; Gonzalez, Baron M. Capecitabine (X) as single agent in elderly patients (p) with metastatic breast cancer (MBC). Journal of Clinical Oncology. 2005; 23(June 1 supplement):843.

7. Piccart MJ, Raymond E, Aapro M, Eisenhauer EA, Cvitkovic E. Cytotoxic agents with activity in breast cancer patients previously exposed to anthracyclines: current status and future prospects. Eur J Cancer. 1995; 31A(1):S1–10. [PubMed: 8562183]
8. Zelek L, Cottu P, Tubiana-Hulin M, Vannetzel JM, Chollet P, Misset JL, Chouaki N, Marty M, Gamelin E, Culine S, Dieras V, Mackenzie S, Spielmann M. Phase II study of oxaliplatin and fluorouracil in taxane- and anthracycline-pretreated breast cancer patients. J Clin Oncol. 2002; 20(10):2551–2558. [PubMed: 12011135]
9. Rixe O, Ortuzar W, Alvarez M, Parker R, Reed E, Paull K, Fojo T. Oxaliplatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. Biochem Pharmacol. 1996; 52(12):1855–1865. [PubMed: 8951344]
10. Caussanel JP, Levi F, Brienza S, Misset JL, Itzhaki M, Adam R, Milano G, Hecquet B, Mathe G. Phase I trial of 5-day continuous venous infusion of oxaliplatin at circadian rhythm-modulated rate compared with constant rate. J Natl Cancer Inst. 1990; 82(12):1046–1050. [PubMed: 2348469]
11. Delpeuch A, Leveque D, Rob L, Bergerat JP. Off-label use of oxaliplatin in patients with metastatic breast cancer. Anticancer Res. 2011; 31(5):1765–1767. [PubMed: 21617237]
12. Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, Vogel C, Osterwalder B, Burger HU, Brown CS, Griffin T. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol. 1999; 17(2):485–493. [PubMed: 10080589]
13. Talbot DC, Moiseyenko V, Van Belle S, O'Reilly SM, Alba Conejo E, Ackland S, Eisenberg P, Melnychuk D, Pienkowski T, Burger HU, Laws S, Osterwalder B. Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines. Br J Cancer. 2002; 86(9):1367–1372.10.1038/sj.bjc.6600261 [PubMed: 11986765]
14. Polyzos A, Gogas H, Markopoulos C, Tsavaris N, Papadopoulos O, Polyzos K, Giannopoulos A. Salvage chemotherapy with oxaliplatin and capecitabine for breast cancer patients pretreated with anthracyclines and taxanes. Anticancer Res. 2009; 29(7):2851–2856. [PubMed: 19596973]
15. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000; 92(3):205–216. [PubMed: 10655437]
16. Scheithauer W, Kornek GV, Raderer M, Schull B, Schmid K, Kovats E, Schneeweiss B, Lang F, Lenauer A, Depisch D. Randomized multicenter phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2003; 21(7):1307–1312. [PubMed: 12663719]
17. Institute NC. [Accessed February 10 2012] Common Toxicity Criteria for Adverse Events v3.0 (CTCAE). 2006. http://ctep.cancer.gov
18. Sparano JA, Vrdoljak E, Rixe O, Xu B, Manikhas A, Medina C, Da Costa SC, Ro J, Rubio G, Rondinon M, Perez Manga G, Peck R, Poulart V, Conte P. Randomized phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2010; 28(20):3256–3263.10.1200/JCO.2009.24.4244 [PubMed: 20530276]
19. Cassidy J, Tabernero J, Twelves C, Brunet R, Butts C, Conroy T, Debraud F, Figer A, Grossmann J, Sawada N, Schoffski P, Sobrero A, Van Cutsem E, Diaz-Rubio E. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. J Clin Oncol. 2004; 22(11):2084–2091.10.1200/JCO.2004.11.069 [PubMed: 15169795]
20. Comella P, Massidda B, Palmeri S, Farris A, Lucia LD, Natale D, Maiorino L, Tafuto S, Cataldis GD, Casaretti R. Biweekly oxaliplatin combined with oral capecitabine (OXXEL regimen) as first-line treatment of metastatic colorectal cancer patients: a Southern Italy Cooperative Oncology Group phase II study. Cancer Chemother Pharmacol. 2005; 56(5):481–486.10.1007/s00280-005-1003-6 [PubMed: 15902461]
21. Xiang XJ, Zhang L, Qiu F, Yu F, Zhan ZY, Feng M, Yan J, Zhao JG, Xiong JP. A Phase II Study of Capecitabine plus Oxaliplatin as First-Line Chemotherapy in Elderly Patients with. Advanced Gastric Cancer Chemotherapy. 2012; 58(1):1–7.10.1159/000335585

22. Ruzzo A, Graziano F, Loupakis F, Rulli E, Canestrari E, Santini D, Catalano V, Ficarelli R, Maltese P, Bisonni R, Masi G, Schiavon G, Giordani P, Giustini L, Falcone A, Tonini G, Silva R, Mattioli R, Floriani I, Magnani M. Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFOX-4 chemotherapy. J Clin Oncol. 2007; 25(10):1247–1254.10.1200/JCO.2006.08.1844 [PubMed: 17401013]

23. Lecomte T, Landi B, Beaune P, Laurent-Puig P, Loriot MA. Glutathione S-transferase P1 polymorphism (Ile105Val) predicts cumulative neuropathy in patients receiving oxaliplatin-based chemotherapy. Clin Cancer Res. 2006; 12(10):3050–3056.10.1158/1078-0432.CCR-05-2076 [PubMed: 16707601]

Table 1
Baseline demographic and clinical characteristics

Characteristic	Number
Number of patients enrolled	N=11
Number of patients included in the analysis	N=10
Age (in years)	
Mean±SD *	54.2±11.7
Median and range	56.5 (36-73)
18-49	4
50-64	4
>65	2
Race/ethnicity	
White non-hispanic	10
Hispanic	0
African American	0
Asian	0
Menopausal status	
Pre-menopausal	4
Post-menopausal	6
Time between initial diagnosis and metastatic disease	
> 24 months	
≥ 24 months	8
	2
Tumor hormone receptor status	
ER+ and/or PR+	9
ER- & PR-	1
HER2/neu status	
Amplified	0
Non-amplified	
Unknown	
Prior receipt of neuropathy-inducing agents	
Adjuvant	0
Metastatic	2 (taxanes)
	1 (vinorelbine)
Sites of metastatic disease	
Visceral	8
Non-visceral	2

Characteristic	Number
Prior cytotoxic chemotherapy for metastatic disease	
Yes	2
No	8
Prior endocrine therapy for metastatic disease	
Yes	8
No	2

* SD for standard deviation

Table 2

Observed responses

Patient	Best response	Prior nthracycline	Number of cycles received	Reason for discontinuation
1	PR	No	6	PD
2	SD	CAF	6	PD
3	Not evaluable[1]	No	1	AE
4	PR	AC	15	PD
6	SD	No	2	AE
7	PR	AC	12	AE
8	SD	AC	4	PD
9	PR	AC	16	PD
10	SD	No	4	Patient wishes
11	PR	AC	1	AE

[1] Patient withdrew before day 15 of cycle 1

AC: doxorubicin and cyclophosphamide

CAF: cyclophosphamide, doxorubicin, and 5-fluorouracil

PR: partial response

SD: stable disease

PD: progressive disease

AE: adverse events

Table 3
Overall adverse events (Number of patients with toxicity)

Toxicity	Any toxicity	Grade 3 or 4 toxicity
Neuropathy	8	0
Pain	7	0
Nausea/vomiting	6	0
Diarrhea	6	3
Mucositis	5	0
Anorexia	1	1
Constitutional/Fatigue	8	1
Hand-foot syndrome	5	0
Transaminase elevation	4	1
Hypokalemia	3	2
Hypophosphatemia	2	2
Infection	4	1
Neutropenia	3	0
Anemia	4	0
Thrombocytopenia	2	0