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A Phase II trial of docetaxel and carboplatin administered every two weeks as preoperative therapy for stage II or III breast cancer: NCCTG Study N0338

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Abstract

Objective—We conducted a multicenter phase II trial to assess the efficacy and toxicity of docetaxel (D) and carboplatin (C) combination as neoadjuvant therapy for stage II or III breast cancer (BC).

Methods—Patients received D 75 mg/m^2 and C AUC 6 on day 1 followed by pegfilgrastim on day 2, every 14 days for 4 cycles, followed by definitive breast surgery. The primary endpoint was the proportion of patients achieving pathologic complete remission (pCR), defined as disappearance of all invasive and in situ tumor in the breast and axilla after chemotherapy.

Results—Fifty-seven women, median age 53 y were enrolled. 38 (67%) had ER+, 31 (54%) PR +, and 6 (11%) HER2+ disease; 9 had triple negative BC (TNBC). Forty-three (75%, 95%CI: 62%–86%) out of 57 eligible patients had clinical response (15 cCR, 28 cPR). Nine (16%, 90% CI :10%–28%) patients had pCR. Four of 9 (44%) pts with TNBC achieved pCR. Thrombocytopenia (5%) was the only grade 4 adverse event (AE). The most common grade 3 AE were thrombocytopenia 19%, fatigue 12%, and anemia 9%.

Conclusions—4 cycles of 2-weekly D and C are feasible with acceptable toxicity and pCR rate of 16%. This regimen can be considered for neoadjuvant therapy of BC, particularly for patients not candidates for anthracycline therapy. High pCR rate of 44% noted in a subset of patients with TNBC is encouraging and needs to be validated in large prospective trial.

Keywords

neoadjuvant; breast cancer; dose-dense; docetaxel; carboplatin

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INTRODUCTION

Surgery is the mainstay of treatment of patients with early stage breast cancer. Adjuvant systemic therapy after local-regional treatment has been shown in randomized trials to result in improved recurrence-free and overall survival. Preoperative systemic therapy (PST) (also known as neoadjuvant therapy or induction therapy) has been utilized for patients with locally advanced breast cancer and phase II studies suggest improved outcomes with this strategy. PST has also been explored for patients with early stage operable breast cancer because this approach may offer some potential benefits, including opportunity to evaluate prognostic and predictive biological markers and opportunity for faster evaluation of newer regimens since responses can be directly observed. Randomized controlled trials show equivalent outcomes with adjuvant therapy or PST with the same agents, but the latter increases the likelihood of breast conserving surgery being possible.[1–3] PST also appears to be associated with better patient compliance than adjuvant therapy.[4]

Response to PST correlates with long-term outcomes. Pathologic complete remission (pCR) is has been shown to be strongly associated with improved overall survival, and may serve as a suitable surrogate endpoint.[3,5] There is intense interest in evaluating newer regimens that can improve pCR rates, which may translate into better survival. Most of the regimens tested for PST have included an anthracycline and / or a taxane in combination or sequence because of their demonstrated activity in adjuvant and metastatic breast cancer. pCR rates of 8 –28% have been reported depending on the agent, combination, dose and duration of treatment.[6–9] Taxanes are one of the most active agents in breast cancer. Objective response rate up to 50% have been described in phase III studies of docetaxel in treatment naïve MBC.[10] Single agent carboplatin also has considerable activity in BC with RR of 25 – 37%.[11,12] Docetaxel and carboplatin have synergistic activity and largely non-overlapping toxicities and the combination was shown to be highly active with overall RR of 60% as first line therapy for metastatic breast cancer, including in anthracycline pretreated patients.[13]

In addition to evaluating novel agents, there is also interest in exploring whether treatment schedule can impact the activity of agents in neoadjuvant setting. The Gompertzian kinetic model of tumor growth, in which the rate of tumor growth is not constant but decreases as the tumor increases in size after cytoreductive therapy, would predict that decreasing the period available for re-growth by more frequent administration of chemotherapy in a dose-dense schedule would lead to improved response rate. The CALGB Intergroup trial C9741 demonstrated improved disease-free and overall survival in patients with axillary node positive breast cancer who received adjuvant therapy with AC → T (paclitaxel) or sequential single agent use of these agents in a dose-dense (every 2 week) schedule compared with the same drugs administered every 3 weeks.[14] Dose dense scheduling is now an established practice in adjuvant therapy for breast cancer. Whether a similar approach will have enhanced efficacy as PST is unknown but available data suggest that dose dense therapy is feasible with tolerable toxicity.[15,16]

Based on the demonstrated efficacy of docetaxel and carboplatin as single agents and in combination as well as the potential of further improving their activity by dose-dense scheduling, we conducted a phase II trial to evaluate the efficacy and tolerability of 4 cycles of docetaxel and carboplatin administered every 14 days with pegfilgrastim support in patients with stage II–III breast cancer. Here we report the efficacy and toxicity of this regimen, describe the surgical experience and highlight some areas for investigation in future PST trials.

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PATIENTS AND METHODS

Eligibility

Women and men over the age of 18 years with previously untreated histologically or cytologically confirmed stage II or III ($T_{2–4}$, $N_{1–3}$) invasive breast cancer were eligible for this multi institution trial coordinated by North Central Cancer Treatment Group (NCCTG). Other key eligibility criteria included ECOG performance status of 0–1, adequate organ function (ANC >= 1500 cells/mL, HgB >= 10.0 g/dL, PLT >= 100,000 cells/mL, creatinine clearance >= 30 mL/min, total bilirubin <= UNL, and AST/ALT/Alkaline phosphatase within the range allowing for eligibility), and ability to give informed consent.

Contraindications to enrollment into the study included the following: any prior therapy (including resection surgery) for invasive breast cancer; active infection; history of severe hypersensitivity reaction to docetaxel, carboplatin, or any drug formulated with polysorbate 80; known hypersensitivity to E.coli derived proteins, filgrastim or pegfilgrastim; peripheral neuropathy >= grade 2; clinical or radiologic evidence of distant metastases(excluding isolated supraclavicular lymph node involvement); and pregnant or nursing women. The study was approved by the Institutional Review Board of all the participating institutions and all patients gave informed written consent prior to entry into the trial.

Treatment Schedule

Study treatment consisted of docetaxel 75 mg/m2 and carboplatin AUC of 6 IV on day 1 and pegfilgrastim 6mg SQ on day 2. Cycles were repeated every 14 days for a total of 4 cycles unless there was progression at any time. Step wise dose reductions in docetaxel (60 mg/m2 and 45 mg/m2) and carboplatin (AUC 4.5 and AUC 3.4) dose were allowed per protocol for toxicity. Treatment was delayed up to a maximum of 21 days if toxicities had not resolved to less than grade 2 prior to the start of next cycle. All patients received dexamethasone premedication before docetaxel and antiemetic prophylaxis per their physicians' discretion. Patients proceeded to definitive surgery after resolution of toxicity but within 42 days after the 4^{th} cycle of chemotherapy. Any treatment, chemotherapy or radiation therapy after definitive surgery was not specified in the protocol and left to the discretion of treating physician.

Response and Toxicity Criteria

Pathologic complete response was defined as disappearance of all invasive and in situ tumor in the breast and axilla after chemotherapy. All patients meeting the eligibility criteria who received at least one cycle of chemotherapy were considered evaluable for response. If a patient failed to proceed to surgery they were considered not to have achieved pCR. Clinical responses were also measured by physical examination and were to be confirmed with the use of mammography, ultrasound, and/or MRI. A clinical complete response (cCR) was defined as the disappearance of all measurable and/or evaluable disease from the breast and axilla by physical exam.

Statistical Design and Analysis

The primary endpoint was the proportion of patients achieving pCR. The study used a two-stage Simon design to test that the pCR rate was at most 15% versus the alternative hypothesis that the true pCR rate was at least 30%, with a significance level of P=0.11 and 91% power. If there were at most 3 pCRs among the first 25 patients, the regimen would be declared ineffective and the trial would stop. Secondary endpoints included adverse event profile, clinical response rate, percent of planned dose administered per cycle. We also collected information to understand the surgical management of operable breast cancer patients who undergo PST. A specific surgical treatment was not mandated in the protocol

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except that axillary staging was required in all patients. The type of breast surgery, and specifics of pre-operative or post-operative sampling were left to the discretion of the treating surgeon. Surgical data were collected by retrospective chart review.

All analysis was conducted on the intent-to-treat principle. The proportion of pCR is estimated by the number of patients who achieved a pCR divided by the total number of evaluable patients. Similarly, the proportion of other events such as clinical responses is estimated by dividing the number of patients who achieved the event in question by the total number of evaluable patients. Exact binomial CIs were constructed for all of the above rates. Adverse event profile, percent of planned dose administered, and surgical data are presented using simple descriptive statistics.

RESULTS

Fifty Seven patients were enrolled over a 22 month period in this multiinstitution trial. All patients were evaluable for response and toxicity. The median age of this all women cohort was 53 years (range: 27–79). Tumor size ranged from 2 – 15.4 cm (median 5 cm). Thirty-eight (67%) had ER+, 31 (54%) PR+, and 6 (11%) HER2+ BC. Nine (16%) patients had ER, PR and HER2 negative cancer. Patient characteristics are presented in Table 1.

Follow-Up

At the time of this report, all 57 women have completed pre-operative chemotherapy and surgical treatment. Forty-eight (84%) completed the study per protocol (i.e. they received all 4 cycles of chemotherapy followed by surgery within the protocol defined time). The remaining 9 women could not complete the study per protocol due to: disease progression (3), adverse events (3 – neuropathy, elevated liver enzymes, and multiple AEs that led to a 3rd dose reduction of chemotherapy), MD discretion (2), and personal choice (1). A median of 4 cycles (range 1–4) of chemotherapy treatment was given. Fifty-one (89%) underwent surgery with in 42 days of the end of chemotherapy (including 3 women who did not successfully complete 4 cycles of chemotherapy). Median followup of surviving patients was 38 months (2–57 months). The progression free survival rates were 89%, 84%, and 76% at 1-year, 2-year and 3-year, respectively. The overall survival rates at these time points were 98%, 96% and 89%, respectively.

Safety and Tolerability

The regimen was well tolerated. The only grade 4 toxicity was thrombocytopenia seen in 5% of subjects. The most common severe (grade 3 or higher) toxicities (possibly, probably, or definitely related to study drug) were decreased platelets (19%), fatigue (14%), anemia (9%), and diarrhea (7%). Other commonly experienced events regardless of grade were: alopecia (93%, nausea (81%), bone pain (53%, myalgia (51%), and peripheral sensory neuropathy (51%). See Table 2 for more toxicity information. Fifty-two of the 57 patients received all 4 planned chemotherapy treatments. The median dose of docetaxel administered was the protocol planned dose of 75 mg/m^2. Sixteen patients required docetaxel dose reductions in 23 instances with the most common reasons being hepatic enzyme elevation (8) and other non-hematologic adverse events (7). The median dose of carboplatin administered was the protocol planned dose of AUC=6. Four patients required carboplatin dose reductions in 4 instances because of: hand/foot syndrome (2), ALT elevation (1), and thrombocytopenia (1). One pegfilgrastim dose reduction occurred due to physician discretion. Treatment delay occurred in 15 patients (23 instances) most commonly due to thrombocytopenia (16).

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Efficacy

Four out of the first 25 (16%, 95% CI: 5–36%) women accrued to the study achieved a pCR allowing us to proceed with stage II of the 2-stage Simon design. Fifty-one patients completed surgery within 42 days of the last chemotherapy according to the protocol. Nine of them (18%; 95% CI: 8–31%) achieved a pCR. If patients were not able to have surgery with in the protocol required time of 42 days after the last chemotherapy, they were considered not to have achieved a pCR. Overall, 9 (16%, 90% CI: 7–28%) of 57 patients achieved a pCR. Four of 9 (44%) pts with ER/PR and HER2 negative BC had pCR. Fourty-three out of 57 eligible patients (75%, 95%CI: 62%–86%) had clinical response; 15 (26%) had cCR, and 28 (49%) cPR.

Complete surgical data, collected retrospectively by chart review, were available for 50 patients. A specific surgical therapy was not mandated in the protocol. The majority of patients underwent mastectomy (n=33, 66%). Of these, 3 (9%) underwent immediate reconstruction and 8 (24%) also underwent a contralateral prophylactic mastectomy. The greatest variation of surgical therapy was noted in axillary staging. Twenty (40%) had axillary staging prior to systemic chemotherapy (5 underwent sentinel lymph node (SLN) biopsy and 15 image-guided axillary biopsy). All the patients found to have a positive SLN or image-guided axillary biopsy prior to PST, had further axillary staging after PST. Those found to be SLN negative pre-PST, had no further axillary surgery whereas those with negative axillary evaluation by imaging and/or biopsy, underwent further axillary staging (1 patient) after PST. Thirty (60%) had axillary staging after systemic chemotherapy. Of those, 17 (67%) patients underwent SLN biopsy whereas 3 (10%) presented with palpable axillary lymph nodes and underwent a complete lymph node dissection. The remaining patients (n=10, 33%) underwent a complete axillary lymph node dissection without documentation of palpable axillary lymph nodes at the initiation or completion of chemotherapy.

DISCUSSION

In this phase II multicenter trial we show that a two-weekly regimen of docetaxel and carboplatin followed by pegfilgrastim is feasible as neoadjuvant therapy for breast carcinoma. This regimen was associated with similar toxicity and pCR rates described with other anthracycline containing regimens. Thrombocytopenia was the only grade 4 toxicity seen in 5% of subjects. It was also the most frequent grade 3 adverse event seen in 14% of individuals. See Table 2 for more details regarding toxicities. Fifty-two of the 57 (91%) of patients were able to complete all four planned chemotherapy regimens although 17 (29%) required dose reduction, mainly in docetaxel dosing, due to toxicity. Ninety percent of patients were able to have surgery within 6 weeks of last chemotherapy and no increase in surgical morbidity or complications was noted.

The regimen was associated with a high rate of clinical responses. Nine of 57 (16%) had a complete pathologic complete response and 4 of the 9 patients (44%) with triple negative breast cancer achieved pCR. Different definitions of pCR have been used in the literature. We defined pCR stringently as absence of invasive and non-invasive cancer in the breast and axilla as recommended by a recent expert panel.[17] Other investigators have defined pCR as absence of residual invasive cancer in the breast or lymph nodes, but residual DCIS is allowed.[18–20] In a retrospective analysis of over 2000 patients, residual DCIS in patients who experienced complete eradication of the invasive cancer in the breast and lymph nodes did not adversely affect survival or local recurrence rate.[21]

pCR rate of 16% seen in our study is comparable to the rates seen in other studies that utilize 4 cycles of anthracycline based therapy in 2 or 3 weekly schedule.[1,3,5,7,15,22–24]

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Being anthracycline free this regimen is particularly suited for patients who are not candidates for anthracycline therapy. Since cumulative cardiac toxicity is not a concern with this regimen, longer duration of treatment (additional cycles of chemotherapy) for 6 or 8 cycles may be possible at acceptable toxicity. The cytoreductive effect of intermittently administered chemotherapy accumulates as additional cycles are administered, till a maximum response is obtained. Thus, the number of chemotherapy courses in the neoadjuvant setting may have a significant impact on response. The optimal duration or number of chemotherapy treatments before definitive surgery is not known and is likely dependent on the characteristics of the tumor as well as the chemotherapy agents being utilized. However, there is some evidence in the literature that more than 4 cycles may be needed for optimal response. In a randomized comparison of 6 versus 3 of epidoxorubicin/docetaxel combination for stage II or III breast cancer, pCR rate of 36% compared to 10% was seen after 6 cycles.[25] Similar improvement in pCR (24% v 17%) and clinical response rate (32% v 20%) was noted with 6 versus 4 cycles of doxorubicin / paclitaxel administered as neoadjuvant therapy.[26] In the Aberdeen trial patients received 4 cycles of CVAP and the responders were randomized to receive either 4 more cycles of CVAP or 4 cycles of docetaxel. Improvement in clinical response rate was seen in both cohorts; cCR was 14% after initial 4 cycles of CVAP, 33% after 4 more cycles of CVAP and 56% after 4 cycles of CVAP followed by 4 cycles of docetaxel.[1] In our study we utilized 4 cycles of chemotherapy followed by surgery. It is possible that additional cycles of therapy may improve clinical and pathological response rates but a large prospective trial will be required to evaluate that possibility.

Triple negative breast cancer (TNBC) is defined by lack of expression of ER, PR or HER2 overexpression. This is a distinct subtype of breast cancer and this phenotype predicts a basal-like gene expression profile with high sensitivity and almost 100% specificity.[27] TNBC exhibit several poor risk characteristics including high grade and proliferative index and have the poorest prognosis of all breast cancer subtypes.[28,29] Impaired BRCA1 function and DNA repair mechanisms in TNBC may render them particularly susceptible to bifunctional alkylating agents and platinum compounds that act by creating interstrand DNA cross linkage.[30] A pCR rate of 44% was noted in patients with TNBC in our cohort. A recent study by Kern et al also found high pCR rates with carboplatin and docetaxel given every 21 days for 6 cycles in their cohort of 13 patients with early stage breast cancer.[31] Further studies are needed to confirm this finding in a larger cohort of TNBC patients.

To summarize, 4 cycles of 2-weekly carboplatin and docetaxel followed by pegfilgratim is an active regimen for neoadjuvant chemotherapy for breast cancer with acceptable toxicity profile and leads to pCR rates similar to other anthracycline containing regimens. This regimen may be particularly attractive for patients who are not suitable candidates to receive anthracycline. An impressive high pCR rate of 44% was seen in TNBC, a finding that needs to be validated in larger prospective trials. Carboplatin / docetaxel combination may serve as a chemotherapy backbone to combine with other targeted therapies in future trials.

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Table 1

Patient Characteristics at Study Entry

Characteristic		N=57	%
Median age in years(range)		53 (27–79)	
Race:	White	51	89
	Black or American African	4	7
	Native Hawaiian or other pacific islander	1	2
	American Indian of Alaska native	1	2
Performance Status:	0	54	95
	1	3	5
Tumor Size median (range)		5 cm (2 – 15.4)	
Cell Type:	Infiltrating ductal	42	74
	Infiltrating lobular	10	18
	Infalmmatory	1	2
	Mucinous(colloid)	1	2
	Other	3	5
Estrogen Receptor:	Positive	38	67
	Negative	15	26
	Unknown	4	7
Progesterone Receptor:	Positive	31	54
	Negative	22	39
	Unknown	4	7
Her2 Status:	Positive	6	11
	Negative	43	75
	Not done	8	14

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Table 2

Toxicity Summary

Toxicity Summary (%)						
Toxicity	**Gr.1**	**Gr.2**	**Gr.3**	**Gr.4**	**Total Severe (Gr.3+4)**	**Total (all grades)**
Thrombocytopenia	30	7	14	5	19	56
Fatigue	30	49	14	0	14	93
Anemia	32	37	9	0	9	77
Diarrhea	40	12	7	0	7	60
Nausea	54	21	5	0	5	81
Hypokalemia	0	0	5	0	5	5
Alopecia	19	74				93
Bone Pain	32	18	4	0	4	53
Myalgia	35	14	2	0	2	51
Peripheral Sensory Neuropathy	42	9	0	0	0	51
Alanine Aminotransferase	35	7	4	0	4	46

Gr. = Grade