

Activity of Combination Chemotherapy, Docetaxel and Epirubicin as Neoadjuvant Therapy for Women with Breast Cancer

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Abstract. *Background:* This study assesses the efficacy of epirubicin and docetaxel as neoadjuvant therapy for women with breast cancer. *Patients and Methods:* This is a single institution, single arm, phase II study of epirubicin given at 75 mg/m² and docetaxel at 75 mg/m² every three weeks for four cycles prior to surgical excision in women with large breast cancers. Pegfilgrastim was routinely administered as primary prophylaxis against febrile neutropenia. *Results:* Out of the 18 patients enrolled on the study, 12 (66.7%) had a clinical response and 13 (72.2%) had a pathologic response, with a pathologic complete response of 5.6%. Pre-menopausal women and patients with estrogen receptor positive tumors had a higher response rate. One patient died due to sepsis and febrile neutropenia. *Conclusion:* Combination chemotherapy with epirubicin and docetaxel is highly active against breast cancer. With close monitoring for toxicity, this combination can be safely administered with mild side-effects.

Over the past few decades there have been several important changes in the diagnosis and treatment of breast cancer. The increased accuracy of diagnostic tests has contributed to bring a dramatic increase in the number of cases of breast cancer diagnosed annually. Improvements in treatment modalities have also helped to improve the morbidity and mortality rates for patients with breast cancer (1, 2). The overall survival rate for women with early stage or localized breast cancer is high, but metastatic breast cancer is essentially incurable (3). Standard therapy for metastatic breast cancer currently ensures a median survival of approximately two years after diagnosis of metastatic disease (4).

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Breast cancer is sensitive to many cytotoxic agents. The most commonly used agents are doxorubicin, fluorouracil, methotrexate, cyclophosphamide and mitomycin, either as single agents or as combination regimens (5). Objective response rates for single agent activity vary between 20-50% with doxorubicin showing the highest single agent activity as first-line therapy with 40-50% response rates. The use of combination chemotherapy has been associated with increased response rates compared to single agents. The most commonly used non-anthracycline containing regimens yield response rates in the range of 50-60% with a median duration of response of 10-12 months. Anthracycline containing regimens have induced response rates in the range of 50-80% with fewer than 10% complete responses. This has led to the acceptance of anthracycline-based regimens as standard for the initial therapy for patients with metastatic breast cancer and also as adjuvant therapy for poor prognosis in early breast cancer (6).

Anthracycline-based combination regimens have produced modest improvements compared to non-anthracycline regimens, but the duration of remission is still very short. The median duration of response is usually between 10 and 18 months with median survival times between 18 and 26 months (5, 7).

Taxanes are another group of chemotherapy agents that have shown promising results in many solid tumors. Taxane monotherapy with paclitaxel had a response rate of 26-44% in a few phase II trials with patients with advanced breast cancer (8-11). First-line treatment with docetaxel as a monotherapy showed response rates of 60-70% with good activity against liver metastases in one trial (12).

The use of taxanes in combination with anthracyclines has been tried in many clinical trials in the search for improved overall outcome and improved survival in both early and advanced breast cancer. A trial using a doxorubicin-paclitaxel combination showed high response rates but with unacceptable cardiac toxicity (13, 14). This has led to the use of epirubicin, an anthracycline with a

better side-effect profile in comparison to doxorubicin. Epirubicin-paclitaxel combination trials reported objective responses of 64-84% with no severe cardiac toxicity (15, 16).

Docetaxel, a semisynthetic taxane, is emerging as one of the most active drugs in the treatment of patients with breast carcinoma. A phase III trial has shown that docetaxel as single agent chemotherapy was more effective than doxorubicin alone in advanced breast cancer and more effective than the combination of mitomycin C and vinblastine as salvage treatment for patients with metastatic breast cancer that progressed after anthracycline-based treatment (17, 18).

Trudeau *et al.* in their review of trials of epirubicin and docetaxel have shown that the dose limiting toxicity for this combination was neutropenia or febrile neutropenia in almost every trial (6). A significant number of patients in each of these trials required granulocyte colony stimulating factor (G-CSF) for varying periods in an effort to overcome this toxicity. Three trials have been conducted in Europe using G-CSF on a scheduled basis along with the above combination regimen of epirubicin and docetaxel and showed a significant decrease in the incidence of neutropenia and febrile neutropenia (19, 20). These trials have also shown that with the addition of G-CSF as standard therapy the entire therapy can be administered on an outpatient basis. This results in a significant decrease in health care cost and improvement in quality of life to the patient. The administration of G-CSF on a scheduled basis also allows for dose escalation of both epirubicin and docetaxel without compromising patient safety.

The initial results of a phase II study using the epirubicin/docetaxel combination as neoadjuvant therapy in women with newly diagnosed locally advanced breast cancer are reported in this study.

Patients and Methods

Patient selection. Eligible patients were women older than 18 years with histologically confirmed breast cancer, stage II or III, with T3 – T4 lesions, or T2 lesions, who were not candidates for breast preservation surgery. All patients were therapy naive and had adequate organ function (hepatic transaminases less than 1.5 x ULN, absolute neutrophil count >1500/mm³, platelet count >75,000/mm³ and a hemoglobin level >10 g/dL), a left ventricular ejection fraction >50%, and ECOG performance status of 0-2. Patients were excluded if they had any of the following: prior chemotherapy, history of other malignancies within five years of the breast cancer diagnosis, neuropathy grade 3 or 4, HIV infection, evidence of metastasis, or life expectancy less than six months.

The study was conducted according to the ethical standards described in the IRB and OU Medical Center Ethics Committees. All patients gave written informed consents prior to enrollment. All patients were assessed for toxicity according to the National Cancer Institute (NCI) Common Toxicity Criteria Version 2.

Treatment schedule. The therapy was administered according to the scheme in Figure 1. Patients received four cycles of neoadjuvant chemotherapy consisting of Epirubicin (Pfizer, New York, NY, USA) at 75 mg/m² and Docetaxel (Sanofi-Aventis, Paris, France) at 75 mg/m² intravenously on day one of a 21-day cycle. Standard premedications included dexamethasone 20 mg, ranitidine 50 mg, diphenhydramine 50 mg, and Granisetron (Roche, Basel, Switzerland) 1 mg orally on day of chemotherapy. Post chemotherapy emesis prophylaxis was provided by the treating physician as necessary. Pegfilgrastim (Amgen, Thousand Oaks, CA, USA) at 6 mg subcutaneous was administered on day two of each cycle. The initial assessment of response to chemotherapy was made at the end of cycle four of therapy just prior to surgical excision. Patients who had a partial or complete response, received four additional cycles of epirubicin/docetaxel post-operatively at the same dose and schedule. Post-operative adjuvant chemotherapy in patients who had no response to neoadjuvant therapy was left to the discretion of the treating physician. Adjuvant radiation therapy was given to all patients who had lumpectomies. Post mastectomy radiation was administered to those patients with T3 or T 4 lesions and those with four or more involved axillary lymph nodes. Adjuvant hormonal therapy (either tamoxifen or an aromatase inhibitor) was given to all patients with tumors that were estrogen and/or progesterone receptor positive. A tumor was defined as estrogen and/or receptor positive if at least 1% of the invasive tumor cells stained positively for the corresponding receptor. Her-2/neu positivity was defined as 3+ by immunohistochemistry or more than two gene copies/cell by fluorescent *in situ* hybridization (FISH). Patients with her-2/neu overexpressing tumors did not receive trastuzumab as this study was conducted prior to the release of data from NSABP B-31, NCCTG 9831 and the HERA trials.

Definition of response. RECIST criteria for response were used and clinical responses were defined as follows. Complete response (CR): Complete disappearance of all measurable disease and no new lesions when the disease was assessed using the same techniques as baseline. Partial response (PR): Greater than or equal to a 30% decrease below the baseline of the greatest diameter of the primary lesion and no new lesions. Stable disease: Responses not qualifying for CR, PR, progression or symptomatic deterioration. Progression: One or more of the following evident: 20% increase in the greatest diameter of the primary lesion using the same techniques as baseline, the appearance of any new lesion/site or death due to disease without prior documentation of progression and without symptomatic deterioration

Pathological responses were classified as: i) complete pathological response, defined as the complete disappearance of all invasive and pre-invasive disease on microscopic evaluation of the resection specimen; ii) partial pathological response defined as significant cytopathological changes suggestive of a chemotherapy effect, such as necrosis and increased apoptosis, but with residual disease on microscopic evaluation; and, iii) no response if none of the above criteria were met.

Results

Between March 2003 and March 2005, eighteen women were enrolled. Patient and tumor characteristics are summarized in Table I. The median age was 50 years (range 33 to 63 years). Seven patients (38.8%) were pre-menopausal at

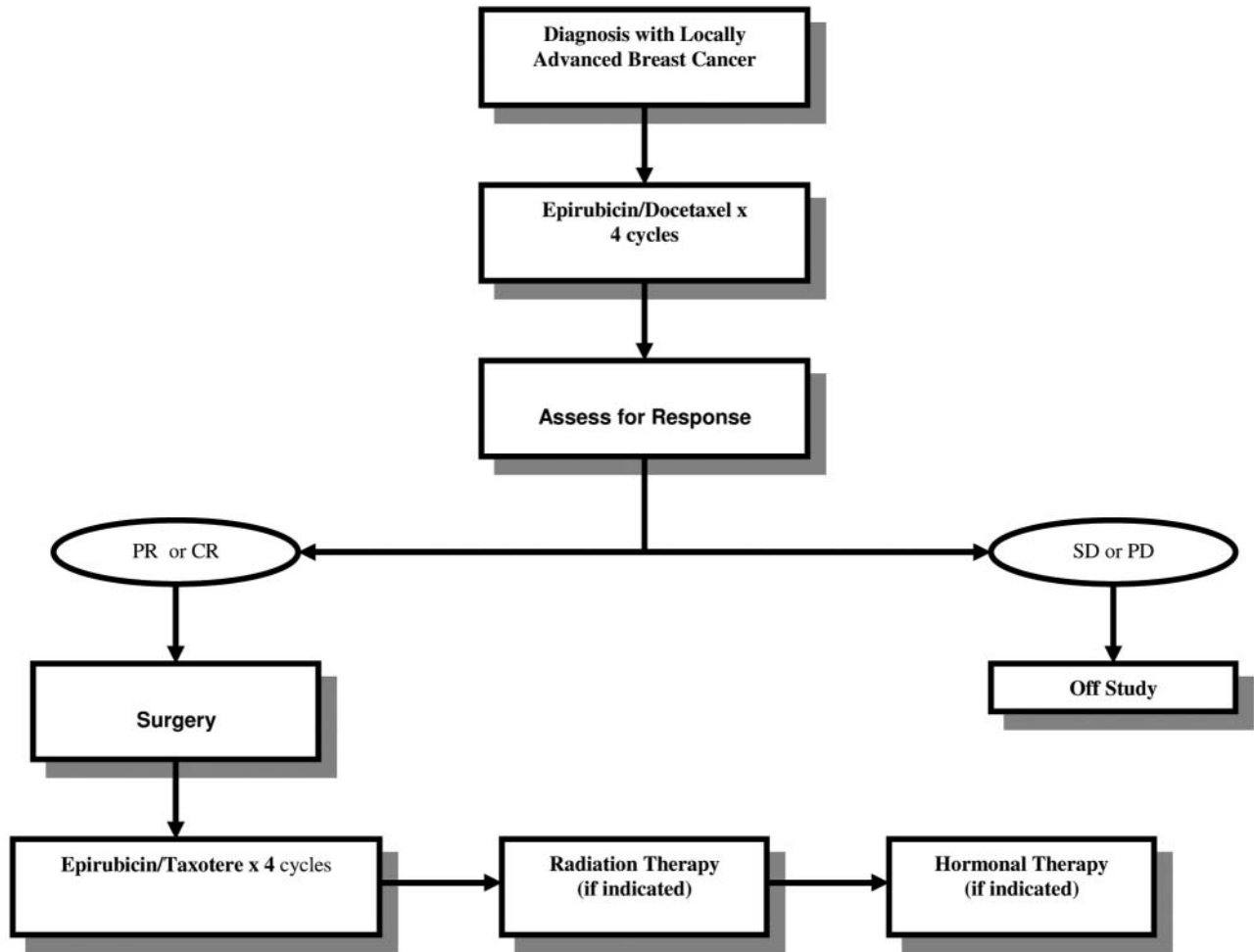


Figure 1. Treatment plan. PR: partial response, CR: complete response, SD: stable disease, PD: progressive disease.

enrollment, and eleven post-menopausal. Racial distribution nicely reflected that of the American population with 16.7% being African American and 11.1% being Hispanic. The majority of patients (94.5%) had an infiltrating ductal carcinoma. Average tumor size was 4.8 cm. Around 55% of patients had a T3 or T4 lesion, with the remaining patients having a T2 lesion. Only 55% of tumors expressed estrogen receptor (ER) and/or progesterone receptor (PR) and 45% of tumors had her-2/neu overexpression.

Efficacy. On clinical evaluation, 12 patients (66.7%) had a response to therapy with three (16.7%) being complete clinical responses (Table II). More responses were seen in premenopausal women compared to postmenopausal patients (85.8 vs. 54.5%, respectively, $p=0.31$). A higher response rate in her-2/neu overexpressing tumors (87.8 vs. 50%, respectively, $p=0.15$). ER and or PR positive tumors had a 70% response

rate compared to a 50% response rate in ER/PR negative tumors ($p=0.63$). Hispanic patients and those with T4 lesions had a slightly lower response rate (50%) compared to other groups but this difference was not statistically significant. No difference in response rate was seen between patients who presented with clinically enlarged axillary lymph nodes (LN) and those who did not (66.7% in both groups).

On pathological evaluation, the whole group had a 72.2% pathological response rate with 5.6% being complete. Like the clinical assessment, more pathological responses were noticed in premenopausal women than in postmenopausal patients (85.7 vs. 54.5%, respectively, $p=0.59$). No significant difference in pathological response rates between ER/PR positive and ER/PR negative tumors (70 and 75%, $p=1$), and between patients with clinically enlarged axillary LN and those without enlarged nodes (75 vs. 66.7%, $p=1$). Four patients (22%) underwent breast conserving surgery.

Table I. Patient and tumor characteristics.

Age (range)	50 years (35-63)	
Menopausal status		
Pre-menopausal	7/18	(38.8%)
Post-menopausal	11/18	(61.2%)
Race		
Caucasian	13/18	(2.2%)
African-American	3/18	(16.7%)
Hispanic	2/18	(11.1%)
Size (range)	4.8 cm (2.4-9.0 cm)	
T stage		
T2	8/18	(44.4%)
T3	6/18	(33.3%)
T4	4/18	(22.3%)
N stage		
N0	7/18	(38.8%)
N1	8/18	(44.4%)
N2	3/18	(16.8%)
Pathology		
Invasive lobular carcinoma	1/18	(5.5%)
Invasive ductal carcinoma	17/18	(94.5%)
Tumor grade (Elston Score)		
Well-differentiated (3-5)	1/18	(5.5%)
Moderately-differentiated (6-7)	6/18	(33.3%)
Poorly-differentiated (8-9)	11/18	(61.1%)
Hormone receptor status		
ER/PR+	10/18	(55.5%)
ER/PR-	8/18	(45.5%)
Her-2/neu status		
Her-2/neu+	8/18	(45.5%)
Her-2/neu-	10/18	(55.5%)

ER/PR+: ER and/or PR positive tumors.

Her-2/neu+: Her-2/neu overexpressing tumors.

Toxicity. Toxicity was assessed after each cycle using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. One patient developed febrile neutropenia and presented to our hospital emergency room with septic shock and multiorgan failure. Aggressive hemodynamic and antibiotic support was not successful and the patient succumbed to her illness.

The remaining 17 patients tolerated the therapy quite well. Only one patient had grade three diarrhea and one patient had grade three fatigue. All other toxicities were grades one and two. The most common toxicities were anemia (43%), nausea (38%), and fatigue (9.8%). The use of pegfilgrastim as a primary prophylactic therapy contributed to the low incidence of febrile neutropenia.

Survival. At a median follow up of 22 months, 16 of the 18 (88%) patients remain alive (Figure 2). One patient died during treatment and one patient died due to breast cancer

Table II. Outcomes.

	Clinical PR+CR (p-value)		Pathological PR+CR (p-value)	
	N	%	N	%
All	12/18	66.7	13/18	72.2
Menopausal status				
Pre-menopausal	6/7 (0.31)	85.7	6/17 (0.59)	35.3
Post-menopausal	6/11	54.5	7/11	63.6
Her-2/neu status:				
Her-2/neu+	7/8 (0.15)	87.5	5/8 (0.60)	62.5
Her-2/neu-	5/10	50	8/10	80.0
Hormone receptor status				
ER/PR+	7/10 (0.63)	70	7/10 (1.0)	70.0
ER/PR-	4/8	50	6/8	75.0
Axillary node status				
Node+	8/12 (1.0)	66.7	9/12 (1.0)	75.0
Node-	4/6	66.7	4/6	66.7

Her-2/neu+: Her-2/neu overexpressing tumors.

ER/PR+: ER and/or PR positive tumors.

Axillary node+: clinically enlarged axillary lymph nodes.

Table III. Toxicities (no. of occurrences-total 112 cycles).

	Grade I-II		Grade III-V	
	N	%	N	%
Anemia	45	40.2		
Thrombocytopenia	1	0.9		
Neutropenia w/o Fever	1	0.9		
Neutropenic Fever			1	0.9
Sepsis			1	0.9
Diarrhea	10	9.0	1	0.9
Oral Mucositis	4	3.6		
Nausea	43	38.4		
Cardiac Toxicity	1	0.9		
Neuropathy	5	4.5		
Myalgias	4	3.6		
Rash	1	0.9		
Constipation	3	2.8		
Nail Changes	4	3.6		
Fatigue	11	9.8	1	0.9
Edema	1	0.9		

15 months after diagnosis. Of the 16 remaining patients, 14 remain disease free, disease-free survival is therefore 77.7%. Two patients have had breast recurrence at 16 and 18 months, respectively.

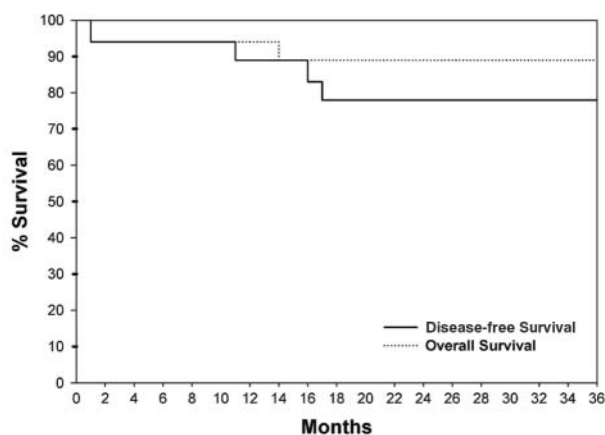


Figure 2. Disease-free and overall survival curves.

Discussion

The use of neoadjuvant chemotherapy in patients with breast cancer allows the clinician to assess drug sensitivity *in vivo* and to modify the chemotherapeutic regimen accordingly. Neoadjuvant chemotherapy has been shown to be safe and effective as compared to adjuvant therapy in patients with breast cancer (21).

This phase II study using combination epirubicin and docetaxel as neoadjuvant therapy for women with large breast cancers demonstrated that the combination is highly active with a response rate commensurate with previously reported studies (17, 19, 20). Our patient population had a particularly poor prognosis given the fact that two thirds of the patients had node positive disease, and almost half of the 18 patients were her-2/neu positive and ER/PR negative. The low pathological complete response rate may be attributed to the strict definition applied, which necessitated the complete disappearance of all invasive and pre-invasive disease.

A previous study using the combination of epirubicin and docetaxel has reported a high incidence of neutropenia and febrile neutropenia (17). This prompted the use of pegfilgrastim as a primary prophylaxis in this study. The incidence of febrile neutropenia was low, but, unfortunately, one death due to febrile neutropenia occurred. This incident highlights the importance of proper patient education and the need to present for urgent medical care if occurs.

Specific patient populations which could derive more benefit from this combination chemotherapy were not identified, largely due to the small sample size of our study. There was a trend towards better responses in pre-menopausal patients and in patients with ER/PR positive tumors, but these differences did not reach statistical significance.

In conclusion, we believe that the combination of epirubicin and docetaxel is an active combination of drugs against breast

cancer. Its response rate is comparable to other combinations including doxorubicin/cyclophosphamide, fluorouracil/doxorubicin/cyclophosphamide, and fluorouracil/epirubicin/cyclophosphamide. Toxicity is manageable particularly with the primary use of granulocyte growth factor support.

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