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Original Article

DOCETAXEL, DOXORUBICIN AND CYCLOPHOSPHARMIDE AS NEOADJUVANT CHEMOTHERAPY WITH PRIMARY PROPHYLACTIC STEM CELL GROWTH FACTOR SUPPORT IN LOCALLY ADVANCED BREAST CANCER (T3 – T4 , NO – 3, MO)

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ABSTRACT

Aim of the Work: To assess the efficacy and the toxicity of combination of docetaxel, doxoribicin and cyclophosphamide as neodjuvant chemotherapy with prophylactic stem cell growth factor support in locally advanced breast cancer.

Patients and Methods: 23 patients with stages IIB and III breast cancer received three to four cycles of neodjuvant decetaxel 75 mg/m^2, doxorubicin 50mg/m^2, and cyclophosphamide 500mg/m^2 (TAC) on day 1, intravenously on a 21–days cycle as well as granulocyte colony stimulating factor (G-CSF) 300 micro gm. subcutaneously daily for 5-7 days starting on day two, also cibrofloxacine 500mg orally every 12 hours for 5-10 days starting on day five of each cycle.

Results: A total of 23 patients with a median age of 42 years (range 32-57 years), were assigned to receive 3-4 cycles of neoadjuvant TAC regimen and primary prophylaxis with G-CSF.16 out of the twenty three patients were stage III B. A total of 86 cycles were given .The overall clinical response rate among the whole group was 91.3% , nine patients obtained complete cCR (39.1%), and twelve patients obtained cCR (52.2%), while complete pathological response (p CR) were confirmed in four (17.4%) patients and microscopic residuals were detected in the breast in three cases and in the axillary lymph nodes in four cases.The treatment was generally safe, well tolerated, there were no cases that needed hospitalization because of toxicity related event.

Conclusion: The combination of docetaxel, doxorubicin and cyclophosphamide with granulocyte colony stimulating factor as given in this study is safe, tolerable and shows good activity in the neoadjuvant setting for locally advanced breast cancer stages IIB to III patients.

Key Words: Breast, cancer-neoadjuvant, chemotherapy

INTRODUCTION

The use of anthracylines in combination therapy is superior to the use of non anthracycline–containing regimens. Anthracyclines have become a key component of routine care for patients with breast cancer[1].

Combination anthracycline–docetaxel regimens are well studied in the setting of metastatic breast cancer; although they are highly myelosuppressive, they produce acceptable levels of cardiotoxicity and are highly active[2,3].

Neoadjuvant chemotherapy (NC), also referred as preoperative, induction or primary chemotherapy, has become established as standard option on the multidisciplinary management of patients with Locally Advanced Breast Cancer (LABC). This approach permits a down stage of the primary tumor, facilitates radical locoregional treatments and increases the rates of breast conversing surgery without compromising survival[4].

Neoadjuvant chemotherapy provides an effective means to test individual chemo-sensitivity in vivo and might eradicate occult distant metastasis. So, achievement of the best clinical response and finally a pathological complete response (PCR) is the main target of neoadjuvant chemotherapy. Although initial randomized trials did not clearly demonstrate survival advantage over adjuvant chemotherapy[5,6]. It seems that patients who achieve a PCR after induction chemotherapy obtain a benefit on survival[7,8].

And currently, many studies are going on to confirm such concept.

The use of taxanes in patients with advanced breast cancer who have failed treatment with anthracycline–based regimens has resulted in overall response rates of 18% to more than 50%[9,10].

Docetaxel, in particular, was shown in two phase II studies to induce responses in over 50% of patients with anthracycline – resistant breast cancer[11,12].

Thus, it is our interest in this study to add docetaxel in combination to AC regimes on day one with primary prophylaxis with granulocyte colony stimulating factor (G–CSF). That might increase clinical and pathological complete response rates when given as primary systemic chemotherapy in patients with locally advanced breast cancer so that to shorten the over all treatment in three to four weeks - 21 days cycles (6–9 weeks). Than other protocols using sequential regimen for a total of eight cycles in 6-9 weeks.

PATIENTS AND METHODS

All female patients with histologically confirmed clinical, stage, IIB to III invasive, breast cancer, were included in this study. They were all >18 years and had to have Eastern Cooperative Oncology Group performance status < 2. Full laboratory tests in the form of adequate blood counts, hepatic and renal profiles were confirmed. Staging work–up included chest radiography abdomino–pelvic ultrasound and isotopic bone scan. Measurable disease was required by physical examination or radiological imaging including mammography and complementary breast ultrasound. Clinical and pathological tumor size – node – metastasis (T-N-M) staging system was based on the American Joint Committee on Cancer Staging Manual (AJCC)[13]. Immuno-histochemical staining was done in all cases for estrogen (ER) and progesterone (PgR) Receptors. Her – 2/neu status was evaluated in all cases by immuno histochemistry (IMC) only.

Treatment Plan:

All patients received 3 to 4 cyclic systemic intravenous (I.V.) combination neoadjuvant TAC regimen. Docetaxel 75mg/m², Doxorubicin 500mg/m² and cyclophosphamide 500mg/m² on day one every three weeks. All patients were required to receive premdication regimen before each cycle that initially consisted of dexamethazone 12mg, ranitidine 50mg, ondansetron or grainsetron 1mg or 8mg, respectively added to 50cc saline or glucose 5% I.V. over 30 minutes, uromitexan 400mg I.V. bolus and diphenhydramine 50mg I.V. or allerfin 1mg I.M. The latter was given about one hour before taxotere infusion.

Post medication regimen included low doses of dexamethazone 8mg/day devided on two doses after meals,ranitidine 150mg once daily before bed time with proton pump inhibitor in the morning for three days, grainsetron 16mg/day for one day to be followed by metoclopromide orally for three days. Primary prophylaxis with G–CSF 300µmg subcutaneously was started 24 hours after finishing chemotherapy regimen, daily for 5–7 days as well as cibrofloxacine 500mg orally every 12 hours for 5–10 days. Starting on day five. Patients received three or four cycles of chemotherapy according to the speed of response as well as concerns of clinical stage. After neoadjuvant chemotherapy, evaluation of response was made and the type of loco-regional treatment was decided according to response whether to be subjected to surgery or not.

Non responder patients were planned to recieve second-line chemotherapy and radiotherapy.

After surgery, patients received two to three cycles of adjuvant chemotherapy. Patients with minor or no response received second line chemotherapy the rest of the patients completed two or three cycles of the same neoadjuvant chemotherapy regimen.

All patients were planned to adjuvant external beam radiation therapy adjuvant hormonal therapy was stared at the end of adjuvant chemotherapy for those with positive hormone receptor tumors.

Safety Assessments:

Adverse events were assessed every week for the duration of the study and graded according to the National Cancer Institute of Canada Common Toxicity Criteria (NCIC-CTC), version 2.0[14]. Data on serious adverse events were collected throughout the study. Laboratory assessment of blood counts; hepatic and renal profiles were done before each cycle and if clinically indicated. Baseline left ventricular ejection fraction was assessed by echocardiography and had to be more than 50%.

Efficacy Assessments:

A- Assessment of clinical response:

Clinical response was assessed following the first cycle and before each following cycle by physical examination. After neoadjuvant treatment response was evaluated clinically and with diagnostic breast imaging. Response was evaluated according to the World Health Organization Criteria; clinical complete (cCR) was defined as the absence of tumor in the breast and regional lymph nodes by clinical examination and diagnostict breast imaging. The response was judjed to be partial (cPR) when the reduction of the breast tumor was 50% or more. Increase of more than 25% in the size of tumor or unequivocal appearance of new lesions was defined as progressive disease (cPD). While those patients whose tumor did not meet the definition of cCR, cPR or cPD were considered

to have stable disease (cSD).

B- Assessment of pathological response:

Complete pathological response was considered (pCR) If there were no viable tumor cells on the examined breast and lymph nodes. While minimal residual disease (MRD) was considered if there were microscopic foci of tumor cells in the breast tumor or in the axillary lymph nodes on the examined specimen.

RESULTS

Patients Demographics:

Between March 2004 and July 2006, twenty three patients were enrolled in this study. Patient characteristics at the time of entering the study are listed in the Table1.

Table 1: Patients Characteristics (n = 23).

Characteristic	Number	Percentage
Age		
Median	42	
Mean	42.9	
Range	32-57	
Menopausal status		
Pre Menopausal	16	69.5
Post Menopausal	7	30.4
Tumor size (cm)		
Mean	7.6	
Range	4-13	
Clinical Status	5	
T3	18	21.7
T4		78.7
Clinical Nodal Status		
N 0	8	34.8
N 1	1	4.3
N 2	13	56.5
N 3	1	4.3
Clinical Stage		
II B	3	13.1
III A	3	13.1
III B	16	69.6
III C	1	4.3
I BC	3	13
Hormone Receptor Status		
ER + ve and/or PgR+ ve	19	82.6
ER and PgR – ve	4	17.4
HER-2/neu Status		
– ve	15	65.2
+ ve	8	34.8

ER: Estrogen Receptor, PgR: Progesterone receptor.
HER -2: Human epidermal growth factor receptor.
IBC:Inflammatory breast cancer.

The mean age of the patients was 42.9 years (Range 32–57 years). Eighteen patients (78.3%) had T4 status while 21.7% (five patients) had T3 status at presentation.

Fifteen patients (65.2%) had clinically positive lymph nodes (4.3% N1, 56.5% N2 and 4.3% N3).

Three patients were staged as IIB and the remaining twenty were stage III; 13% of the later were stage IIIA, 69.6% were stage III B which constitute the majority of the cases (16) and 4.3% (one patient) was stage IIIC. It is to be noted that there were three cases (13%) out of the whole group presented with inflammatory breast cancer (IBC).

Neoadjuvant Chemotherapy:

A total of 86 cycles were administered in this study. Six cases received 3 cycles of neoadjuvant chemotherapy and seventeen cases received four cycles (Table 2). Because of cancers of clinical stage and speed of response.

All patients received chemotherapy regimen at full prescribed doses, no dose reduction occurred. Delay of one week of the treatment was needed for three patients where as 20 patients finished their treatment without any delay.

Table 2: Number of Neo adjuvant chemotherapy cycles in relation to the clinical stage (n = 23)

Clinical stage	No of Patients	No of cycles gives
II B	2	3
	1	4
III A	2	3
	1	4
III B	2	3
	14	4
III C	1	4

Clinical Response:

The overall clinical response rate among the 23 patients was 91.3%. 9 patients obtained a cCR (39.1%) and 12 patients obtained cPR (52.2%). Stable disease was observed in two patients (8.7%) while non of the whole group of patients experienced diseases progression (Table 3). The combined clinical response includes physical examination as well as mammography/ultra songraphy.

Table 3: Clinical and Pathological responses to Neoadjuvant TAC regimen (n=23).

Characteristic	No.	Percentage
Clinical Response		
Complete	9	39.1
Partial	12	52.2
Stable	2	8.7
Progressive	-	-
Over all response rate	21	91.3
Pathological Response		
Complete	4	17.4
Microscopic Residuals		
In Primary tumor	3	13
In axillary lymph nodes	4	17.4

Surgical Treatment:

After neoadjuvant chemotherapy, all the patients had undergone surgery. Breast conservation surgery including axillary lymph nodes dissection was done in 14 patients (60.9%) while the reaming 9 cases (39.1%) had undergone modified radical mastectomy including the three cases with inflammatory breast cancer at presentation.

Pathological Responses:

The whole group of patients were evaluated for pathological response after neoadjuvant chemotherapy and surgery where complete pathological response was obtained in foudszr cases (17.4%) both in the primary tumor as well as in the axillary lymph nodes where tumoral necrosis, surrounded by active fibroblastic tissue with excess aggregates of foamy and hemosiderin- laden histiocytes constituted the microscopic pictures in the pathological specimens.

Residuals were present in 7 cases (30%); three of them showed residuals in the primary tumor and four cases showed residuals in the axillary lymph nodes. So, a total of 11 cases (47.8%) achieved favorable pathological response including complete pathological responses and microscopic residuals.

Toxicity:

A total of 86 cycles of TAC regimen were given to the whole study group with primary prophylaxis with Granulocyte Colony Stimulating Factor (G – CSF) and cibrofloxacine. The treatment was generally well tolerated There were no cases that needed hospitalizations because of toxicity related events: toxicity data for the whole group of patients according to the criteria of NCIC-CTC, version-2 is summarized in table 4.

Table 4: Toxicity profile according to NCIC-CTC (n=23).

Toxicity	NCIC Grade No. of Patients (%)	
	1	2
Hematological		
Leukopenia	2 (8.7)	1 (4.3)
Neutropenia	1 (4.3)	1 (4.3)
Anemia	6 (2.6)	3 (13)
Thrombocytopenia		
Castro-Intestinal		
Nausea-vomiting	1 (4.3)	4 (17)
Constipation	2 (8.7)	3 (13)
Skin		
Pigmentation	16 (70)	5(22)
Nail changes	7 (30)	4(17)
Peripheral Neuropathy	6 (26)	5(22)
Allergic reaction		
Musculoskeletal		
bony pains	13 (57)	8(35)
Fatigue	4 (17)	4(17)

* NCIC-CTC National Cancer Institute of canada common toxicity criteria

DISCUSSION

Primary end points in phase II trials of neoadjuvant chemotherapy for breast cancer are usually clinical and pathological response. Clinical response rates are in the range of 60%-90% and it has been correlated with outcome[15]. This wide range may reflect the disconcordance between physical examination and diagnostic breast imaging in predicting response to neoadjuvant chemotherapy. In this study, we reported three cases out of the nine that experienced complete clinical response had residual lesions by breast imaging (mammography or ultrasound), on the other hand, those cases that showed complete radiological responses were confirmed by clinical examination.

Achievement of pCR should be the main goal of neoadjuvant chemotherapy however the proportion of patients whose tumors disappeared completely on histopathological examination after primary systemic chemotherapy and who therefore had an expectation of a good outcome, has been disappointingly low. Skipper[16] proposed that micrometastatic clones of cancer cells would likely not respond to systemic treatment in the same way as the primary tumor but the results of the B-

18 trial and other primary systemic chemotherapy studies indicate that this hypothesis is incorrect[8, 17].

The rate of pCR to neoadjuvant chemotherapy with new combinations is in the range of 10% to 30%. These differences between the studies concerning of pCR are difficult to interpret because of lack of universally pathological response classification system used among different studies[18-21] where some studies reported pCR in the breast only, others include cases of carcinoma in situ in the pCR and rarely to refer pCR to both the primary breast tumor and axillary lymph nodes. Herein this study we reported pCR in both breast and axillary lymph nodes in four bout of the 23 cases (17.4%) which is comparable to that reported by Aguiar et al.[22] when using Epirubicin, cyclophosphamide and weekly paclitaxel as neoadjuvant treatment where they reported (15.1%) pCR but lower than that was reported by Marjorie et al.[23] when using weekly paclitaxel followed by FAC with 28.2% pCR which may be explained by the fact that most of their patients were staged II (84%) while most of our patients in this study were stage III (87.0%). The largest phase III study, NSABP-27, compared patients receiving docetoxel (D) once every three weeks for four cycles after four cycles of doxorubicin and cyclophosphamide (AC) with patients who only received four cycles of AC. Patients receiving AC followed by D achieved a pCR of 25.6% in the breast alone compared with a pCR of 13.7% for patients receiving only AC regime[24], however, residual disease in the axilla can negatively predict survival[25].

We found a trend to a better response in patients with Her-2/neu negative and hormone-receptor positive tumors (Table 5).

Table 5: Correlation between favorable pathological response (pCR and microscopic residuals) and Hormone receptor, Her-2/neu ststus (n=23 patients).

	ER & PgR + ve/ Her-2/neu-ve	ER and / or PgR + ve		ER & PgR – ve / Her-2/ neu-ve
		Her-2/neu – -ve	Her-2/neu + ve	
pCR	2	2	0	0
Microscopic				
Residuals in	1	1	1	0
Primary				
Tumor				
Microscopic				
Residuals in	1	2	1	0
Lymph				
nodes				
Total	4	5	2	0

ER: Estrogen Receptor PgR: Progesterone receptor
HER-2: Human epidermal growth factor receptor

Where in 11 patients (hormone-receptors positive) who experienced a favorable pathological response which include complete pathological response and microscopic residuals in either the primary tumor or axillary lymph nodes, there were two patients with Her-2/neu positive disease and this finding is more or less matched with that repented by Aguiar et al.[22] when using Epirubicin, cyclophosphamide and weekly pacliteal as neoadjuvant therapy where they found one case with Her-2/neu positive out of eleven cases with good pathological responses including pCR and minimal residual disease.

RECOMMENDATIONS

The combination of docetaxel, doxorubicin and cyclophosphamide with granulocyte colony stimulating factor as given in this study is safe, tolerable and shows good activity in the neoadjuvant setting for locally advanced breast cancer stages IIB to III patients.

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