ORIGINAL ARTICLE

Evaluation of Paclitaxel and Carboplatin Versus Combination Chemotherapy with Fluorouracil Doxorubicin and Cyclophosphamide as a Neoadjuvant Therapy in Patients with Inoperable Breast Cancer

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ABSTRACT

Objective: To compare the results of patients with locally advanced breast cancer receiving two different regimens Fluorouracil, Doxorubicin and Cyclophosphamide (FAC) and Paclitaxel and Carboplatin.

Study Design: Comparative study.

Place and Duration of Study: The Oncology Department, Institute of Nuclear Medicine and Oncology (INMOL), Lahore, from March 2007 to September 2008.

Methodology: Patients with inoperable locally advanced breast cancer of stage were included. Sixteen patients were given FAC regimen and 9 patients were given Paclitaxel and Carboplatin, each combination was cycled after 21 days for four times. Before enrollment, detailed medical histories, physical examinations and performance status assessments were done as well as postchemotherapy evaluation with regular follow-up visits was done. Complete Response (CR, ↓100%) is defined as the disappearance of all known disease parameter i.e. disappearance in detectable tumour size, node free disease and surgery is possible. Paratial Response (PR, ↓ > 50%) was defined by 50% or greater decrease in the sum of the areas of bidimensionally measured lesions i.e. change of N2 to N1 or no status and some surgical procedure is possible to downstage the disease. Minor Response (MR) was defined as a decrease in the tumour insuffieceint to quality for partial responce. Static disease or no evaluable reflected no significant change in disease and no evidence of new disease. Progression of disease (> 25%) was defined as a 25% or greater increase in the area of any lesion ≥ 2 cm or in the sum of the products of the individual lesions or the apprearance of new malignant lesions, surgery not possible.

Results: Twenty five patients completed neoadjuvant chemotherapy. Sixteen (66%) patients received FAC and 9 (37%) patients received PC chemotherapy. Overall CR (breast and axilla) was 54%, PR was 16% and minor response (MR) was 8%. FAC treatment induced more emesis, mucositis, alopecia and cardiotoxicity. No death occurred.

Conclusion: The Paclitaxel and Carboplatin regimen was better tolerated; both regimens were effective in improving disease and overall survival.

Key words: *Breast cancer. Neoadjuvant. Chemotherapy. FAC. Paclitaxil. Carboplatin.*

INTRODUCTION

Locally advanced breast cancer (LABC) is a particular biological entity of breast cancer characterized by the primary tumour extent in the breast, as well as by locoregional lymphatic spread. It includes the America Joint Committee on Cancer (AJCC) stages IIIA (T3 and N1-2, T1-2 and N2) and IIIB (T4 and any N or N3 and any T).[1] In USA, LABC represents 5% of all new breast cancer cases. In developing countries 50-80% of breast cancer patients present at advanced stage.[2] Combined modality treatment using chemotherapy, surgery and radiotherapy is regarded as preferred treatment. Hormone therapy is added if receptors are positive and today biological therapy where appropriate and affordable.

The use of neoadjuvant chemotherapy (NC) originates from the treatment of locally advanced and inoperable breast cancer. Response rates are traditionally 60-80% with pathological complete response being < 10%, but better responses are seen with newer agents. The major role of NC in inoperable breast cancer is to render the disease operable. In contrast, in operable breast cancer, NC is used to downstage tumours to facilitate breast conservation in patients who would otherwise undergo mastectomy or to enable surgical resection with the best possible cosmetic outcome.[3] NC takes advantage of the less favourable growth kinetics for metastasis characteristic of early breast cancer, thus potentially eliminating micrometastases and improving survival.[4]

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Following the demonstration of the feasibility of neoadjuvant chemotherapy in phase II trials, several phase III trials including National Surgical Adjuvant Breast and Bowel Project B-18 (NSABP B-18) trial have been performed to compare mastectomy, local control and survival rates with those of conventional treatment in operable disease.[5,6] After a follow-up of 5 years, patients demonstrating complete response were found to have a significantly improved disease-free survival (p=0.0014), but not overall survival.

Typical regimen for neoadjuvant Chemotherapy used in the local set up is one incorporating cyclophosphamide, adriamycin and 5-fluorouracil (FAC). Patients with cardiac problem should have other options. Taxane may be another option alone or in combination as a part of the regimen.

In this study, the objective was to compare the treatment results of the patients presenting with locally advanced breast cancer receiving two different regiems either FAC or Paclitaxel and Carboplatin.

METHODOLOGY

This study was carried out in Oncology Outdoor INMOL Hospital, Lahore, from February 2007 to October 2008. Patients with inoperable breast cancer stage T3 N0 M0, T4 N0 M, T3 N1 M0, T4 N1 M0, T3 N2 M0 or T4 N2 M0 (biopsy proven) were included of any age with no evidence of distant metastasis and not taken prior chemotherapy/radiotherapy. Patients with heart failure or ejection fraction ≤ 45% were excluded. All patients were required to provide written informed consent.

Before enrollment, detailed medical history, physical examinations and performance status assessments was done for each patient. Blood samples were obtained for complete blood counts, electrolytes and renal and liver functions. Twenty four hours urine creatinine clearance measurement was used for Calvert's dosing equation for Carboplatin. Baseline ECG or MUGA scan, chest X-ray, ultrasound of the abdomen and bone scan were also carried out. After initiating chemotherapy, physical examinations were performed daily. CBCs and routine serum chemistry studies, i.e. total protein, albumin, total cholesterol, RFTs, LFTS, alkaline phosphatase and urinalysis were performed weekly. Follow-up chest X-ray, ultrasound of the abdomen and bone scan were also done.

Patients were divided in 2 groups according to the regimen. Group A included 16 patients out of 25 receiving combination chemotherapy (FAC) (1), including Cyclophosphamide 500 mg/m^2 on day 1 and 2, Doxorubicin 50 mg/m^2 and 5-Fluorouracil 500 mg/m^2 on day 1 only, cycled every 21 days for 4 times.

Group B included 09 patients who received Paclitaxel 175 mg/m^2 and Carboplatin 300 mg/m^2 on day 1, cycled every 21 days for 4 times. Both therapies were as prescribed by NCCN protocol.

Carboplatin and Paclitaxel doses were determined for every course using recent creatinine clearance and body weight. The Carboplatin dose was calculated as the target AUC 6 mg/ml/minutes, using the Calvert equation. Paclitaxel was administered as a 3 hours intravenous infusion followed by 1-hour infusion of Carboplatin. All patients received premedication with Dexamethasone (20 mg) and Ranitidine (50 mg) and Diphenhydramine (50 mg). Toxicity of given regimen is also monitored. Two out of 16 patients in group A were given FAC initially but then shifted on to Paclitaxel and Carboplatin regiemen (group B) due to poor cardiac status.

A 50% dose reduction of all drugs was done in grade 4 myelosuppression on day 21 or bilirubin level is 2-3 mg/dl while 25% dose reduction was done in febrile neutropenia or platelet count is ≤ 20,000/µl. Treatment was stopped in case of serum bilirubin > 3 mg/dl or serum creatinine > 2 mg/dl. In grade 1-3 myelo-suppression on day 21, the treatment was delayed until recovery. If a patient did not recover to WBC count 4000/µl, neutrophil count 2000/µl or platelet count 100,000/µl during the 6 weeks from the start of chemotherapy, the study protocol was discontinued. Granulocyte colony-stimulating factor was given for grade 4 leukopenia/neutropenia. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. Complete Response (CR, ↓ 100%) is defined as the disappearance of all known disease parameter i.e. disappearance in detectable tumour size, node free disease and surgery is possible. Paratial Response (PR, ↓ > 50%) was defined by 50% or greater decrease in the sum of the areas of bidimensionally measured lesions i.e. change of N2 to N1 or no status and some surgical procedure is possible to downstage the disease. Minor Response (MR) was defined as a decrease in the tumour insuffieceint to quality for partial responce. Static disease or no evaluable reflected no significant change in disease and no evidence of new disease. Progression of disease (> 25%) was defined as a 25% or greater increase in the area of any lesion ≥ 2 cm or in the sum of the products of the individual lesions or the apprearance of new malignant lesions, surgery not possible.

The primary end point of this study was to assess overall objective response after chemotherapy with two groups either FAC or PC based. The statistical analyses were done using the Statistical Program for Social Sciences (SPSS) version 10.0 for windows. Chi-square test was applied for categorical variables. P-value less than 0.05 was considered significant.

RESULTS

Total 31 patients were enrolled in this study between Febraury 2007 and October 2008. Four patients were considred ineligible because either they got distant metastasis on detailed examination or did not have measureable disease. Rest of 27 patients were eligible and received chemotherapy as shown flow diagram of the enrolled patients (Table I). Twenty five patients were finally included.

All patients had good performance status. The patients were between 35 and 70 years old, with a median age of 58 years. All were females. The majority of patients had stage III disease with nodal status N0, N1 or N2 with adenocarcinoma was the most frequent histology. Assignment of patients to FAC or PC was done according to patients clinical performance status and patient consent in table of random numbers. The median number of chemotherapy courses in a patient was two (range, 1-4) and a total of 4 courses were delivered. Dose reduction was done in 03 patients receiving FAC chemotherapy. No dose reduction was done in Carboplatin and Paclitaxel. Overall, patients received nearly 85% of planned doses in the FAC arm and nearly 95% in the PC arm (Table II).

Two patients were non-evaluable for clinical response in the breast and axilla; in one case, this was because follow-up lymph node measurements were not performed, and one patient was lost to follow-up. Two patients in the FAC arm and one patient in the paclitaxel arm had progressive disease during the induction phase. Both patients with progressive disease on FAC were crossed over to the paclitaxel arm but had continued progression of disease. One patient with progressive disease on paclitaxel therapy was crossed over to the FAC arm and subsequently experienced further disease progression.

As shown in Table III, after 04 cycles of neoadjuvant chemotherapy there was an overall complete response (in both groups) was 44%, partial response was 16%, minor response (MR) was 12%, static disease condition was 12% and progressive disease was observed in 12%.

Table I: Flow diagram of the enrolled patients.

31 patients enrolled
↓ 4 out of 31 patients ineligible (3 patients get stage IV) (1 patient did not have measureable disease)
27 patients eligible
↓ 02 out of 27 patients didn't complete chemotherapy; 01 patient has unrelated toxicities; 01 patient withdrew consent
25 (92%) patients completed neoadjuvant therapy (04 cycles)
↓ 16 pateints received FAC; 09 patient received PC
23 (84%) patients completed surgery per protocol
↓ 01 patient choose not to have surgery; 01 patient lost to follow-up
02 patients were shifted from FAC to carboplatin and paclitaxel
01 patient was shifted from carboplatin and paclitaxel to FAC.

FAC= Fluorouracil, Doxorubicin and Cyclophosphamide; PC=Paclitaxel and Carboplatin.

Table II: Patients' characteristics.

Characteristics	Group A (n=16)		Group B (n=09)	
	No.of patients	%	No.of patients	%
Age				
< 50 years	13	52	2	8
> 50 years	3	12	7	28
Median years	48	-	57	-
Clinical tumour status				
T2	0	-	0	-
T3	9	36	6	24
T4	7	28	3	12
Clinical nodal status				
N0	0	-	1	4
N1	9	36	5	20
N2	7	28	3	12
Receptor status				
ER^+/PR any status	6	25	5	20
ER^-/PR any status	8	33	4	16
Unknown	2	8	-	-
Median breast tumour (greatest diameter, cm)	7.5	-	8.2	-

T= Tumour size; N= Palpable regional lymph node; ER = Estrogen receptor; PR= Progesterone receptor.

Table III: Response to chemotherapy.

Parameters	Group A (n=16)		Group B (n=09)		p-value
	No.of patients	%	No.of patients	%	
Clinical response					
CR	7	43	4	50	0.595
PR	3	18	1	12	
Minor response	3	18	0	-	
No change	1	6	2	25	
Progressive disease	2	12	1	12	
Residual disease in breast at surgery					
None	0	-	0	-	0.319
In situ	3	18	1	12	
Minimum < 1 cm	1	6	4	50	
Moderate	9	56	2	25	
Extensive	3	18	1	12	
Nodal disease at surgery					
Negative	10	62	6	66	0.096
1-3	5	31	2	22	
4-10	1	6	1	12	
> 10	0	-	0	-	
Pathological stage after neoadjuvant therapy					
0	6	37	3	37	0.130
In situ	3	18	2	25	
1	0	-	0	-	
2	2	12	1	12	
3	6	37	1	12	

CR= Complete response; PR= partial response; p-value < 0.05 significant.

In group B patients who received PC chemotherapy complete response (CR) was observed in 50% as compared to 43% in group A patients treated with FAC, (p=0.05). Partial response observed in group B (18%) showed significant difference as compared to group A (12%) patients. Significant difference was also observed in minor response among group A as compared to group B. No significant difference was observed in progression of disease in either group. Residual disease in the breast at the time of surgery showed significant difference between both groups ($p < 0.05$), while more extensive disease pattern was noted in group A. Somewhat higher proportion of patients in group A had

no residual disease in the breast at the time of surgery as compared to group B, though more patients in group B had reduced tumours size ≤ 1 cm. Distributions of nodal disease detected at the time of surgery were almost similar between the treatment groups. It showed no significant difference at p=0.05. Among 16 FAC treated patients who underwent surgery, 9 (55.4%) achieved stage 0 disease or had only *in situ* disease on histologic specimens; corresponding to results for PC treated patients were 05 responders among 08 surgery cases (63.1%). The median time to progression was 8.9 months (range 0.5 to 14.6+ months), whereas the median survival time had not been reached at the time of the study report.

There were no deaths due to therapy during the study period. Among group A, the most frequently reported hematologic toxicity was grade 3/4 neutropenia (34%), while emesis, mucositis, alopecia, anemia and thrombocytopenia were each reported for 6%. Among group B, a less severe incidence of grade 3/4 neutropenia (6%) was observed, but the rates of grade 3/4 myalgia (53%), anemia (14%), and thrombocytopenia (7%) were higher. During neoadjuvant FAC treatment, grade 3/4 non hematologic toxicities were reported for 41% patients while 30% patients with PC treatment suffered from non-hematologic toxicities.

DISCUSSION

When treated with local therapy alone, patients with locally advanced breast cancer have a poor prognosis with a 5-year overall survival (OS) rate of only 5-20%.[7,8] Generally 3-4 pre-operative chemotherapy cycles were administered followed by a number of postoperative chemotherapy cycles. The reported clinical response rates vary between 30% and 80% with 10-30% clinical complete remissions and long-term survival in 15% of the patients.[1-3,9] Taxanes and anthracyclines represent the most potent drugs used in breast cancer. Indeed, the concomitant administration of these agents has shown promise in the phase II setting, although only the final peer-reviewed results of several ongoing phase III studies will definitively confirm the improved survival rate. Initially, the taxanes were introduced in metastatic breast cancer for which they are now standard second-line therapy, with an emerging first-line role. Paclitaxel and Carboplatin have significant anti-tumour activity and realize their cytotoxicity via tubulin stabilization and cell cycle arrest. They have been shown to promote apoptosis, inhibit angiogenesis and induce several genes that mediate diverse cellular processes.[10-13] Phase III studies have confirmed that increased tumour response and increased time-to-treatment failure or progression can be achieved with taxane-based therapy.[14,15] In addition, 50% of patients with anthracycline-resistant disease have been shown to respond to taxane chemotherapy.

Various doses and schedules of administration of this drug have been evaluated. In this study, the selected schedule (24-hours infusion) was the already being evaluated at IM in patients previously treated with anthracycline. This dose and schedule had high anti-tumour activity that was clinically comparable to FAC which is the most common regimen offered locally. Significant fraction of patients had better clinical response and partial response with Paclitaxel and Carboplatin as compared to FAC arm and very few patients had no response to either therapy. There was less residual disease in the breast and axilla in the FAC arm. The fraction of patients in whom breast preservation was feasible and performed was similar in the two arms of the study. A slightly higher fraction of patients had segmental mastectomy and axillary dissection in the paclitaxel subgroup of women. The residual disease in lymph nodes after neoadjuvant therapy provides important prognostic information regarding the subsequent prognosis of these patients. These results tend to rule out a large difference in pathologic response in favour of Paclitaxel and Carboplatin but are consistent with the possibility of a sizable difference in favour of FAC. Chemotherapy-induced toxic effects were less severe in intensity in group B as compared to group A patient. Most of the patient tolerated Paclitaxel and Carboplatin well. Dose modification was required only in 01 patient in group B and 03 patients in group A.

The other ramification of effective neoadjuvant systemic therapy such as FAC and Paclitaxel/Carboplatin is that surgery could evolve into minimally invasive approaches to the primary tumour. Because axillary irradiation or sentinel node lymphatic mapping may substitute for an axillary node dissection in patients with a clinically negative axilla, these primary tumour ablation techniques could be accomplished in an outpatient setting. The hurdle will be the histologic assessment of residual tumour and margin status.

It is known that taxanes have activity in Anthracycline resistant disease, which prompted the design of the NSAPB B-27 study. Preliminary results from the trial demonstrate that AC+ docetaxel is associated with a statistically significant greater rate of pCR (Pathological complete response) than AC (Adriamycin and Cyclphosphamide) alone (18.7% compared with 9.8%) and a statistically significant greater rate of pathologically negative nodes at the time of surgery (58.1% compared with 50.7%, NSABP (National Surgical Adjuvant Breast and Bowel Project) 2001. The impact of this on survival is unknown as yet. In earlier randomized trials, continued use of same therapy beyond a few cycles did not result in further reduction in risk of recurrence or improvement in survival.[16] This concept has been evaluated in a large intergroup prospective study in the adjuvant setting. The preliminary results of that study illustrated that patient prognosis was favourably altered by this approach.[17,18]

Several phase II studies have shown that combination therapy with Carboplatin and Paclitaxel is active and reasonably well tolerated as first-line treatment of patients with metastatic breast cancer. The North Central Cancer Treatment Group evaluated Carboplatin/Paclitaxel in the first line treatment of metastatic breast cancer.[18-20]

Leaving Carboplatin aside, there are suggestive data indicating a higher rate of pathologic complete response in patients receiving weekly paclitaxel compared with those receiving an q3w dose of 225 mg/m^2 when administered before four cycles of FAC chemotherapy. There was less residual disease in the breast and axilla in the FAC arm. The fraction of patients in whom breast preservation was feasible.

Neoadjuvant therapy provided an early surrogate end point, i.e. downstaging information. In the long-run, the clinical course of the disease in these patients depends on response and to what stage the tumour is down-staged. Patients with persistent significant residual disease could be offered alternate non–cross-resistant therapies. Main drawback of this study was that the follow-up was short and limited information had been reported, so longer follow-up is basically needed.

CONCLUSION

Paclitaxel and Carboplatin was effective in downstaging the disease and gave better response regardless of age of the patient, in comparison with the patients treated with FAC regimen. These results suggest that taxane-containing regimens may be a reasonable option for neo-adjuvant chemotherapy in locally advanced breast cancer.

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