Original Research Paper

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PROSPECTIVE STUDY TO COMPARE CLINICAL, PATHOLOGICAL RESPONSE AND ACUTE TOXICITIES IN PACLITAXEL, DOXORUBICIN AND CYCLOPHOSPHAMIDE (PAC) REGIME VERSUS 5-FLUOROURACIL, DOXORUBICIN AND CYCLOPHOSPHAMIDE (FAC) REGIME AS NEO-ADJUVANT CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER.

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ABSTRACT **Background:** Treatment outcome and prognosis of patients with locally advanced breast cancer is poor due to higher rate of relapse despite of advanced treatment protocol. Neo-adjuvant chemotherapy helps to down stage the large size tumor and also arrests micro-metastasis in the earliest. Pathological complete response after neo-adjuvant chemotherapy showed better long term survival. The aim of our study was to compare clinical and pathological response and acute toxicities in Paclitaxel, doxorubicin and cyclophosphamide (PAC) regime versus Fluorouracil, doxorubicin and cyclophosphamide (FAC) regime as neo-adjuvant chemotherapy in patients with locally advanced breast cancer.

Materials And Methods: Locally advanced Invasive ductal carcinoma of breast of female patients were included in our study. All patients received median 4 cycles of neo-adjuvant chemotherapy. 20 patients in Control group received FAC regimen: Injection 5-Fluorouracil 500mg/m2, Doxorubicin 50mg/m2, Cyclophosphamide 500mm/m2 in D1. 20 patients in Study group received PAC regimen: Injection Paclitaxel 175mg/m2, doxorubicin 50mg/m2, Cyclophosphamide 500mg/m2 in D1.

Results: Complete clinical response was 10% in control group (FAC regime) and 30% in study group (PAC regime). Complete pathological response was more in PAC regime group (25%) compare to FAC regime group (10%). In our study grade 1 and 2 toxicities developed which were manageable but there was no grade ¾ toxicities.

Conclusion: PAC regime showed higher rate of complete clinical and pathological response with acceptable acute toxicities compare to FAC regime in locally advanced breast cancer patients.

KEYWORDS : Locally advanced breast cancer, Neo-adjuvant chemotherapy, Pathological complete response

INTRODUCTION:

Breast cancer is the commonest cancer of women in worldwide and it is also leading cause of death in female patients [1]. In our country 75000-80000 new breast cancer patients diagnosed per year [2,3]. In our country locally advanced breast cancers accounts for 30%-60% of newly diagnosed cases while 10-20% in United States [4]. Locally advanced breast cancer is defined as clinical stage T3N1M0 or T4 and/or N2-3M0. Treatment outcome and prognosis of patients with locally advanced breast cancer is poor due to higher rate of relapse despite of advanced treatment protocol [5]. The standard therapy for all patients with locally advanced breast cancer is neo-adjuvant chemotherapy [6,7]. Neo-adjuvant chemotherapy helps to down stage the large size tumor and also arrests micro-metastasis in the earliest. Outcome of patients treated with neo-adjuvant chemotherapy depends on combination of drugs therapy [8]. Long term survival of patients treated with neo-adjuvant chemotherapy depends on pathological response of tumors. Pathological complete response after neo-adjuvant chemotherapy showed better long term survival [9]. Paclitaxel and Docetaxel are taxane group anticancer drugs. Docetaxel based neo-adjuvant chemotherapy is more effective than doxorubicin [10]. Docetaxel and Paclitaxel are used in combination with anthracycline group doxorubicin to improve effectiveness of therapy in patients with locally advanced breast cancer [11]. The aim of our study was to compare clinical and pathological response and acute toxicities in Paclitaxel, doxorubicin and cyclophosphamide (PAC) regimen versus 5-Fluorouracil, doxorubicin and cyclophosphamide (FAC) regimen as neo-adjuvant chemotherapy in patients with locally advanced breast cancer.

MATERIALS AND METHODS:

Our study was done in the Department of Radiotherapy, College of Medicine & Sagore Dutta Hospital, Kolkata. The study period was October 2018 to December 2019. Locally advanced breast cancer clinically T3-4 or N2-3 and histopathology proven invasive ductal carcinoma of breast of female patients were included in our study. Total 40 patients, meeting inclusion and exclusion criteria, willing to participate were included in our study. Among them 20 patients were assigned to receive FAC regimen denoted as control group and 20 patients were assigned to receive PAC regimen denoted as study group. All patients had Karnofsky Performance status ≥70. Patients with cardiac disease, renal disease, inflammatory breast carcinoma, distant metastasis, past history of cancer, chemotherapy and radiotherapy were excluding from our study. Clinical examination, tru-cut biopsy, immunohistochemistry, chest x ray PA view, USG bilateral breast and axillary region, USG of whole abdomen, CECT thorax and whole abdomen and PET-CT scan, ECG, Echocardiography, blood for CBC, LFT, urea, creatinine, fasting and PP sugar were done before the study. Both control group and study group received 3 to 5 cycles (until clinically operable) neo-adjuvant chemotherapy. Control group received FAC regimen: Injection 5-Fluorouracil 500mg/m2, Doxorubicin 50mg/m2 in 100ml normal saline over 20 mints, Cyclophosphamide 500mg/m2 in 400ml 5% Dextrose run over 1hr in D1 with proper premedication and repeated the cycle 3 weekly. Study group received PAC regimen: Injection Paclitaxel 175mg/m2 in 400ml normal saline (glass bottle) intravenous infusion over 3 hrs, doxorubicin 50mg/m2, Cyclophosphamide 500mg/m2 in D1 with proper premedication and repeated the cycle 3 weekly. Injection Filgrastim 300microgram subcutaneously was given in PAC group 24 hrs after chemotherapy for 3 days. FAC group received injection Filgrastim if absolute neutrophil count less than 1500/mm3. After each cycle of neo-adjuvant chemotherapy each and every patient examined at breast and axilla to assess tumor size and operability and also assessed chemotherapy induced toxicities. After completion of 3rd cycle of neo-adjuvant chemotherapy tumor size was assessed as per Response Evaluation Criteria in Solid Tumors (RECIST).

Toxicities were graded according to Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE V4.0) scale. All patients in both the groups were done modified radical mastectomy after completion of neo-adjuvant chemotherapy and histopathological examination was done each post- operative specimen. After modified radical mastectomy patients received same regimen chemotherapy for total 6 cycles and followed by adjuvant radiotherapy.

RESULTS:

In both groups total 40 (20 patients in each group) patients were included in our study and they completed the study successfully. The median age of the patients were 49 yrs in FAC regime group and 48 yrs in PAC regime group. The majority of the patients in both the groups were in clinical stage T4N2M0, 50% in control group and 55% in study group (Table 1). All patients had histopathology invasive ductal carcinoma. Most of the patients in both the groups were pre-menopausal, 60% in control group (FAC) and 65% in study group (PAC). Most of the patients had negative ER/PR status.

All patients received median 4 cycles of neo-adjuvant chemotherapy and treatment tolerated well. Complete clinical response was 10% in control group (FAC) and 30% in study group (PAC) [Table 2]. Partial response was 60% in control group (FAC) and 65% in study group (PAC). Progressive disease was 10% in control group (FAC) and there was no progressive disease in study group (PAC). Complete pathological response was more in PAC regime group (25%) compare to FAC regime group (10%).

Non-hematological and hematological toxicities are given in Table 3. In our study grade 1 and 2 toxicities developed which were manageable but there was no grade ¾ toxicities. Nausea and vomiting was 60% in control group (FAC) and 75% in study group (PAC). Oral mucositis was 50% in FAC regime and 65% in PAC regime group. All patients developed alopecia. Myalgia and peripheral neuropathy were seen 55% and 10% respectively in PAC regime group but there were no myalgia and neuropathy in FAC regime group. Anemia, neutropenia and thrombocytopenia were seen more in PAC group compare to FAC regime group.

Table 1: Patient Characteristics In Control Group (FAC regime) And Study Group (PAC regime)

Characteristics	Control group (n=20) (FAC regime)	Study group (n=20) (PAC regime)
Median Age (yrs)	49	48
Clinical Stage (AJCC 7th Edition)		
T3N1M0	6 (30%)	6 (30%)
T4N2M0	10 (50%)	11 (55%)
T4N3M0	4 (20%)	3 (15%)
Histopathology		
Invasive ductal carcinoma	20 (100%)	20 (100%)
Menopausal status		
Pre-menopause	12 (60%)	13 (65%)
Post-menopause	8 (40%)	7 (35%)
Estrogen receptor status		
Positive	9 (45%)	8 (40%)
Negative	11 (55%)	12 (60%)
Progesterone receptor		
Positive	10 (50%)	9 (45%)
Negative	10 (50%)	11 (55%)

Table 2: Comparison Of Clinical Response, Pathological Response In Two Groups

Disease response	Control group (n=20) (FAC regime)	Study group (n=20) (PAC regime)
Clinical Response		
Complete Response	2 (10%)	6 (30%)
Partial Response	12 (60%)	13 (65%)
Stable Disease	4 (20%)	1 (5%)
Progressive Disease	2 (10%)	0
Pathological Complete Response	2 (10%)	5 (25%)

Table 3: Comparison Of Chemotherapy Induced Acute Toxicities In Two Groups

Toxicities	Control group (n=20) (FAC regime)	Study group (n=20) (PAC regime)
Non-hematological toxicities		
Nausea & Vomiting	12 (60%)	15 (75%)
Oral mucositis	10 (50%)	13 (65%)
Diarrhea	2 (10%)	3 (15%)
Alopecia	20 (100%)	20 (100%)
Myalgia	0	11 (55%)
Peripheral Neuropathy	0	2 (10%)
Hematological toxicities		
Anemia	4 (20%)	7 (35%)
Neutropenia	4 (20%)	6 (30%)
Thrombocytopenia	3 (15%)	4 (20%)

DISCUSSION:

Breast cancer is the commonest cancer of women in worldwide and it is also leading cause of death in female patients [1]. Treatment outcome and prognosis of patients with locally advanced breast cancer is poor due to higher rate of relapse despite of advanced treatment protocol [5]. The standard therapy for all patients with locally advanced breast cancer is neo-adjuvant chemotherapy [6,7]. Neo-adjuvant chemotherapy helps to down stage the large size tumor and also arrests micro-metastasis in the earliest.

In our study median age of the patients were 49 yrs in FAC regime group and 48 yrs in PAC regime group. Mathew J et al. reported in their study median age was 49 yrs in FAC group and 51 yrs in TEC (Docetaxel, Epirubicin, Cyclophosphamide) group [8]. Majority of the patients in our study stage was T4N2M0, 50% in FAC group and 55% in PAC group then T3N1M0, 30% in FAC group and 30% in PAC group. Gupta D et al. reported in their study that stage of most of the patients was T4,N1-2 [12].

In our study all patients received median 4 cycles of neo-adjuvant chemotherapy. Complete clinical response were 10% in control group (FAC) and 30% in study group (PAC) and Complete pathological response was more in PAC regime group (25%) compare to FAC regime group (10%). Gupta D et al. reported in their study complete pathological response was 18.9% in docetaxel chemotherapy arm and 13.2% in anthracycline chemotherapy arm [12]. National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27 study reported 26% complete pathological response in AC followed by Docetaxel group and 21% in AC group [13]. Andrade JM et al. reported in their study complete clinical and pathological response was more in TAC (Docetaxel, Doxorubicin, Cyclophosphamide) regime compared to 5-FU, Epirubicin, cyclophosphamide (FEC) regime [14].

Batra U et al. reported in their study oral mucositis, diarrhea, neutropenic fever were more common side effect in TAC regime compare to FAC regime and nausea, vomiting occurred less in TAC regime compare to FAC regime [15]. In our study nausea, vomiting, oral mucositis, diarrhea were more in PAC regime group compare to FAC regime group and myalgia (55%), peripheral neuropathy (10%) were seen only in PAC regime due to paclitaxel. In our study hematological toxicities anemia, neutropenia and thrombocytopenia occurred more in PAC regime group compare to FAC regime group and there was grade 1 and 2 toxicities which were manageable but there was no grade ¾ toxicities. Martin M et al. [16] showed in their study that grade ¾ neutropenia occurred in TAC regime if prophylactic Filgrastim was not given. In our study there was no grade ¾ neutropenia due to every patient in PAC regime group received prophylactic Filgrastim.

However, our study contains a small number of patients and comparatively short period of follow-up that represents a major limitation for conclusion.

CONCLUSION:

In our study PAC regime showed higher rate of clinical and pathological response and manageable acute toxicities compare to FAC regime in female patients with locally advanced breast cancer. However, this results need to be further confirmed by large sample size study.

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