Pathological Response Rate of Paclitaxel Based Dose Dense and Conventional Neoadjuvant Chemotherapy in Locally Advanced Female Breast Cancer Patients

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ABSTRACT

BACKGROUND
Locally advanced female breast cancer patients have the highest risk of recurrence and distant metastasis. Taxane-based neoadjuvant chemotherapy gives a more pathological response. The purpose of this study was to assess the pathological response rate of paclitaxel-based dose-dense and conventional neoadjuvant chemotherapy in locally advanced female breast cancer patients

METHODS
In this observational study, a total of hundred locally advanced female breast cancer patients were randomly selected for neoadjuvant chemotherapy. Fifty patients received three weekly paclitaxel 200 mg/m^2 (4 courses) and other fifty patients received weekly paclitaxel 80 mg/m^2 (10 courses) along with three weekly doxorubicin 50 mg/m^2(4 courses in both arms). Chemotherapy-induced clinical response in both arms was weekly assessed by tumour and lymph node size measurements, change in consistency and fixity. Pathological response of chemotherapy in each arm was assessed by taking the difference of mean tumour volumes and presence of chemotherapy-induced fibrosis and collections of histiocytes in lymph nodes.

RESULTS
There was statistically significant pathological reduction after neoadjuvant chemotherapy was seen in three weekly arms (68.18 cm^3 to 37.22 cm^3 P-value 0.000), in the weekly arm (68.42 cm^3 to 18.04 cm^3 P-value 0.000) and difference in reduction of tumour volume (more in weekly arm -50.38 cm^3 versus 30.86 cm^3, P-value 0.000)

CONCLUSIONS
Locally advanced female breast cancer patients receiving neoadjuvant chemotherapy with paclitaxel showed a better pathological response rate. It was more in the weekly paclitaxel arm.

KEY WORDS
Pathological Response Rate, Neoadjuvant Chemotherapy, Locally Advanced.

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BACKGROUND

Locally advanced breast cancer is a non-metastatic invasive breast cancer with involvement of chest wall and/or skin or patients with a group of axillary and/or supra-clavicular nodal spread.[1] Main treatment of it is by chemotherapy, surgery, radiation, biological and hormonal therapies.[2] Neoadjuvant chemotherapy means chemotherapy given before complete surgery. It gives pathologic complete response[3] and can decrease the tumour size and increase the breast-conserving therapy. About 15 – 25 % of locally advanced breast cancer patients will have complete pathological responses to neoadjuvant chemotherapy with anthracycline and taxane.[4,5,6,7] Imaging like mammography, ultrasonography, and/ or MRI are used to measure the size of the tumour during therapy.

Objectives

To study pathological response rate of weekly and three paclitaxel neoadjuvant chemotherapy in locally advanced female breast cancer patients.

METHODS

This is an observational study design involving 50 locally advanced female breast cancer patients selected from the Department of Oncology, Medical College, Thiruvananthapuram between January 2011 and November 2012.

Inclusion Criteria

1. Patients having locally advanced breast cancer and aged between 25 to 65 years.
2. Breast cancer should be biopsy-proven.
3. Patients having normal haemoglobin (more than or equal to 10 gm %), WBC count (5000 - 11000/mm^3), platelet count (70000 - 300000/ mm^3), liver function test and renal function tests.

Exclusion Criteria

Patients with

1. Any previous cancer treatment
2. Uncompensated congestive heart failure, renal failure and diabetes mellitus
3. Supraclavicular lymph nodes and distant metastasis from breast cancer
4. Ulcerative and inflammatory breast cancer
5. Poor performance status
6. Pregnancy

Study Procedure

In our department, locally advanced female breast cancer patients received different types of paclitaxel containing neoadjuvant chemotherapy. In one pilot study, it had been observed that weekly paclitaxel improved pathologic complete remission in locally advanced female breast cancer patients when compared with paclitaxel once every 3 weeks. In our study, we selected the locally advanced female breast cancer patients receiving dose-dense (weekly) and conventional (three weekly) paclitaxel and compared their pathologic response during neoadjuvant chemotherapy. Before initiation of therapy, all patients underwent an evaluation that included a complete medical history and physical examination, a complete blood count, a chemistry profile, and a chest radiograph, mammography, ultrasonography or computed tomography scan to measure the size of tumour and number of lymph nodes.

Fifty patients received three weekly paclitaxel 200 mg/m^2 and doxorubicin 50 mg/m^2 (4 courses) and the other fifty received weekly paclitaxel 80 mg/m^2 (10 courses) along with three weekly doxorubicin 50 mg/m^2 (4 courses). All patients received dexamethasone 8 mg, diphenhydramine 50 mg and ranitidine 50 mg intravenously as paclitaxel premedication at 12 hours and 30 minutes before starting chemotherapy. Antiemetic ondansetron 8 mg was given intravenously in both arms before starting chemotherapy. Prophylactic growth factor support was given after 72 hours of paclitaxel in all patients.

Total cumulative dose - Paclitaxel – 800 mg / m^2 (three weekly - 200 mg / m^2 × 4, weekly - 80 mg / m^2 × 10) and doxorubicin 200 mg /m^2 in both arms (50 mg / m^2 × 4). There was no dose reduction in both arms during neoadjuvant chemotherapy. Anaemia, neutropenia, myalgia, gastrointestinal symptoms and infection in both arms were treated before each cycle and surgery.

After four weeks of neoadjuvant chemotherapy, patients underwent modified radical mastectomy and axillary clearance. Histopathological examination was done to assess the response to chemotherapy. In histopathological report contained the measurements of the largest gross 3 dimensions of tumour bed which showed the average cancer cellularity (percentage) across the entire tumour bed and lymph node metastasis (all cancer), whether invasive or in situ). The volume of the residual breast cancer was measured as the number of tumour foci encompassing the area of the tumour. Pathological tumour response of neoadjuvant chemotherapy in each arm was assessed by taking the difference of mean tumour volume between clinical tumour volume before chemotherapy and post-operative tumour volume in each arm. The pathological response of neoadjuvant chemotherapy between two arms was assessed by taking the difference of postoperative mean volume of two arms. Treatment effects in regional lymph nodes assessed by the presence of chemotherapy-induced fibrosis and collections of histiocytes in lymph nodes or lymph nodes may become small and atrophic after neoadjuvant chemotherapy.

After two weeks of surgery, all patients received adjuvant three weekly chemotherapy (FAC fluorouracil 500 mg / m^2, doxorubicin 50 mg / m^2, cyclophosphamide 500 mg / m^2 four-course), external beam radiotherapy dose of 50 Gy in 25 fractions, 5 days / week total of 5 weeks using co radioactive isotope (average energy of 1.25 MeV), with medial and lateral tangential beams and supraclavicular on the field. Adjuvant hormone therapy (Premenopausal patient –tamoxifen, post-menopausal patients- letrozole/ anastrozole) is given after radiation for those who have receptor status positive.

This present study was approved by the Ethics Committee. The aim of the research and interview method

was explained to the participants. All patients signed informed consent. Patients who refused to enter the study were excluded.

Statistical Analysis

All statistical calculations were performed using the SPSS 17.0 statistical software. Quantitative variables were expressed as mean and standard deviation; Qualitative variables were expressed as frequency and percentage. Comparison of quantitative variables between two groups was analysed by unpaired t-test and that of qualitative variables was analysed by chi-square test. A P-value < 0.05 was considered statistically significant.

RESULTS

Clinical and Biographical Information	Category 3 Weekly Number	Weekly Number	Total Number
Stage			
3a	28	30	58
3b	14	12	26
3c	8	8	16
Age			
≤ 50 years	28	29	57
≥ 50 years	22	21	43
Age of menarche			
10 - 13 years	12	10	22
14 - 16 years	38	37	75
> 16 years	0	3	3
Parity			
Null parity	1	3	4
1 child	5	7	12
2 children	38	37	75
3 children	6	3	9
Menopause status			
Premenopause	12	14	26
post menopause	38	36	74

Table 1. Patients Clinical and Biographical Information

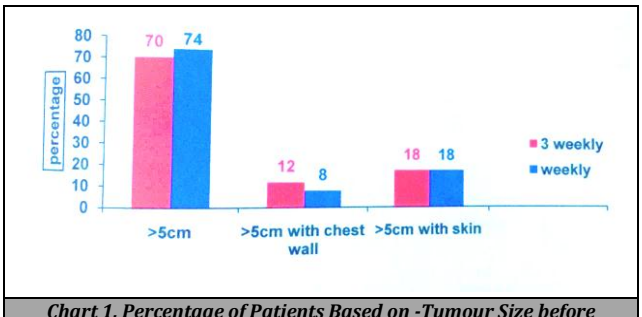

Chart 1. Percentage of Patients Based on -Tumour Size before Neoadjuvant Chemotherapy

All patients had a tumour size of more than 5 cm in the greatest dimension. 10 patients had chest wall infiltration- 6 patients in three weekly arms and 4 patients in the weekly arm. 18 patients had skin involvement- 9 patients in each arm. In three-weekly arm, tumour size ranged from 5.3 cm to 7.8 cm (mean- 6.2 cm) and tumour volume ranged from 53.22- 155.86 cm^3 (mean -68.18 cm^3). In weekly arm, tumour size ranged from 5.4 cm to 7.6 cm (mean- 6.3 cm) and tumour volume ranged from 55.41- 158.11 cm^3 (mean -68.42 cm^3).

Lymph node status before neoadjuvant chemotherapy based on site. Level 1 and 2 axillary nodes- 42 patients in three weekly and 43 patients in the weekly arm. Level 3 axillary nodes- 2 patients in three weekly and 1 patient in the weekly arm. Internal mammary nodes- 6 patients in each arm More than 85 % of patients' tumours were located at more than three quadrants and all of the tumours extended into the central areolar region.

Residual Tumour Status in Greatest Dimension	Category 3 Weekly Number	Weekly Number	Total In Both Arm Number	p
No tumour	3	12	15	0.008
1 mm-10 mm	2	5	7	
11 mm-10 mm	14	17	31	
21 mm -35 mm	5	3	8	
Less than 35 mm	24	37	61	
36 mm-50 mm	26	13	39	
Total	50	50	100	

Table 2. Postoperative Tumour Size after Neoadjuvant Chemotherapy

A complete pathological response was observed in 15 patients. [12 (24 %) in weekly arm and 3 (6 %) in three weekly arms]. All patients were histopathologically margin negative. Reduction in tumour size less than 35 mm was more in the weekly arm (74 %) as compared to three weekly arms (48 %), which showed that there was a statistically significant partial response (At least a 30 % decrease in the target lesions) in the weekly arm than three weekly arms (P-value 0.008)

Category		No.	Mean Volume cm^3	SD	t	P
3 weekly	Before chemotherapy	50	68.18	7.45	22.306	0.000
	After chemotherapy	50	37.22	5.49		
Weekly	Before chemotherapy	50	68.42	6.63	28.965	0.000
	After chemotherapy	50	18.04	12.84		
3 weekly	Difference in reduction of tumour volume	50	30.96	10.07	-8.246	0.000
Weekly	Difference in reduction of tumour volume	50	50.38	12.30		

Table 3. Pathological Response (Tumour Volume) after Neoadjuvant Chemotherapy

There was statistically significant pathological response seen after neoadjuvant chemotherapy in three weekly arms (68.18 cm^3 to 37.22 cm^3 P-value 0.000) and weekly arm (68.42 cm^3 to 18.04 cm^3 P-value 0.000) pathological response was more in weekly arm than three weekly arms (50.38 cm^3 verse 31.84 cm^3)which is also statistically significant (P-value 0.000)

Postoperative Lymph Node Status	Lymph Nodes Based on Site	Category 3 Weekly N	%	Weekly N	%	Total N	%	p
Negative nodes		12	24	21	42	33	33	0.056
Positive nodes	Axillary nodes	33	66	28	56	67	67	
	Internal mammary nodes	2	4	1	2			
	both site nodes	3	6	0	0			

Table 4. Postoperative Lymph Node Status

N- Number, %-percentage

After neoadjuvant chemotherapy, a pathological nodal response rate of 24 % (95 % CI 19.73 - 28.27) of patients in three weekly arms and 42 % (95 % CI 37.06 - 46.93) patients in weekly arm. Weekly arm patients had better lymph node response to neoadjuvant chemotherapy than three weekly arm patients. But the difference was not statistically significant.

DISCUSSION

Neoadjuvant therapy reduces the size of primary breast carcinoma tumours and lymph node metastases and improves operability. It also provides a pathological complete

response, disease-free and better survival in a subgroup of young patients after extended follow-up.[8-27] High clinical response rate was seen in advanced or metastatic breast cancer treated with weekly paclitaxel than three weekly paclitaxel.[28-30] Symmans et al.[31] study found that neoadjuvant weekly paclitaxel induces more programmed tumour cell death. The NSABP B-2[32] trial found that neoadjuvant weekly docetaxel followed by three weekly doxorubicin-cyclophosphamide therapies had a high pathologic complete response rate of 26.1 %.

In our study, patients treated with weekly paclitaxel had a higher pathological complete tumour mass response (24 %) and nodal response (42 %) rate than three weekly paclitaxel patients (complete tumour mass response (6 %) and nodal response rate (24 %). In our study, a complete pathological response was observed in 15 patients. (12 in weekly arm and 3 in three weekly arms). Both neoadjuvant chemotherapy arms showed statistically significant tumour response by comparing clinical tumour volume and post-chemotherapy pathological residual tumour volume. (P-value 0.000 in both arms). Reduction in tumour size less than 35 mm was more in the weekly arm (74 %) as compared to three weekly arms (48 %), which show that there is a statistically significant partial response in the weekly arm than three weekly arms (P-value 0.008). When comparing both arms neoadjuvant chemotherapy tumour mass response was more in the weekly arm, which is also statistically significant (P-0.000). Weekly arm patients had better lymph node response to neoadjuvant chemotherapy than three weekly arm patients. But the difference is not statistically significant. (P-0.056).

Marjorie c. Green[7] study in locally advanced breast cancer showed patients receiving weekly paclitaxel had a higher pathological complete tumour mass response (30.50 %) and nodal response (28 %) rate than three weekly paclitaxel patients [complete tumour mass response (21.3 %) and nodal response rate (17 %)]. The difference in nodal response was statistically significant. (P - 0.02)

CONCLUSIONS

Neoadjuvant treatment permits a rapid assessment of the response of the primary tumour to a particular chemotherapy regimen. This present study which compares the tumour and nodal response to paclitaxel based weekly paclitaxel and three weekly paclitaxel neoadjuvant chemotherapy in locally advanced female breast cancer patients showed statistically significant response in dose-dense weekly arm than conventional three weekly arms. These two neoadjuvant chemotherapies are good in downstaging the breast cancer and making surgery feasible.

Limitations

There was no dose reduction in both arms during neoadjuvant chemotherapy. Anaemia, neutropenia, myalgia, gastrointestinal symptoms, and infection in both arms were treated before each cycle and surgery.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.
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