Acute Toxicity of Paclitaxel Based Dose Dense and Conventional Neoadjuvant Chemotherapy in Locally Advanced Female Breast Cancer Patients

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ABSTRACT

BACKGROUND

Breast cancer is a systemic disease that requires treatment with surgery, chemotherapy, radiation, endocrine therapy and biological therapy. Neoadjuvant chemotherapy is the recent treatment of locally advanced breast cancer. The purpose of this study was to assess the acute toxicity of paclitaxel-based dose-dense and conventional neoadjuvant chemotherapy in locally advanced female breast cancer patients.

METHODS

In this study, neoadjuvant paclitaxel was given to a hundred locally advanced breast malignancies of female patients. Three weekly paclitaxel 200 mg/m² (4 courses) was given for fifty patients and weekly paclitaxel 80 mg/m² (10 courses) was given for fifty patients along with four-course of three weekly doxorubicin 50 mg/m² given in both arms. Chemotherapy-induced acute toxicities in both arms were assessed weekly.

RESULTS

There was a significant increase in the incidence of anaemia in weekly chemotherapy patients at 7th week (28 % verse 10 %, P - value 0.022) and neutropenic infection at 11th week (28 % verse 10 %, P - value 0.022). There was a non-statistically significant increase in the incidence of leukopenia, thrombocytopenia and paraesthesia and myalgia in the weekly arm. There was a significant increase in the incidence of gastrointestinal toxicity like grade 3 stomatitis (at 4th - week), nausea and vomiting (at 4th, 7th, and 11th week) in three weekly chemotherapy patients.

CONCLUSIONS

In this study, acute neurological and haematological toxicities were more in the weekly neoadjuvant chemotherapy arm and acute gastrointestinal toxicities were more in the three weekly neoadjuvant chemotherapy arm.

KEYWORDS

Acute Toxicity, Neoadjuvant Paclitaxel Chemotherapy, Locally Advanced Breast Malignancy.

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BACKGROUND

Surgery, chemotherapy, radiation, biological and hormonal therapies are the main treatments of breast cancer,¹ Locally advanced breast cancer is a tumour without distant spread.² It includes tumour that is more than 5 cm in size with regional lymphadenopathy, or skin / the chest wall infiltration, or both, or lymph nodes at supraclavicular, axillary, infraclavicular or internal mammary area. Patients receiving chemotherapy before radical surgery is called neoadjuvant chemotherapy. Now anthracycline and taxane-based neoadjuvant treatment is recommended for locally advanced breast malignancy patients.^{3,4,5} Paclitaxel is the first taxane that exerts cytotoxicity by promoting tubulin polymerization. Peripheral neuropathy, joint pain and myalgia, infections (febrile neutropenia), anaemia, thrombocytopenia, hair loss, hypersensitivity reaction, stomatitis, vomiting and diarrhea⁵ are the adverse effects of paclitaxel. Weekly paclitaxel 80 - 100 mg / m² neoadjuvant chemotherapy has more complete pathological reduction than every 3-weekly paclitaxel [175 mg / m²] chemotherapy in locally advanced breast malignancy patients.^{6,7,8,9,10}

Anthracyclines (doxorubicin and epirubicin) are antibiotics. Bone marrow suppression, hyperpigmentation of skin and nails, loss of hair, vomiting, diarrhoea, hepatic impairment etc.,¹¹ are the adverse effect of anthracyclines.

Objectives

1. To assess the acute toxicities of three weekly and weekly neoadjuvant paclitaxel chemotherapies in locally advanced breast malignancy of female patients
2. To compare the acute toxicities between the two neoadjuvant paclitaxel chemotherapy patients.

METHODS

It is an observational comparative study involving 50 breast malignancy patients from the Department of Radiotherapy, Medical college, Thiruvananthapuram from 01/01 2011 to 30/11/2012 for a period of 23 months.

Inclusion Criteria

Patients with

1. Locally advanced female breast cancer and age between 25 and 60 yrs.
2. Biopsy proven breast malignancy
3. Hb-(more than or equal to 10 gm %/dl), WBC count (4×10^3 - 11×10^3 /mm³), platelet count (5×10^4 - 30×10^4 /mm³),
4. Normal liver and renal function test.

Exclusion Criteria

1. Patients with a history of early malignancy management.
2. Patients with a history of heart failure, hepatic disease, renal disease, and diabetes mellitus.
3. Patients with metastasis, ulcerative and inflammatory breast cancer.

4. Patients with poor performance status.
5. Patients with age more than 60 years.
6. Pregnant breast cancer patients.

Premedication (steroid and antihistamine) and antiemetics were given prior to paclitaxel infusion. Neoadjuvant chemotherapy-induced acute toxicities in both arms were assessed weekly and compared on 1st, 4th, 7th, and 11th week by interview, general and systemic examination. There was no dose reduction in both arms during this study.

Incidence of anaemia, leukopenia, thrombocytopenia was assessed by blood investigation done every week. Grade of acute toxicity was assessed by World Health Organisation Toxicity Criteria. Anaemia was corrected by blood transfusion, neutropenia corrected by a granulocytic stimulating factor and neutropenia infection was treated with antibiotics, antifungal etc. Gastrointestinal symptoms were corrected by intravenous fluids, antiemetics, and antidiarrhoeal drugs.

Ethical committee approval was obtained before starting this study. All data were analysed by using SPSS statistical software.

RESULTS

	Clinical and Biographical Information	Category		Total Number
		3 Weekly Number	Weekly 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
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

Incidence of grade 1 anaemia developed after 1st week of chemotherapy in three weekly patients. Incidence of grade 2 and 3 anaemia and leucopenia was more in weekly patients and grade 3 anaemia developed earlier (after 4th week of chemotherapy) in weekly patients. Incidence of grade 4 leucopenia developed after 7th week of chemotherapy in weekly patients. There was no incidence of grade 4 leucopenia in three weekly patients. Incidence of thrombocytopenia was more in weekly patients arm. Incidence of grade 3 thrombocytopenia developed after 7th week of chemotherapy only in weekly patients. No patients had grade 4 thrombocytopenia in both arms.

Anaemia

There was a marked increase in the percentage of incidence of anaemia after the 1st week of chemotherapy, which was more in the weekly patients. There was a statistically significant difference in the percentage of incidence of anaemia at 7th week between two-arms (28 % verse 10 %, P-value 0.022)

Anaemia- gm/dl	3 Weekly								Weekly							
	1 st	4 th	7 th	11 th	1 st	4 th	7 th	11 th	1 st	4 th	7 th	11 th	1 st	4 th	7 th	11 th
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Grade 1- >10	3	75	3	75	2	40	2	22.2	2	100	2	33.3	1	7.14	2	16.6
Grade 2- 8-10	1	25	1	25	2	40	5	55.5	3	50	10	71.4	8	66.6		
Grade 3-6.5-7.9					1	20	2	22.2	1	26.6	3	21.4	2	16.6		
Grade 4-<6.5																
Total	4	4	5	9	2	6	14	12								
Leucopenia-Cell/μL																
Grade 1- 3000-3500	4	59	4	44	5	45.4	4	36.3	11	84.6	8	61.4	2	13.3	2	10.5
Grade 2- 2000-2999	3	41	5	56	5	45.4	5	45.4	2	15.4	5	38.6	6	40	9	26.3
Grade 3- 1000-1999					9	18.2					5	33.3	9	47.3		
Grade 4<1000											2	13.3	3	15.7		
Total	7	9	11	11	13	15	19									
Thrombocytopenia-10 ³ Cell/μL																
Grade 1- 75-150	0	2	100	4	57.2	4	57.2	0	3	100	9	69	9	69		
Grade 2- 50<75				3	42.8	3	42.8				3	23	3	23		
Grade 3- 25<50											1	7.9	1	7.9		
Grade 4-<25																
Total	0	2	7	7	0	3	13	13								

Table 2. Haematological Toxicity-Based on World Health Organisation Toxicity Criteria

n-number, wk-week, % =percentage

Weeks	Haematological Toxicity	Category				P
		3 Weekly		Weekly		
		Number	%	Number	%	
1 st	Anaemia	4	8	2	4	0.400
	Leucopenia	7	14	13	26	0.134
	Thrombocytopenia	0	0	0	0	
4 th	Anaemia	4	8	6	12	0.505
	Leucopenia	11	22	13	26	0.640
	Thrombocytopenia	2	4	3	6	0.646
7 th	Anaemia	5	10	14	28	0.022
	Leucopenia	11	22	15	30	0.362
	Thrombocytopenia	7	14	13	26	0.134
11 th	Anaemia	9	18	12	24	0.461
	Leucopenia	11	22	19	38	0.081
	Thrombocytopenia	7	14	13	26	0.134
Table 3. Haematological Toxicity						

Table 3. Haematological Toxicity

Leucopenia

26 % of patients had an incidence of leucopenia at 1st and 4th week in the weekly arm; further incidence of leucopenia was seen after the 7th week in the weekly arm. But in three weekly arms, incidence of leucopenia increased at 1st, 4th and 7th week and no further increase in incidence. The incidence of leucopenia was more in weekly patients.

Thrombocytopenia

There was no incidence of thrombocytopenia at 1st week in both arms. But in three weekly arms, incidence of thrombocytopenia did not increase after the 7th week. The incidence of thrombocytopenia was more in weekly patients.

At the End of First Week

Percentage of incidence of anaemia (8 % vs. 4 %) was more in three weekly arms and leucopenia (14 % vs. 26 %) was more in patients in the weekly arm. There were no patients with thrombocytopenia.

At the End of Fourth Week

Percentage of incidence of anaemia (12 % vs. 8 %), leucopenia, 26 % vs. 22 %) and thrombocytopenia 6 % vs. 4 %) was increased in patients in both arms, more in the weekly arm. There was no increase in the incidence of leucopenia in the weekly arm. The percentage of incidence of patients with thrombocytopenia was more in patients in the weekly arm than in the three-weekly arm (6 % vs. 4 %).

At the End of Seventh Week

There was a statistically significant increased incidence of anaemia in the weekly patients (28 % vs. 10 %), (P - value 0.022). The percentage of incidence of leucopenia was

increased more in weekly patients (30 % vs. 22 %). Percentage of incidence of thrombocytopenia was more in weekly patients (26 % vs. 14 %).

No.	Acute Toxicity of Paclitaxel	1 st -Weeks			4 th -Week			7 th -Week			11 th -Week		
		Patients		P	Patients		P	Patients		P	Patients		P
		3 wk	wk		3 wk	wk		3 wk	wk		3 wk	wk	
		N	N		N	N		N	N		N	N	
1	Neutropenic fever	7	13	0.134	11	13	0.640	11	15	0.362	11	19	0.081
2	Neutropenic infection	4	2	0.400	4	6	0.505	9	12	0.461	5	14	0.022
3	Non-Neutropenic infection	0	3	0.079	1	3	0.307	2	1	0.558	3	1	0.307
4	Myalgia =grade-1	16	10	0.171	20	11	0.052	24	16	0.102	27	24	0.548
5	Myalgia =grade-2	0	4	0.076	9	5	0.249	11	10	0.806	15	18	0.523
6	Myalgia=grade-3	0	0		2	3	0.646	7	5	0.538	10	12	0.629
7	stomatitis=grade-3	9	2	0.025	13	4	0.017	11	6	0.183	13	8	0.220
8	Nausea =grade-3	16	8	0.061	30	12	0.001	36	12	0.000	42	21	0.000
9	Vomiting =grade-3	12	7	0.202	21	9	0.009	28	12	0.001	36	22	0.005
10	Diarrhoea =grade-3	3	0	0.079	5	2	0.240	7	4	0.338	9	5	0.249
11	Paraesthesia =grade-3	6	7	0.766	11	12	0.813	17	22	0.305	31	35	0.398
Table 4. Acute Toxicity of Paclitaxel													
n-number, wk-week													

At the End of Eleventh Week

The percentage of incidence of anaemia was decreased in patients in the weekly arm (28 % to 24 %) and it increased in the three-weekly arm (10 % to 18 %). Patients had more percentage of incidences of leucopenia in the weekly arm (38 % vs. 22 %). There was no increase in the percentage of incidence of leucopenia in the three-weekly arm. Percentage of incidence of patients with thrombocytopenia is the same as in the seventh week in both arms (26 % vs. 14 %).

Percentage of incidence of neutropenic fever and neutropenic infection increased in both arms. After the 4th week, the incidence of neutropenic fever increased in weekly patients and it was not increased in three weekly patients. In the 11th week, incidence of neutropenic infection was more in weekly patients (28 % vs. 10 %) (P = 0.022), that was statistically significant. Incidence of non-neutropenic infection was less than neutropenic infection in both arms. Incidence of non-neutropenic infection increased as completing each cycle in three weekly arms.

The percentage of incidence of chemotherapy-induced myalgia increased after every chemotherapy cycle in patients in both arms. Percentage of incidence of grade 1 myalgia was more in the three-weekly arm (54 % vs. 48 %) at 11th week. but the incidence of severe (grade 2 and 3) myalgia was more in patients in the weekly arm, mainly after 3rd and 4th cycles. Incidence of gastrointestinal toxicities like grade 3 stomatitis, nausea, vomiting, and diarrhoea increased after every chemotherapy cycle in patients in both arms, but more in three weekly patients. That is significant statistically. Percentage of incidence of paraesthesia increased in both chemotherapy arms as advancing each chemotherapy cycle. It was increased more in weekly patients. Loss of hair in all patients, blackish discolouration of nail bed were seen in most of the patients in both arms. 60 % of premenopausal

patients in weekly arms and 50 % premenopausal patients in three weekly arms had ceased their menstruation during chemotherapy.

DISCUSSION

Neoadjuvant chemotherapy was first used in locally advanced breast cancer patients. All anticancer therapy causes adverse effects, so oncologists continue to search new methods of treatments that can produce a high response with less severity and incidence of adverse effects. In node-positive patients, three weekly paclitaxel and anthracycline showed more overall and disease-free survival¹²⁻¹⁴ with weekly paclitaxel having more overall survival advantages.¹⁵ Peripheral neuropathy is the commonest toxicity of paclitaxel.^{16,17} The high-dose weekly paclitaxel schedule in Marjorie C. Green¹⁵ study showed a better response with higher toxicity. But the chemotherapy toxicity was short duration to permit surgery rapidly after best response. In the CALGB 9840 trial,¹⁸ in metastatic breast cancer patients weekly paclitaxel had higher grade 3 neuropathy (24 vs. 12 %, P = 0.0003). In non-metastatic breast cancer, Praveen Kumar Shenoy trial showed that weekly paclitaxel chemotherapy alone or combination had more acute toxicities.¹⁹ In postoperative breast cancer, Sparano et al.²⁰ studies show that weekly paclitaxel patients had higher grade neuropathy and three weekly patients had higher grade arthralgia, myalgia and neutropenia.

In our study, percentage of incidence of anaemia (28 %), leucopenia (38 %), thrombocytopenia (26 %), neutropenic fever (38 %), neutropenic infection (28 %) and paraesthesia (70 %) were more in patients in the weekly arm than three weekly arms. Percentage of incidence of stomatitis (26), nausea (84 %), vomiting (72 %), diarrhoea (18 %) and myalgia (54 %) were more in patients in three weekly arms than a weekly arm. Comparison of anaemia between the two groups, after 1st week incidence of anaemia more in the three-weekly arm, but later (after 4th week) the percentage of anaemia was more in the weekly regimen (maximum 28 %) as compared to three regimens (maximum 18 %). Leucopenia was more in weekly regimen (maximum 38 %) than 3 weekly (maximum 22 %). Patients with anaemia on weekly regimen progressed to grade 3 more than three weekly arm (12 % verse 6 %). The differences in incidence of anaemia were statistically significant in the 7th week (p=0.022). There is no statistically significant difference in percentage of increase in incidence thrombocytopenia between two arms. Grade 3 and 4 neutropenia was more common in patients receiving weekly regimen. There was statistically significant more incidence of nausea and vomiting in three weekly patients (at 4th, 7th, and 11th-weeks) and grade 3 stomatitis (at 4th - weeks). There was no dose reduction done in both arms during this study.

In Marjorie c. Green¹⁵ study showed that chemotherapy related toxicities, [stomatitis- grade 3 (24 % vs. 0 %), vomiting, grade 3 (1 % vs. 0 %) diarrhoea, grade 3,- (5.5 % vs. 5.3 %)], neurological toxicities (paraesthesia – 38 % vs. 23 %) neutropenic infection (9.5 vs. 1 %) myalgias (29 % vs. 19%) were more in three weekly patients than weekly patients. Haematological toxicities were very less in both arms (dose modification done to reduce the incidence). 25 % weekly

paclitaxel dose was reduced in patients with higher grade neurotoxicity and 20 % weekly paclitaxel dose was reduced in patients with higher grade nonhematological toxicity¹⁵ (National Cancer Institute toxicity criteria version 2.0)

CONCLUSIONS

Patients with locally advanced malignancy of breast were previously treated with surgery, palliative chemotherapy and radiation. Prognosis was very poor and malignancy finally spread to other sites. Long-term survival has been greatly improved with aggressive treatment with the use of neoadjuvant chemotherapy. Weekly neoadjuvant paclitaxel in locally advanced malignancy of breast shows high pathological complete response rates and different toxicity profile. Acute neurological toxicities and haematological toxicities were more in weekly chemotherapy patients. Gastrointestinal toxicities were more in three weekly chemotherapy patients.

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

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