

Chemotoxicity in Carcinoma Breast Patients - Its Incidence and Trends in Severity - An Observational Study

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ABSTRACT

BACKGROUND

Chemotherapy has improved the survival of the carcinoma breast patients. But the use of cytotoxic drugs causes multiple chemotoxicities such as nausea, vomiting, weight changes and leucopenia reducing the quality of life of the patients, thereby making the patients defaulters and thus, increasing the chances of recurrence. Very few studies were done in India where patients have different physical, mental, social & cultural characteristics that affect the response & outcomes of treatment differently. We wanted to assess the prevalence & severity of chemotoxicity in carcinoma breast patients receiving chemotherapy along with its comparison amongst commonly used regimens of chemotherapy.

METHODS

Fifty female patients diagnosed with carcinoma breast (excluding the ones having poor performance status, receiving chemotherapy with different regimes) were included in this single centre study. Prevalence and trends of different chemotoxicities like hair loss, nausea, vomiting, fatigue, leucopenia, thrombocytopenia, weight changes were observed using Common Terminology Criteria for Adverse Events version 4 (CTCAE V4.0) guidelines and were compared at the end of 1st, 3rd & 6th cycle of chemotherapy. Categorical variables were presented in numbers and percentages (%) and continuous variables were presented as mean \pm SD and median. Qualitative variables were correlated using chi-square test / Fisher's exact test. A P value of < 0.05 was considered statistically significant. The data was analysed using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

Hair loss was detected in 98 % of patients with increasing trend of severity; nausea & vomiting were experienced by 100 % & 54 % respectively, with decreasing trend of severity. One patient suffered with extravasation of chemotherapeutic drug, 52 % of patients had nail changes with non-significant trend in severity, 24 % patients experienced weight gain while rest had weight loss. All of the patients experienced varying grades of fatigue with increasing trend of severity. Leukopenia was seen single or multiple times (21 times) amongst 16 patients during chemotherapy, while thrombocytopenia was observed 22 times among 15 patients. There was no prevalence of neuropathy, cardiotoxicity, and oral ulcers; also, there was minimal prevalence of severe grades of chemotoxicity with no life-threatening event.

CONCLUSIONS

Hair loss and nausea were seen with increasing and decreasing tendency respectively. No particular regimen was found to be more toxic or safer than the other. With the prevalence and severity trends, patients can be counselled properly regarding chemotoxicity and prepared for these adverse effects. This would have lesser impact on the quality of life.

KEY WORDS

Chemotherapy, Chemotoxicity, Alopecia, Nausea, Vomiting, Fatigue, Leukocytopenia, Thrombocytopenia, Carcinoma Breast

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BACKGROUND

Breast cancer is the most common cancer among females worldwide accounting for nearly a quarter (25 %) of all cancers, with an estimated 1.67 million new cancer cases diagnosed in 2012. Women from less developed regions (8,83,000 cases) have slightly greater number of cases compared to more developed (7,94,000) regions.¹ In India, although age adjusted incidence rate of breast cancer is lower (25.8 per 100 000) than United Kingdom (95 per 100 000) but mortality is at par (12.7 vs. 17.1 per 100 000) with United Kingdom.² There is a significant increase in the incidence and cancer-associated morbidity and mortality in Indian subcontinent as described in global and Indian studies.^{3,4,5,6} Now a days, a multimodal approach with combination of surgery, chemotherapy either adjuvant or neoadjuvant and radiotherapy is the standard protocol for almost all stages of breast carcinoma in most of the treatment centres.⁷ Incorporation of chemotherapy in the treatment protocol has improved the survival of the patient. But the use of cytotoxic drugs used in the chemotherapy regimens result in various toxic side effects or chemotoxicities such as nausea, vomiting, fatigue, impairment in cognitive and sexual functioning that eventually reduce the quality of life of the patients undergoing chemotherapy.⁸ Chemotoxicity is a quite common occurrence during chemotherapy which has a high impact value on mind-set of the patients, which results in compromise with quality of life of the patient then may end in patient becoming defaulter leading to increased chances of recurrences due to inadequate treatment. Indexed study aimed at assessment of prevalence & severity of chemotoxicity in carcinoma breast patients receiving chemotherapy along with its comparison amongst commonly used regimens of chemotherapy.

METHODS

This observational study was conducted at Acharya Vinoba Bhawe Rural Hospital, a tertiary care teaching hospital situated in the rural area of Wardha District, from September 2017 to

August 2019. Approval from institutional ethics committee was obtained. [Letter no: DMIMS (DU) / IEC / 2017 - 18 / 6647] Consent was made available both in English and patient's native language & was taken accordingly. This study included 50 patients after applying inclusion & exclusion criteria. All the diagnosed patients of carcinoma breast during the study duration who received chemotherapy with adriamycin-cyclophosphamide, cyclophosphamide-adriamycin-5FU, adriamycin-cyclophosphamide with paclitaxel & cyclophosphamide-adriamycin-5FU with paclitaxel regimes were included as per recent National Comprehensive Cancer Network (NCCN) guidelines. The patients who did not consent for the research and having poor performance status (Eastern Cooperative Oncology Group-ECOG scale 3 or more)¹⁴ were excluded. The demographic data of the patients along with the diagnostic criteria were collected. Other information including pre-chemotherapy haemoglobin, total leucocyte count & platelet count; similarly, post chemotherapy counts were assessed after 7 days of receiving chemotherapy. Chemotoxicity was assessed under thrombophlebitis, extravasation, nail changes, hair loss, nausea, vomiting, neuropathy, cardiotoxicity, weight, appetite, oral ulcer, fatigue, miscellaneous as per Common Terminology Criteria for Adverse Events (CTCAE) version 4 grading system (Table 1).¹⁵ All the observed parameters were noted while taking history at the time of admission and during daily rounds as per prevalence and or severity on a scale and their trends in prevalence and severity were compared at the end of first, third and sixth cycles of chemotherapy.

Statistical Analysis

Categorical variables are presented in number and percentage (%) and continuous variables are presented as mean ± SD and median. Qualitative variables were correlated using chi-square test / Fisher's exact test. A P-value of < 0.05 was considered statistically significant. The data was entered in MS Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nail changes	None	Discoloration, koilonychia or pitting	Partial or complete onycholysis or pain at the nail bed	Interfering with activities of daily living	-	-
Hair loss	None	< 50 % of normal, that is not obvious from a distance but on a close inspection.	> 50 % of normal that is readily apparent to others. individual need wig	-	-	-
Nausea	None	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnourishment	Inadequate oral calorie or fluid intake; tube feeding, total parenteral nutrition, hospitalisation indicated	-	-
Vomiting	None	1 - 2 episodes / 24 hrs.	3 - 5 episodes / 24 hrs.	> 6 episodes / 24 hrs.; tube feeding, total parenteral nutrition, hospitalisation indicated	Life threatening consequences, urgent intervention required	Death
Fatigue	None	Fatigue relieved by rest	Fatigue not relieved by rest, limiting activities of daily life	Fatigue not relieved by rest, limiting activities of daily life as well as self-care	-	-
Leucopenia	Within normal range	Lower normal limit - 3000 / ml	3000 - 2000 / ml	2000 - 1000 / ml	< 1000 / ml	-
Thrombocytopenia	Within normal range	Lower normal limit - 75000 / ml	75000 - 50000 / ml	50000 - 25000 / ml	< 25000 / ml	-

Table 1. Common Terminology Criteria for Adverse Events (CTCAE) Version 4 Grading System¹⁵

RESULTS

Fifty female patients of carcinoma breast who received chemotherapy with either one of four regimens with mean age of patients at presentation being 50.9 years (mostly in range of 41 – 50 years) were studied for prevalence and severity of chemotoxicities.

Chemotoxicity	Prevalence (with Trend)	Trend of Severity
Nail changes	48 % (no rising or decreasing trend)	Increasing (statistically non-significant trend)
Hair loss	98 % (Increasing trend)	Increasing (statistically significant trend)
Nausea	100 % (decreasing trend)	Decreasing (statistically significant trend)
Vomiting	54 % (decreasing trend)	Decreasing (statistically significant trend)
Weight gain	24 %	Neither increasing nor decreasing significant trend
Weight loss	76 %	Neither increasing nor decreasing significant trend
Reduction in appetite	76 %	Neither increasing nor decreasing significant trend
Fatigue	100 % (increasing trend)	Increasing (statistically significant trend)
Leucopenia	32 % (increasing trend)	Increasing (statistically significant trend)
Thrombocytopenia	30 % (increasing trend)	Increasing (statistically non-significant trend)

Table 2. Results for Chemotoxicities in the Indexed Study

Chemotoxicity	Nail Changes (percentage in bracket)	Hair Loss (percentage in bracket)	Vomiting (percentage in bracket)	Fatigue (percentage in bracket)	
1 st Cycle	Grade 0	24 (48 %)	26 (52 %)	23 (46 %)	5 (10 %)
	Grade 1	26 (52 %)	24 (48 %)	24 (48 %)	45 (90 %)
	Grade 2	-	00	3 (6 %)	00
	Total	50 (100 %)	50 (100 %)	50 (100 %)	50 (100 %)
3 rd Cycle	Grade 0	24 (48 %)	1 (2 %)	40 (80 %)	1 (2 %)
	Grade 1	26 (52 %)	37 (74 %)	10 (20 %)	34 (68 %)
	Grade 2	-	12 (24 %)	00	15 (30 %)
	Total	50 (100 %)	50 (100 %)	50 (100 %)	50 (100 %)
P value	0.841	< 0.0001	0.001	0.0001	
6 th Cycle	Grade 0	24 (48 %)	1 (2 %)	47 (94 %)	00
	Grade 1	26 (52 %)	27 (54 %)	3 (6 %)	30 (60 %)
	Grade 2	-	22 (44 %)	00	20 (40 %)
	Total	50 (100 %)	50 (100 %)	50 (100 %)	50 (100 %)
P value	0.841	< 0.0001	< 0.0001	< 0.0001	

Table 3. Prevalence of Nail Changes, Hair Loss, Vomiting & Fatigue

Chemotoxicity	Nausea (percentage in bracket)	Leucopenia (percentage in bracket)	Thrombocytopenia (percentage in bracket)	
1 st Cycle	Grade 0	00	49 (98 %)	44 (88 %)
	Grade 1	30 (60 %)	00	3 (6 %)
	Grade 2	17 (34 %)	1 (2 %)	1 (2 %)
	Grade 3	3 (6 %)	00	2 (4 %)
	Total	50 (100 %)	50 (100 %)	50 (100 %)
3 rd Cycle	Grade 0	26 (52 %)	39 (78 %)	46 (92 %)
	Grade 1	22 (44 %)	8 (16 %)	4 (8 %)
	Grade 2	2 (4 %)	3 (6 %)	00
	Grade 3	00	00	00
	Total	50 (100 %)	50 (100 %)	50 (100 %)
P value	< 0.0001	0.006	0.364	
6 th Cycle	Grade 0	37 (74 %)	41 (82 %)	45 (90 %)
	Grade 1	13 (26 %)	3 (6 %)	4 (8 %)
	Grade 2	00	4 (8 %)	1 (2 %)
	Grade 3	00	2 (4 %)	00
	Total	50 (100 %)	50 (100 %)	50 (100 %)
P value	< 0.0001	0.057	0.541	

Table 4. Prevalence of Nausea, Leucopenia & Thrombocytopenia

Chemotoxicity	Weight Changes (percentage in bracket)	Appetite Changes (percentage in bracket)	
1 st Cycle	Increased	12 (24 %)	-
	Decreased	38 (76 %)	38 (76 %)
	No change	-	12 (24 %)
	Total	50 (100 %)	50 (100 %)
3 rd Cycle	Increased	12 (24 %)	-
	Decreased	38 (76 %)	38 (76 %)
	No change	-	12 (24 %)
	Total	50 (100 %)	50 (100 %)
P value	0.815	0.815	
6 th Cycle	Increased	12 (24 %)	-
	Decreased	38 (76 %)	38 (76 %)
	No change	-	12 (24 %)
	Total	50 (100 %)	50 (100 %)
P value	0.815	0.815	

Table 5. Prevalence of Weight & Appetite Changes

Results of the study are given in Table 2, 3, 4 & 5. Total of 32 % patients had leucopenia, single or multiple times during chemotherapy. Amongst 16 patients, leucopenia was observed 21 times during chemotherapy with statistically significant trend in increasing severity when compared between 1st & 3rd cycle; but the trend of severity was statistically insignificant between 3rd & 6th cycle.

Total 30 % patients had thrombocytopenia, single or multiple times during chemotherapy. Amongst 15 patients there was 22 times of occurrences of thrombocytopenia with statistically insignificant trend.

In this study apart from 80 % prevalence of nail changes amongst study population who received cyclophosphamide (AC) with paclitaxel group, no other finding was statistically significant proving one specific regimen superior or inferior to others with respect to chemotoxicity.

In this study there was minimal prevalence of severe grades of chemotoxicity with no life-threatening event.

DISCUSSION

The treatment modalities for carcinoma breast take heavy toll on the overall health of the patient; physically, socially or mentally. Especially chemotherapy. With all the cytotoxic drugs used, prevalence of side effects of chemotherapy is also significant as is their therapeutic potential.

Nail Changes

Several of the drugs from class of anthracyclines & taxanes are known to cause toxic changes in nails namely drug induced nail pigmentation (DHNP) most frequent of them; onycholysis, paronychia, subungual or periungual erythema, etc. (Table 2, 3) In this study patients with AC & paclitaxel combination had more prevalence (80 %) of nail changes than other regimens, but the regimen was a combination of two different drugs anthracycline & taxane, both of which are known to cause nail changes & were used in combination with each other in this regimen. So, exact analysis & conclusion could not be drawn for sub regimen that was more toxic. Can G et al. 2012,¹⁶ in their study had 50.5 % of prevalence with increasing trend in severity which was a consistent finding with this study. While

in a study Yorulmaz et al. 2016,¹¹ concluded a prevalence of 34.1 % which was an inconsistent finding with this study, but they also concluded that no specific regimen was more toxic in terms of nail changes which was consistent with this study. In this study, along with nail pigmentation, tongue pigmentation was also noted in one patient.

Hair Loss

Hair loss is a toxicity of chemotherapy drugs that has a high impact on the psychological well-being of the patient.¹⁷ In this study only one patient from AC regimen did not have hair loss. (Table 2, 3) In their study, Partridge et al. 2001,⁹ found more than 95 % of prevalence of alopecia which was a consistent finding with indexed study.

In another interventional study, Kinoshita et al. 2019,¹⁸ compared prevalence of alopecia in patients undertaking chemotherapy using scalp cooling device and in a control group without such device. It had resulted in 100 % prevalence amongst patients in control group which is a consistent finding with this study.

In this study 4 % of patients also reported of having loss of eyelashes (madarosis) which is a known toxicity of chemotherapy.¹⁹

Nausea

Out of the 100 %, only 6 % of patients experienced grade 3 nausea, those 3 patients hailed from 3 different regimens AC with paclitaxel, AC regimen & 5-fluorouracil (CAF) regimen each. (Table 2, 4)

There was statistically significant decreasing trend of severity which was consistent with Montemurro et al. 2015,¹³ but inconsistent with Hayashi et al. 2019,²⁰ & Buzdar et al. 1999,¹² which showed less prevalence of nausea of 46.66 % than indexed study and CAF regimen being more toxic than others respectively as compared to indexed study where no particular regimen was more toxic. Increased prevalence can be attributed to nausea being subjective and psychological feeling of being unwell which may vary in different study population.

Vomiting

(Table 2, 3) Montemurro et al. 2015,¹³ showed there was statistically significant decreasing trend of severity which was consistent with this study. While Hayashi et al. 2019,²⁰ & Buzdar et al. 1999,¹² showed less prevalence of just 15 % and CAF regimen being more toxic respectively which were inconsistent findings with this study.

Weight Changes

The causes of weight gain in a patient of carcinoma breast undergoing chemotherapy are given as fat accumulation & alteration in the deposition of body fat that results due to hormonal changes as result of amenorrhoea secondary to chemotherapy drugs.²¹ (Table 2, 5)

This study had results of more patients experiencing weight loss than weight gain. Which are inconsistent findings

with studies of Lankester et al. 2001,²² & Demark-Wahnerfried et al. 2001,²³ which showed 64 % patients gaining weight compared to 5 % experiencing weight loss and a median weight gain of 2.1 kg respectively for both studies. This can be attributed to the fact that most of the patients included in our study group belonged to lower economic strata which meant apathy towards general health on patient's part as well as economic, social, psychological problems affecting the diet of the patient.

Demark-Wahnerfried et al. 2001,²³ showed increase in the weight of the study population attributing to sarcopenic obesity which is weight gain in the presence of lean tissue loss or absence of lean tissue gain.

Appetite Changes

(Table 2, 5) Montemurro et al. 2015,¹³ in their study showed 54 % subjects experiencing reduced appetite, inconsistent with this study having more prevalence of the same. More prevalence can be resulted because of poor patient tolerance to chemotherapy drugs due to multiple factors like increased nausea, vomiting, reduced mental health status, increased fatigue, anaemia, neutropenia resulting in reduced overall health status of the patient which resulted in reduced appetite of the study population.

Fatigue

Findings of 100 % prevalence of varying grades with significantly increasing trend of severity of fatigue was consistent with similar results of Broeckel et al. 1998.¹⁰ (Table 2, 3).

Leucopenia

(Table 2, 4) Findings of this study was inconsistent with studies done by Partridge et al. 2001,⁹ & Buzdar et al. 1999,¹² with both studies having more prevalence (51 - 95 % & 42.5 % respectively) as well as Buzdar et al. 1999,¹² having more subjects with higher grades of leucopenia with paclitaxel being more toxic than CAF regimen.

Thrombocytopenia

Amongst 30 % (15 out of 50) patients of this study there was 22 times occurrences of thrombocytopenia with statistically insignificant trend. (Table 2, 4) which was inconsistent with the study of Partridge et al. 2001,⁹ showing prevalence of 6 - 20 % for AC regimen; 21 - 50 % for CAF regimen.

The results of the study were compared with other studies. Partridge et al. 2001,⁹ did a meta-analysis over the prevalence of short term as well as long term chemotoxicities in patients of carcinoma breast who received any form of chemotherapy with different regimens including cyclophosphamide, methotrexate, and 5-fluorouracil (CMF); doxorubicin and cyclophosphamide (AC); cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF); 5-fluorouracil, epirubicin, and cyclophosphamide (FEC); methotrexate and 5-fluorouracil

(MF) and the results were frequent prevalence (51 - 95 %) for nausea and neutropenia, common prevalence (21 - 50 %) for vomiting, uncommon prevalence (6 - 20 %) for thrombocytopenia, almost always prevalence (> 95 %) for alopecia and almost no prevalence (< 1 %) for neuropathy for AC regimen; whereas always prevalence (> 95 %) for alopecia, frequent prevalence (51 - 95 %) for neutropenia, thrombocytopenia, common prevalence (21 - 50 %) for vomiting and nausea, uncommon prevalence (6 - 20 %) for neuropathy for CAF regimen. Broeckel et al. 1998,¹⁰ compared prevalence of fatigue between a group of women who received adjuvant chemotherapy and a control group of healthy women. And the results were average level of fatigue experienced by women previously treated with adjuvant chemotherapy was approximately 50 % greater than that reported by a comparison group of women with no history of cancer. Additional findings suggested that these differences were clinically as well as statistically significant. Yorulmaz et al. 2016,¹¹ studied prevalence of nail changes in patients receiving adriamycin & paclitaxel. 34.1 % of the patients demonstrated clinical signs of nail pigmentation.

Nail pigmentation was observed in 30.8 % of patients, who had received doxorubicin; in 35.7 % of patients, who had received taxanes (docetaxel and paclitaxel). There was no statistically significant relationship between the nail pigmentation and the type of the chemotherapeutic regimen administered, Buzdar et al. 1999¹² compared side effects between paclitaxel & CAF. The observations were 21 % prevalence of grade 3 nausea in CAF with 10 % in paclitaxel group; 7 % grade 3 vomiting in CAF to 2 % in paclitaxel; 16 % grade 3 stomatitis in CAF to 13 % in paclitaxel; 9 % paraesthesia in CAF to 51 % in paclitaxel; 21 % prevalence of neutropenia in CAF to 53 % in paclitaxel.

Montemurro et al. 2015,¹³ conducted a study in Italy on 604 patients irrespective of the regimen receiving chemotherapy for carcinoma breast in 11 centres. They tabulated the observations for prevalence & severity of nausea during chemotherapy as per CTCAE grading version 4. They concluded that there was decreasing trend in prevalence as well as severity of nausea and vomiting in the patients while 54 % prevalence with no trend in either increase or decrease in severity for appetite; there was 77 % of prevalence of fatigue in the study population with no significant increase in severity along the course of chemotherapy. Very few similar studies were conducted in India where patients have different physical, mental, social & cultural characteristics that affect the response & outcomes of treatment differently and many patients still end up as defaulters as chemotoxicities affect their quality of life seriously.

CONCLUSIONS

Different chemotoxicities have different prevalence, peaking at different times during the course of chemotherapy with different trends of severity which will help the medical practitioners and the patients to watch out for the probable causes leading to defaulters at different times during the

course and thereby formulating guidelines regarding the prevention of the same.

Limitations

Long term chemotoxicity parameters could not be observed adequately due to time constraint.

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

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