DOI: 10.22270/jmpas.V10I6.2464 ISSN NO. 2320–7418

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Research article

A retrospective observational study of comparison of hematological parameters along with the effect of chemotherapy and radiotherapy in different stages of breast cancer

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ABSTRACT

Breast cancer is one of the top leading causes of death and most common malignancies among women all over the world. Chemotherapy and radiotherapy are the predominant treatment measures of cancer along with surgery. The current study aims to compare the hematological parameters in patients undergoing chemotherapy and radiotherapy in different stages of breast cancer. A decline in hematological parameters is most commonly seen trend in patients undergoing these treatments, which adversely influences the outcome of cancers. The study also evaluates the prevalence of thrombocytopenia, neutropenia and anemia in patients who received radiotherapy, chemotherapy and concurrent therapy. A total of 103 female breast cancer cases were collected in which 23 patients received radiotherapy, 44 patients received chemotherapy and 36 patients received concurrent therapy. The hematological parameters were found to be declined at different stages of cancer. The patients also showed decline in blood counts at each treatment, but all the parameters were declined in patients undergone concurrent therapy. Thus, this study helps to evaluate the requirement of complete blood count investigation before and during the therapy in order to assist the dosage adjustment and dietary modifications to minimize the risk of therapy related fatigue and infections and thus improving the efficacy of treatment outcome and health related quality of life of patients.

Keywords: Adriamycin, Chemotherapy, Cyclophosphamide, Hematological parameters, Radiotherapy.

Received – 24/11/2021, Reviewed - 08/12/2021, Revised/ Accepted- 26/12/2021

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INTRODUCTION

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. The second leading cause of death on the planet is cancer. Every year, one in every six people dies in cancer. The five most common dietary and behavioral hazards account for around one-third of cancer fatalities. Late-stage presentation along with inaccessible diagnosis and treatment are common.

Breast cancer is the cancer that forms in the tissues of breast, usually the ducts (tubes that carry milk)and lobules (glands that produce milk).Ductal carcinoma in situ (DCIS) also called intra ductal carcinoma is the clonal proliferation of malignant – appearing cells with mammary duct lumens without evidence of invasion beyond the epithelial basement membrane. It is the precursor lesion of breast cancer[1].DCIS represents 20 – 25% of all breast cancers upon the detection by screening programs[2].Breast cancer is one of the most frequent and deadly cancers affecting women around the world. For the year 2020, the estimated number of cancer patients in India among females is 712,758 (103.6 per 100,000). Breast cancer affects one out of every 29 women in their lifetime (0-74 years of age) [3].Local and systemic therapy are used in the treatment of breast cancer. Surgery and radiotherapy are examples of local treatment. Chemotherapy and hormonal therapy are examples of systemic treatments radiotherapy include EBRT (External Beam Radiation Therapy) and brachytherapy. Concurrent chemo-radiation (CCRT) is defined as the chemotherapy administered on the same day as radiotherapy.

Chemotherapy is most effective systemic therapy that kills cells that are rapidly dividing. AC regimen is a combination of 2 drugs, Doxorubicin (Adriamycin) and Cyclophosphamide. The regimen is used to treat primary breast cancer. It can be given as both adjuvant and neoadjuvant therapy. Various neutropenic complications develop during chemotherapy with Adriamycin for patients on FAC regimen with metastatic breast cancer [4].

Due to the synergistic effect of radiotherapy along with chemotherapy, it has been used before, during and after chemotherapy as an adjuvant in susceptible cancers. Radiation therapy is commonly applied to the cancerous tumor because of its ability to control cell

growth. The most common type of radiation therapy for women with breast cancer include EBRT including 3D conformal radiation therapy and intensity modulated radiotherapy and brachytherapy. Adjuvant radiation is the treatment of choice for ductal as well as invasive carcinoma after mastectomy [5].

Complete blood count is the most pre-requisite investigation. It is requested from all cancer patients before the initiation of surgery, chemotherapy and radiotherapy [6]. Any kind of abnormalities has a direct impact on blood parameters. So, it is necessary to review the changes in hematological parameters in breast cancer patients, at regular intervals during treatment of chemotherapy and radiotherapy. Normally, blood cells are placed among the foremost rapidly dividing cells within the body and therefore are most sensitive to chemotherapy and radiotherapy. Abnormal parameters adversely influence the outcome of cancers. The improvement in the life expectancy of women with breast cancer raises questions on how to improve the quality of life for women sustaining complications of breast cancer treatment [7,8].Therefore, hematological parameters and markers of the systemic inflammatory response are the key predictors of disease severity and mortality risk in several malignancies.

Thrombocytopenia is a term used to indicate a remarkable reduction or drop in platelet counts. Chemotherapy induced bone marrow damage results in thrombocytopenia and anemia that threaten the patient's life quality and the overall effectiveness of anticancer treatments[9].About 10-25% of solid cancer patients (i.e. breast cancer, ovarian) that have been treated with intensive chemotherapy, suffer from incidence of thrombocytopenia. During radiotherapy, gamma irradiation induces alterations on RBCs different functional units in membrane such as lipid bilayer, protein and cytoskeleton[10].Moreover, radiation induces lipid peroxidation of fatty acids[11].The production of peroxides and cross-linkages in the membrane can disorder the upper region of the bilayer favor the diffusion of water and finally it causes hemolysis of cells[12]. Chemotherapy and radiotherapy may cause decrease in RBCs count and hemoglobin levels of cancer patients[13].The erythroblasts and megakaryocytes survival, production, and differentiation are coordinated by combinations of cytokines and mediators present within specific bone marrow niches[14,15].

MATERIAL AND METHOD

A103 cases of female breast cancer were randomized in this study in which 44 patients received chemotherapy, 23 received radiotherapy, 36 patients received concurrent therapy. Complete blood count investigation chart was reviewed for the values of haematological parameters and assessed.

Source of data: Patient case report form

Study location: Erode Cancer Centre, Tamilnadu, India

Duration of study 6 Months (February2020-July2020)

Type of study Retrospective observational study

Study Population: 103 cases of female breast cancer patients based on study criteria.

Inclusion criteria

- Female patient age between 25 years to 65 years.
- Patients who have received radiation therapy, histologically confirmed and diagnosed with breast cancer.
- Patients receiving chemotherapy Cyclophosphamide & Adriamycin (AC regimen) confirmed with breast cancer.
- All patients with operable breast lumps.
- Recurrent breast lump raised in a previously operated case of carcinoma breast.
- ECOG performance status.

Exclusion criteria

- Pregnant women.
- Patients with benign breast disease.
- Patients with bleeding disorders /gastric bleeding, local tumour invasion bleeding.
- Patients receiving folic acid supplements, filgrastim, entomophagy etc.
- Patient who has history of cancer other than breast cancer.
- Patient with ongoing or active infections

Statistical analysis

Haematological parameters were analysed. Statistical analysis was performed using SPSS (IBM SPSS statistics version 23). Continuous data were presented as mean ± SD. Comparative analysis was performed with randomised one-way ANNOVA. A p value ≤ 0.05 was considered statistically significant.

RESULT AND DISCUSSION

Breast cancer is one of the most common causes of cancer-related mortality in females, and it is a significant cause of death worldwide. The majority of people with breast cancer respond to standard treatments such as tumor excision, medication treatment, and radiation. However, each therapy contains flaws that contribute to therapeutic resistance and illness recurrence, and eventually therapeutic failure. When the condition recurs, it quickly spreads to other organs and ultimately death.

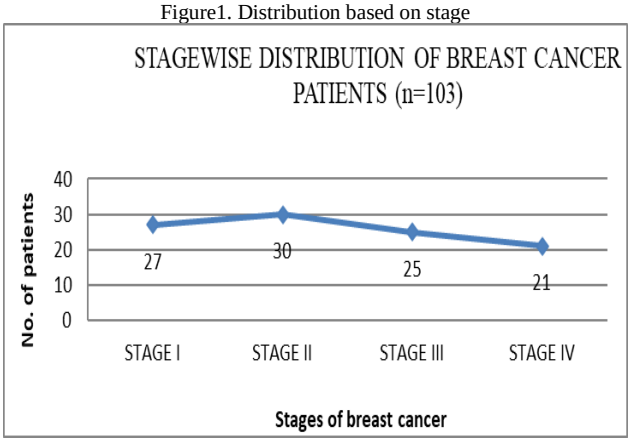
Table1. Age wise distribution of patients with breast cancer

Age group (years)	No. of patients (n=103)	Percentage (%)
25-35	18	17.40
36-45	23	22.30
46-55	28	27.10
56-65	34	33.00

In our study, out of 103 study subjects, the incidence of breast cancer was found to be higher among the age group of 56-65 years(33.00%), followed by the age group 46-55 years (27.10%), 36-45 years (22.30%), 25-35 years (17.40%).A comparable study was done by Haleema Sadia *et al* in 2019 which concludes that age wise distribution of breast cancer patients was higher between 46-55 years(46.66%)[16].From this we conclude that the breast cancer mainly

occurs in between age group of 56-65 years(33%) as shown in Table.1.

Figure1. Distribution based on stage



Our study was conducted based on Tumor Node Metastasis (TNM) staging and among the study population of 103 the incidence of breast cancer was found to be higher in Stage 2 (29.10%), followed by Stage 1(26.20%), Stage 3(24.20%), Stage 4(20.50%). From this we conclude that most of the patients were diagnosed at Stage 2 and the incidence were lower at Stage 4 as shown in Figure.1.

Among the study population, 39 patients were at grade 2, 35 patients at grade 3 and 30 patients at grade 1, which coincide with the study conducted by Haleema Sadia*et al* (2019) revealed that prevalence of grade III tumors was quite common (33.90%)[16]. From the above data, we conclude that the incidence of breast cancer was higher at grade 2(37.80%) followed by grade 3(33.90%) and grade 1(29.10%) as shown in Table.2.

Table.2.Distribution of patients based upon the grades of breast cancer

Grading of breast cancer	No. of patients (n=103)	Percentage (%)
I	30	29.10
II	39	37.80
III	34	33.90

Based on menstrual history, the study population can be distributed as pre- and post-menopausal groups. Out of 103 patients 62(60.10%) developed post-menopausal breast cancer and 41 (39.80%) developed pre-menopausal breast cancer which coincide with the study conducted by Aruna Surakasula in (2013) concludes that among them, the incidence of breast cancer was higher within post-menopausal women [17].Menopause does not cause cancer, but the risk of developing cancer increases as a women age due to hormonal factors. Therefore, we can conclude that women who have been through natural menopause are more likely to develop cancer as shown in Table.3.

Table.3.Distribution of pre- and post-menopausal breast cancer

Menstrual history	No. of patients (n=103)	Percentage (%)
Pre-menopausal	41	39.80
Post-menopausal	62	60.10

In our study group, the hematological parameters were found to be declining with Stage. The Hb values were higher in Stage 1(10.05), followed by Stage 2(9.60), Stage 3(9.40) and Stage 4 (9.25). Total leukocyte counts were higher in Stage 2 (5.55) followed by Stage 1 (5.25), Stage 3 (4.96) and Stage 4(4.57). PMN counts were higher in Stage 1 (45.20), followed by Stage 3 (44.48), Stage 2 (43.90) and Stage 4(43.20). Lymphocyte counts were found to be 27.5 at Stage 2, followed by Stage 1(24.87), Stage 3(22.80) and Stage 4(21.50). Monocyte counts were higher at Stage 3 (3.04) followed by Stage 1(2.90), Stage 2(2.70) and Stage 4(2.44).Eosinophil counts were higher at Stage 1(2.90),followed by Stage 1(2.73),Stage 4 (2.60) and Stage 2(2.40).Basophil counts were higher at Stage 1(0.16) followed by Stage 4(0.06), Stage 2(0.00) and Stage 3(0.00). RBC counts were found to be higher at Stage 2(3.70)followed by Stage 3 (3.67), Stage 1(3.45) and Stage 4(3.20). Platelet count were higher at Stage 3(1.59), followed by Stage 4(1.56) Stage 1(1.50) and Stage 2(1.48).A comparable study was conducted by Srivastava *et al* in 2016,which concludes that Hb level gradually decreases with stages while other parameters were also deranged but not specific trend observed[18]. Stage-specific mean values of lymphocytic counts of breast cancer can be employed as a useful guide to assess the progression of disease. The above findings in our study suggest that hematological parameters were declining with respect to stages of the breast cancer as shown in Table.4.

Table.4. Comparative mean of hematological parameters in different stages of breast cancer

Hb (g/dl	TLC X109/L	PMN %	LYM %	MON %	EOS %	BAS %	RBC X1012/L	PLT X109 /L
10.05	5.25	45.20	24.87	2.90	2.73	0.16	3.45	1.50
9.60	5.55	43.90	27.50	2.70	2.40	0.00	3.70	1.48
9.40	4.96	44.48	22.80	3.04	2.90	0.00	3.67	1.59
9.25	4.57	43.20	21.50	2.44	2.60	0.06	3.20	1.56

Analyzing the stage wise distribution of breast cancer patients underwent chemotherapy, radiotherapy and concurrent therapy, the following results can be drawn: In stage 1, out of 27 patients,9 received chemotherapy (33.33%),13 received radiotherapy (48.15%) and 5 underwent concurrent therapy (18.52%) as shown in Table.5.

Table.5. Stage I Distribution of breast cancer patients undergone chemotherapy, radiotherapy, and concurrent therapy

Therapy	No. of patients (n=27)	Percentage (%)
Chemo	9	33.33
Radio	13	48.15
Concurrent	5	18.52

In Stage 2, out of 30 patients,11 received chemotherapy (36.66%),10 received radiotherapy (33.33%) and 9 received concurrent therapy (30.01%) as shown in Table.6.

Table 6. Stage II Distribution of breast cancer patient's undergone chemotherapy, radiotherapy, and concurrent therapy

Therapy	No. of patients (n=30)	Percentage (%)
Chemo	11	36.66
Radio	10	33.33
Concurrent	9	30.01

In Stage 3, out of 25 patients,10 received chemotherapy (40.00%),7 received radiotherapy (28.00%) and 9 received concurrent therapy (32.00%) as shown in Table.7.

Table.7.Stage III Distribution of breast cancer patient's undergone chemotherapy, radiotherapy, and concurrent therapy

Therapy	No. of patients (n=25)	Percentage (%)
Chemo	10	40.00
Radio	7	28.00
Concurrent	8	32.00

In Stage 4, out of 21 patients, 6 received chemotherapy (28.58%), 7 received radiotherapy (33.33%) and 8 underwent concurrent therapy (38.09%) as shown in Table.8.

Table.8. Stage IV distribution of breast cancer patients undergone chemotherapy, radiotherapy, and concurrent therapy

Therapy	No. of patients (n=21)	Percentage (%)
Chemo	6	28.58
Radio	7	33.33
Concurrent	8	38.09

From this we can conclude that radiotherapy is preferred in initial stage (Stage1), concurrent therapy in stages 2 and 3, chemotherapy is preferred in stage 4. Among the study population 103 patients were selected according to inclusion and exclusion criteria, in which 44 patients underwent chemotherapy (42.71%),23 patients underwent radiotherapy (22.33%) and 36 patients received concurrent therapy (34.96%) as shown in Table.9.

Table.9. Distribution of breast cancer patients undergone chemotherapy, radiotherapy, and concurrent therapy

Therapy undergone	No. of patients (n=103)	Percentage (%)
Chemo	44	42.71
Radio	23	22.33
CO	36	34.96

In our study, 23 subjects who underwent radiotherapy showed a significant decline in certain hematological parameters such as Hb, RBC and PMNs.The mean values of Hb, RBC and PMNs are 9.63, 3.30 and 44.90 respectively. The study conducted by Swati Srivastava*et al* in 2016 can be compared with our study which concludes that during radiotherapy, gamma irradiation induces alterations on RBCs different functional units in the membrane such as lipid bilayer, protein and cytoskeleton[18]. Radiation also induces lipid peroxidation of fatty acids. The production of peroxides and cross-linkages in the membrane can disorder the upper region of the bilayer that favor the diffusion of water and finally causes hemolysis of cells. From this, we can conclude that Hb, RBC and PMN values are decreased during radiotherapy as shown in Table.10.

Table.10.Effect of radiotherapy on comparative mean of hematological parameters in breast cancer patients

CBC	Hb g/dl	TLC $X10^9$/L	PMN %	LYM %	MON %	EOS %	BAS %	RBC $X10^{12}$ /L	PLT $X10^9$/ L
Mean	9.63	5.16	44.9	27.39	3.07	3.00	0.10	3.30	1.51

The 44 patients who underwent chemotherapy (AC regimen), showed a significant decline in Hb, RBC, PMNs, lymphocytes and platelets. The mean values of Hb, RBC, PMNs, lymphocytes and PLTs are 9.83, 3.63, 42.20, 26.50 and 1.30 respectively. Similar study was conducted by Swati Srivastava*et al.* in 2016 chemotherapy induced bone marrow damage results in thrombocytopenia and anemia that threaten the patient's life quality and the overall effectiveness of anticancer treatments[18]. Deranged WBC counts shows the increased susceptibility to infections. From this we concluded that Hb, RBC, PMNs, lymphocytes and PLTs are decreased during chemotherapy as shown in Table.11.

The patients who underwent concurrent therapy (n=36) showed a significant decline in all the parameters such as Hb, TLC, PMNs, lymphocytes, monocytes, eosinophils, basophils, RBCs and PLTs. The mean values of Hb, TLC, PMNs, lymphocytes, monocytes, eosinophils, basophils, RBCs and PLTs are 9.40, 4.20, 42.80, 24.90, 2.80, 2.60, 0.00, 3.16 and 1.20 respectively.

Table.11. Effect of chemotherapy (AC regimen) on comparative mean of hematological parameters in breast cancer patients

CBC	Hb g/dl	TLC $X10^9$/ L	PMN %	LYM %	MON %	EOS %	BAS %	RBC $X10^{12}$ /L	PLT $X10^9$/ L
MEAN	9.83	4.85	42.20	26.50	3.61	2.72	0.00	3.63	1.30

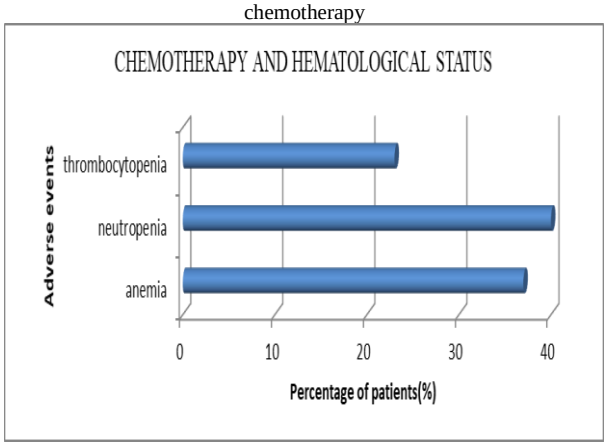
Similar study was study conducted. that showed that the patients who were on radio-chemotherapy (both) had decreased mean values in all parameters as compared to individual therapies[18]. From this we concluded that Hb, TLC, PMNs, lymphocytes, monocytes, eosinophils, basophils, RBCs and PLTs were decreased during concurrent therapy as shown in Table.12.

Table.12. Effect of concurrent radiotherapy and chemotherapy on comparative mean of hematological parameters in breast cancer patients

CBC	Hb g/dl	TLC X109 /L	PMN %	LYM %	MON %	EOS %	BAS %	RBC X101 2/L	PLT X109 /L
MEAN	9.40	4.23	42.8	24.90	2.80	2.60	0.00	3.16	1.20

In the current study, the patients who received chemotherapy (n=44) were found to have anemia (36.38%), neutropenia (40.92%) and thrombocytopenia (22.70%). A study conducted by Fisher B, *et al.* in 1990 revealed that the incidence of neutropenia is higher compared to anemia and thrombocytopenia as shown in Figure.2

Figure 2. Percentage of patients experienced adverse events during chemotherapy



The patients who received radiotherapy(n=23) were found to have anemia (65.21%) and neutropenia (34.79%). A similar study conducted by Fisher B, *et al.* in 1990 showed that anemia is frequent in cancer patients and its incidence increases with chemotherapy[19]. Also, it negatively affects the survival and accentuates fatigue in cancer patients. Thrombocytopenia is not observed as an adverse effect during radiotherapy. From this we can conclude that the incidence of anemia is higher compared to neutropenia and thrombocytopenia is not observed as shown in Figure.3.

The patients who received concurrent therapy (n=36) were found to have anemia (52.78%), neutropenia (30.56%) and thrombocytopenia (16.66%). showed a significant decrease in all the hematological parameters [19]. The above findings suggest that the

concurrent therapy results in pancytopenia in breast cancer patients as shown in Figure.4.

Figure 3. Percentage of patients experienced adverse events during radiotherapy

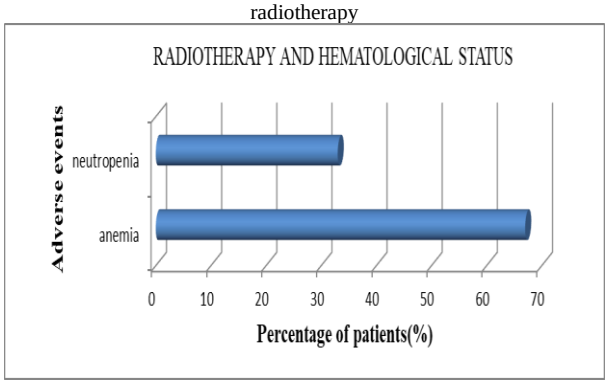
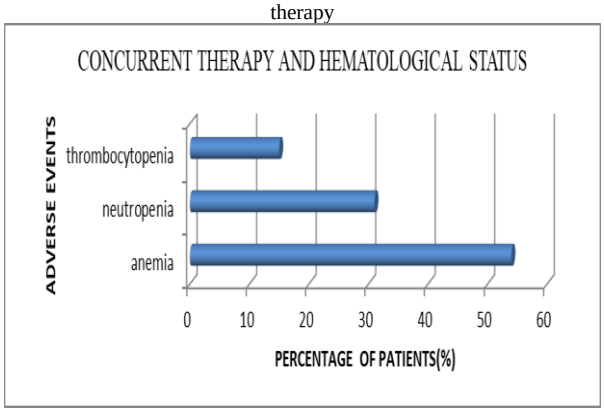


Figure.4. Percentage of patients experienced adverse events during concurrent therapy



CONCLUSION

Breast cancer is one of the most common and top leading causes of cancer death among women worldwide. The management of breast cancer includes local (radiotherapy) and systemic therapy (chemotherapy). Complete blood count is a prerequisite investigation requested from all cancer patients before surgery, use of chemotherapy and radiotherapy. Hematological parameters are usually deranged during chemotherapy and radiotherapy. Poor parameters adversely influence the outcome of cancers and are correlated with the prognosis of several malignancies. From the present study, we conclude that the hematological parameters were deranged at different stages of breast cancer. Further observation after receiving respective treatment regimens, showed a significant decline in hematological parameters, which may adversely influence the outcome. We observed anemia, neutropenia and thrombocytopenia in breast cancer patients. The data also indicated that patients who were on concurrent (radio and chemo) therapy have more deranged and decreased levels of hematological parameters as an adverse effect of treatment. Hematological investigations play a significant role in treatment and follow up of breast cancer patients. It can also help in the assessment of disease progression and the behavior of different malignancies. Therefore, we suggest regular monitoring of hematological parameters every two weeks prior to each treatment cycle. We recommend the active involvement of clinical pharmacist at the time of intending in order to tailor the dosage regimen. Subsequent cycles should be delayed until the ANC is greater than 1000/microL. If there is more than a 3-week delay in the treatment, a dose reduction of 25% of doxorubicin is recommended. Clinical pharmacists can also involve in identifying radiation related toxicities in cancer patients. The team work of clinical pharmacists along with the radiation oncologists can improve the radiation safety reporting and can ensure required medical and supportive care to manage RRAEs.

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How to cite this article

T Kumutha, Ruthmol Baby, N Shabana Parveen, Subin Biju, Anjala Sunny, K Velavan, 2021. A retrospective observational study of comparison of hematological parameters along with the effect of chemotherapy and radiotherapy in different stages of breast cancer. J. Med. P'ceutical Allied. Sci. V 10 - I 6, 2464, P- 4066 - 4071. doi: 10.22270/jmpas.V10I6.2464