FREQUENCY OF NEUTROPENIA IN ADRIAMYCIN BASED NEO ADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER.

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ABSTRACT

Background: Breast cancer is the leading cause of cancer death in women worldwide. **Objective:** To determine the Adriamycin-based Neoadjuvant Chemotherapy, Neutropenia Incidence in Locally Advanced Breast Cancer**. Methods:** This descriptive case series research was performed at the Karachi Institute of Radiotherapy & Nuclear Medicine Karachi Department of Clinical Oncology from 16-11-2017 to 16-05-2018. Non probability consecutive sampling was applied. Inclusion criteria were biopsy proven locally advanced breast carcinoma stage II/III, ECOG performance status 0 and 1,no prior specific treatment, age between 20 to 70 years with normal cardiac, renal and liver functions and adequate bone marrow reserves. Exclusion criteria were any treatment chemotherapy, radiotherapy, or surgery prior to presentation,.had neutropenia prior to the start of chemotherapy. Neutropenia grading were performed on basis of common terminology criteria for adverse events.The data were analysedon software SPSS version 21.0. **Results:** Ninety six patients were enrolled. The mean age of our sample cases was 52.43 ± 10.08 years with a minimum age of 30 years. While maximum age was noted to be 69 years. The mean period of the disease was 10.49 ± 4.98 months and the minimum duration of the disease was 6 months and 24 months was the maximum duration of the disease. Mean neutrophil count was noted to be 1589.58 ± 350.21/$mm^3$with minimum neutrophil counts was 1100 while maximum neutrophil count was 2500/mm^3). Neutropenia was noted in 51 (53.1%) of our study cases.Among these 51 who developed neutropenia, 22 (43.13 %) developed after first cycle of chemotherapy, 12 (23.52%) developed after 2nd cycle, 9 (17.64%) after 3rd cycle, 4 (7.84%) after 4th cycle and 4 (7.84%) after 5th cycle of chemotherapy (p=0.000). **Conclusion**: Neutropenia should be tested at an early stage in patients receiving neoadjuvant therapy with Adriamycin, which plays an important role in the treatment modalities of these patients, thereby enhancing the quality of care of these patients and reducing the frequency of hospitalization due to neutropenia.

Key words: Neutropenia, Breast carcinoma, Filgristism, Neo Adjuvant.

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INTRODUCTION

With reported new cases of 232,340 patients and deaths of 39,620 patients in the United States in 2013, breast cancer is the leading cause of cancer death in women worldwide. Nearly half of breast cancer cases and 60 percent of deaths are estimated to occur in economically developed countries. [2, 3] Pakistan has the largest rate of breast cancer among the Asian population. At some point in their lives, approximately one of every nine Pakistani women will suffer from breast cancer, which is primarily due to illiteracy and lack of awareness.[4] In Pakistan more than 60% of patients presents in locally advanced stage presenting a major impediment in management. Locally advanced breast cancer (LABC) is a common diagnosis involving all stage III and a subset of stage IIB diseases. 5 Non-metastatic T3 or T4 tumors as well as N2/N3 disease are also included in the clinical description of LABC.[6] Neoadjuvant therapy is treatment given before surgery and it has been used for many years for locally advanced or inflammatory breast cancer and now has become the standard of care. [7,8] The goal of neoadjuvant chemotherapy is to reduce the tumor sufficiently to make breast-conserving surgery effective and to make irresistible tumors respectable. The use of chemotherapy can induce neutropenia, which could end with febrile neutropenia (FN), which is common type of myelosuppression in patients receiving chemotherapy.In the literature, Yunwei et al study mentioned the incidence of neutropenia in 53% of patients.[9] Moreover Chan et al reported in thee study the incidence of neutropenia in 13.8% of patients with breast cancer receiving Adriamycin based chemotherapy.[10]

METHODS:
Karachi Institute of Radiotherapy & Nuclear Medicine Karachi from 16-11-2017 to 16-05-2018. Through non-probability consecutive sampling, ninety six patients were registered. Before entering therapy, written informed consent was approved and properly signed by the patients. Ethical review committee of Karachi Institute of Radiotherpay and Nuclear Medicine;(KIRAN) had already approved this study.Inclusion criteria were biopsy proven locally advanced breast carcinoma stage II/III, ECOG performance status 0 and 1,no prior specific treatment, age between 20 to 70 years with normal cardiac, renal and liver functions and adequate bone marrow reserves. Exclusion criteria were any treatment chemotherapy, radiotherapy, or surgery prior to presentation, left ventricular ejection fraction less than 45%,. had neutropenia prior to the start of chemotherapy.Patients enrolled in this study were assessed clinically, radiological studies and by routine laboratory tests i-e CBC, LFT, Urea, creatinine. Baseline & periodically left ventricular ejection was assessed in enrolled patients to minimize cardiotoxicty of adrimycin. Patients were planned for neo adjuvant chemotherapy AC regimen, which comprises of Inj: Adriamycin (Doxorubacin) 60mg/m^2 IV and Inj: Cyclophoshamide 600mg/m^2 IV on Day 1 every 3 weekly for a total of 6 cycles. On 10^{th} day after the chemotherapy cycle blood tests were performed to assess the white blood cells i.e. neutropenia. Neutropenia grading was performed on basis of common terminology criteria for adverse events. Descriptive statistics from the case series included mean ± standard deviation (SD) of continuous data, such as age, disease period. Frequencies and percentages, such as period of disease, stage of disease, frequency of chemotherapy, and patients with Neutropenia, were determined from categorical data (Outcome Variable). Effect modifiers were guided by age stratification in groups, disease length, stage, and no chemotherapy cycles. The post-stratification chi square test with a p value of $\leq$ 0.05 was considered to be important. The data was analyzed using SPSS software version 21.0.

RESULTS:
Ninety six patients were enrolled. Mean age of patients was 52.43 ± 10.08 years with minimum age was 30 years while maximum age was noted to be 69 years. The majority of patients have age group ranging from 41-70 years presented in figure no-01. Mean duration of disease was 10.49 ± 4.98 months with minimum disease duration was 6 months while maximum disease duration was 24 months majority of patients i.e. 65 (67.7%) had disease duration less than 12 months. shown in figure no-02. Fifty seven (59.4%) had breast cancer with stage III while 39 (40.6%) belonged to stage II shown in figure no-03. Mean neutrophil count was noted to be 1589.58 ± 350.21/mm^3 (with minimum neutrophil count was 1100 while maximum neutrophil count was 2500/mm^3). Neutropenia was noted in 51 (53.1%) of our study cases. Among these 51 who developed neutropenia, 22 (43.13 %) developed after first cycle of chemotherapy, 12 (23.52%) developed after 2^{nd} cycle, 9 (17.64%) after 3^{rd} cycle, 4 (7.84%) after 4^{th} cycle and 4 (7.84%) after 5^{th} cycle of chemotherapy (p=0.000) represented in figure no: 04 & 05 respectively. Neutropenia was stratified with regards to age, disease duration, stage of disease, no. of cycles of chemotherapy. and p – values were noted to be p=0.246, p=0.000, p=0.000, p=0.000 respectively & presented in table no:1 to 04.

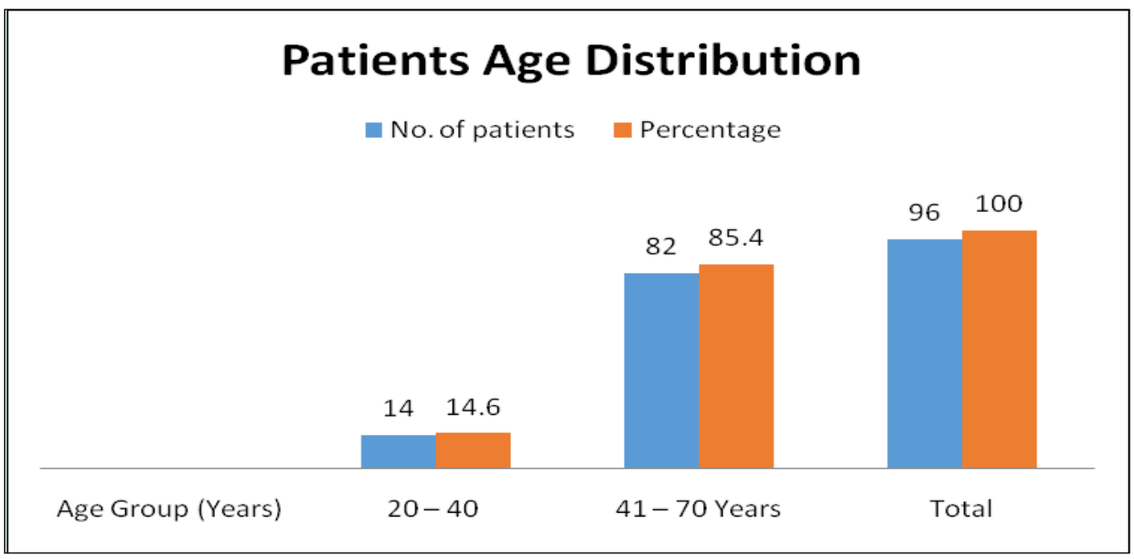

Figure -1.Age Distribution (n=96)

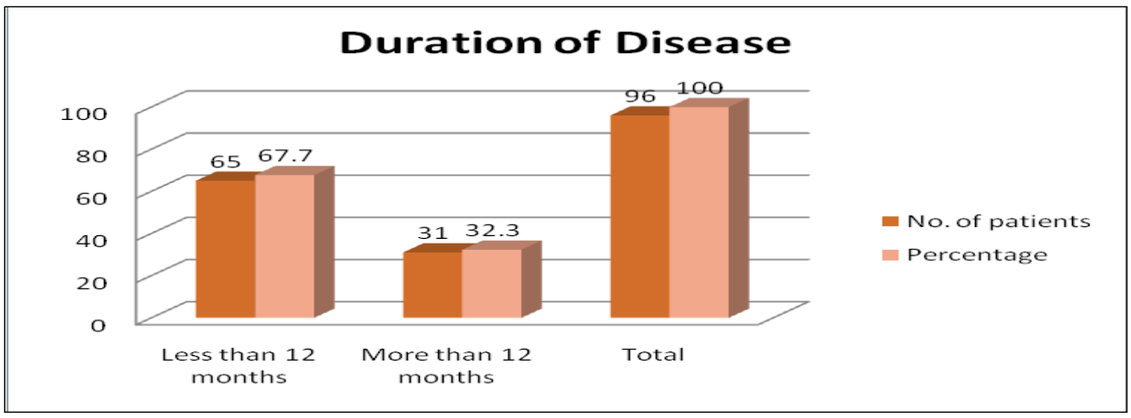

Figure -02. Duration of disease(n=96)

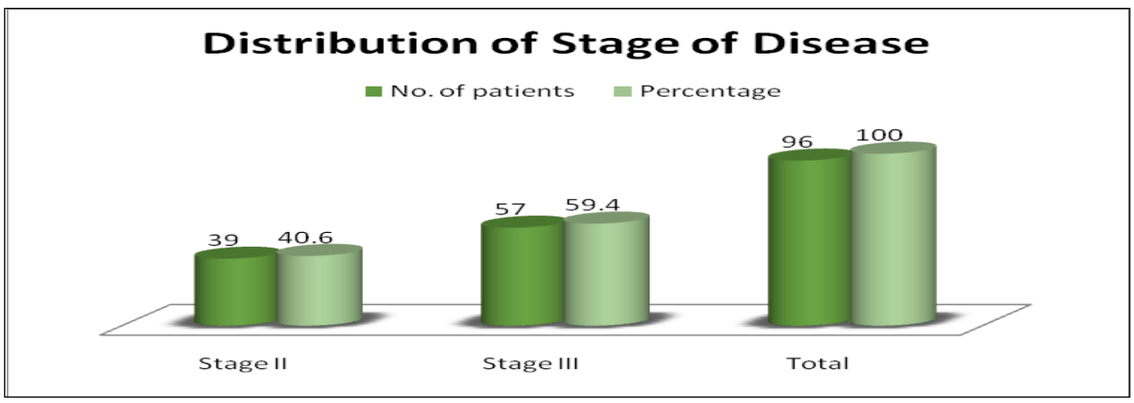

Figure :03. Distribution of stage of disease(n=96)

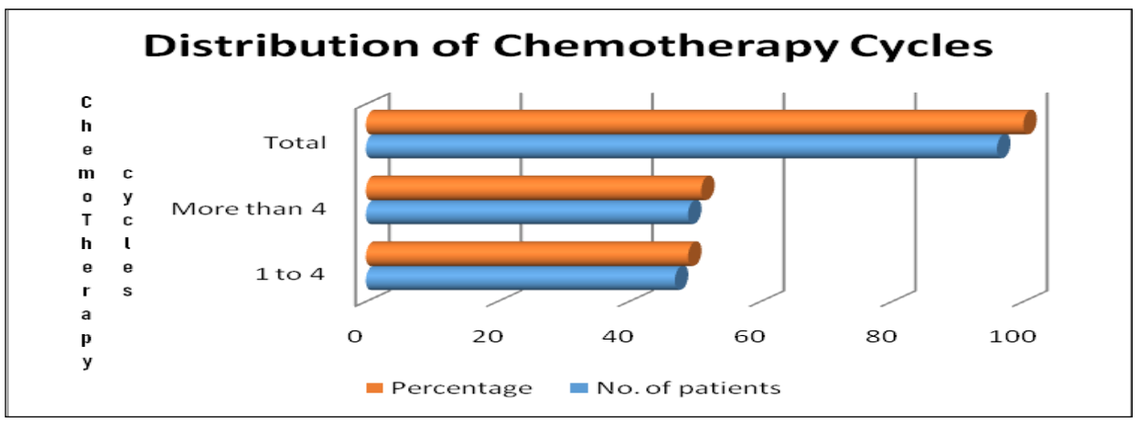

Figure-04-Disribution of chemotherapy cycles(n=96)

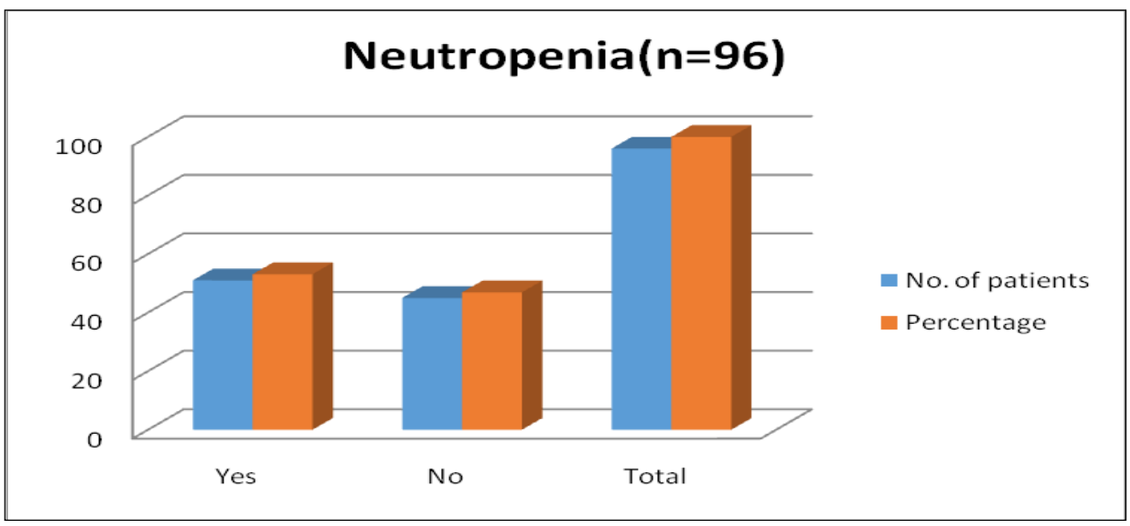

Figure:05. Frequency of neutropenia (n=96)

Table -01.Stratification of neutropenia with regards to age (n=96)			
Age groups (In Years)	**Neutropenia**		**P - value**
	Yes (n=51)	**No** (n=45)	
20 – 40 Years (n=14)	05	09	**0.246**
41 – 70 Years (n=82)	46	36	
Total	**96**		

Table -02.Stratification of neutropenia with disease duration(n=96)			
Disease duration	**Neutropenia**		**P - value**
	Yes (n=51)	**No** (n=45)	
Less than 12 months (n=65)	**20**	**45**	**0.000**
More than 12 months (n=31)	**31**	**00**	
Total	**96**		

Table- 03.Stratification of neutropenia with regards to stage of disease(n=96)			
Stage of disease	**Neutropenia**		**P - value**
	Yes (n=51)	**No** (n=45)	
Stage II (n=39)	**09**	**30**	**0.000**
Stage III (n=57)	**42**	**15**	
Total	**96**		

Table -04.Stratification of neutropenia with regards to no. of chemotherapy cycles(n=96)			
No. of cycles	**Neutropenia**		**P - value**
	Yes (n=51)	**No** (n=45)	
1-4 (n=47)	47	00	**0.000**
5 -6 (n=49)	04	45	
Total	**96**		

DISCUSSION:

Breast cancer is the second leading cause of mortality in women. Mortality from breast cancer has decreased due to early detection and more efficient early-stage treatments.[11]The breast cancer management is complex process.Breast cancer management plan depends upon histopathologic type of tumor and stage of tumor.Treatment options include breast conserving surgery with axillary clearance, modified radical mastectomy,neo adjuvant and adjuvant chemotherapy,hormonal therapy and external beam radiotherapy.Systemic chemotherapy can reduce burden of tumor resulting down size of tumor.Cancer chemotherapy also reduce risk of tumor relapse by eliminating malignant cells in primary site and malignant cells have escaped from breast and regional lymph nodes. For neoadjuvant and adjuvant chemotherapy, the response rate is the same in terms of overall survival and disease-free survival. Therefore patient selection is crucial for planning for neo adjuvant chemotherapy for optimizing outcome of disease.

Neoadjuvant chemotherapy in breast cancer converts unresectable tumors to resectable ones, and reduces the extent of surgery needed to achieve adequate resection. Neo adjuvant chemotherapy is used as bridge therapy in

locally advanced breast cancer. Neo adjuvant chemotherapy is gold standard treatment option in inflammatory breast cancer. It gives disease-free and general survival for locally advanced breast cancer. Neutropenia is an oncological emergency result of chemotherapy. Neutropenia may result in delays in the schedule of treatment, decreasing the dosage of chemotherapy, which may potentially compromise the effectiveness of chemotherapy. Neutropenic patients requires administration of granulocytes colony stimulating factor,antibiotics,antifungal, and often require isolation and hospitalization. Mortality stimulated by neutropenia can increase significantly in patients with subsequent infections, particularly those who are immunized and have multiple co-morbid conditions. It is therefore advisable to take all steps to avoid the development of neutropenia, such as the judicious use of prophylaxis of the granulocyte colony stimulating factor (G-CSF). Patients have inherent risk of febrile neutropenia with chemotherapy more than twenty percent in such patients routine usage of granulocytes colony stimulating factor is highly indicated. [12] Neutropenia risk can be mitigated by reducing chemotherapy dose or extending dosing intervals.[13] an independent risk factor for breast cancer is Increasing of age and the mean age of our case studies was 52.43 ± 10.08 years (with minimum age was 30 years while maximum age was noted to be 69 years). Similar findings have been reported in many national and international studies. A study conducted by Han et al [9]reported mean age of 52 years, which is close to our study results. Another study conducted by Gillani et al[14] reported 47.5 ± 11.02 years mean age of patients with breast cancer, these findings were simulate to our study results. An other study conducted at Lahore by Bhattyet al[15] reported mean age of 47 years which is close to our study results. Bokkhariet al[16] reported age range in breast cancer patients was ranging from 28 to 68 years; these results are in accordance with the findings of our analysis. The majority of patients in our study belonged to an age group of between 41 and 70 years of age were similar to study conducted by Naeem et al [17] showing age group range from 40 to 60 years. Mean duration of disease was 10.49 ± 4.98 months (with minimum disease duration was 6 months while maximum disease duration was 24 months), majority of patients i.e. 65 (67.7%) had disease duration less than 12 months. Fifty seven (59.4%) had breast cancer with stage III while 39 (40.6%) belonged to stage II. Similar pattern has been reported by Kazmi et al [18] reported stage III breast cancer in 59.2% patients which is similar to that of our study results.

Neutropenia, with a neutrophil count below 1.5x109/L, is characterized by a decrease of white blood cells. Among the patients who have undergone chemotherapy treatment, the probability of this occurrance activity ranges from 16 percent to 81 percent. In our study mean neutrophil count was noted to be 1589.58 ± 350.21/mm^3 (with minimum neutrophil count was 1100 while maximum neutrophil count was 2500/mm^3). Neutropenia was noted in 51 (53.1%) of our study cases. The frequency of neutropenia in 53% of patients of our study results are close to that of Han et al.[14] A study conducted by Wang et al [19] reported 66 % neutropenia which is slightly higher than our study results. Another study reported 63.3 % neutropenia among targeted population which is close to our results. Moreover Chan et al reported in thee study the incidence of neutropenia in 13.8% of patients with breast cancer receiving Adriamycin based chemotherapy.[10]these values are quite lesser than that observed in our study. Among these 51 who developed neutropenia, 22 (43.13 %) developed after first cycle of chemotherapy, 12 (23.52%) developed after 2nd cycle, 9 (17.64%) after 3rd cycle, 4 (7.84%) after 4th cycle and 4 (7.84%) after 5th cycle of chemotherapy (p=0.000). Similar pattern has been reported by do-Noscimentoet al.[20] and results of this study compliance with that of our study results.

CONCLUSION:

The frequency of neutropenia observed in this study is compatible with current research findings. In our research, high frequency neutropenia was observed in locally advanced breast cancer patients with adriamycin-based chemotherapy. The most common and major adverse effect occurring during neoadjuvant treatment was neutropenia. The length of the disease, the stage of breast cancer and the number of chemotherapy cycles were significantly correlated with neutropenia.

Neutropenia should be tested at an early stage in patients undergoing neoadjuvant therapy with Adriamycin, which plays an important role in the treatment choices of these patients, thus enhancing the quality of life of these patients and reducing the frequency of hospitalization due to neutropenia.

ETHICS APPROVAL: The ERC gave ethical review approval

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin

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AUTHORS' CONTRIBUTIONS: All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the work to take public responsibility of this manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST: No competing interest declared.

REFERENCES:

1. American Cancer Society: Cancer Facts and Figures 2013. Atlanta, Ga: American Cancer Society,2013.

2. Jemal A, Center MM, Desantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev, 2010;19:1893-907.
3. Autier P, Boniol M, LaVecchia C, Vatten L, Gavin A, Héry C, et al. Disparities in breast cancer mortality trends between 30 European countries: retrospective trend analysis of WHO mortality database. BMJ 2010;341:c3620.
4. Mahmood S, Rana TF, Ahmad M. Common determinants of Ca Breast - a case control study in Lahore. Ann King Edward Med Coll 2006;12:227–8.
5. Edge SB, Byrd DR, Compton CC, et all. In:AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer Verlag; 2017; 347-76.
6. Lee MC, Newman LA. Management of patients with locally advanced breast cancer. Surg Clin N Am 2007;87:379-98.
7. Wikipedia, the free encyclopedia 2013.www.en.wikipedia.org/Neoadjuvant therapy.
8. Rajan R, Poniecka A, Smith TL, Yang Y, Frye D, Pusztai L, et al. Change in tumor cellularity of breast carcinoma after neoadjuvant chemotherapy as a variable in the pathologic assessment of response. Cancer 2004;100:1365–73.
9. Han Y, Yu Z, Wen S, Zhange B, Cao X, Wang X. Prognostic value of chemotherapy induced neutropenia in early stage breast cancer. Breast Cancer Res Treat 2012;131:483-90.
10. Chan A1, Chen C, Chiang J, Tan SH, Ng R. Incidence of febrile neutropenai among early stage breast cancer patients receiving anthracycline-based chemotherapy. Support Care Center 2012 Jul;20(7):1525-32.
11. Berry DA,Cronin KA,Plevritis Sk,et al.Effect of screening and adjuvant therapy on mortality from breast cancer.N Engl J Med 2005;353:1784-1792.
12. Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP, Charles Weaver, et al: Adjuvant docetaxel for node-positive breast cancer. N Engl J Med, 2006;352:2302-2313.
13. Kosaka Y, Rai Y, Masuda N, Takano T, Saeki T, Nakamura S, et al. Phase III placebo-controlled, double-blind, randomized trial of pegfilgrastim to reduce the risk of febrile neutropenia in breast cancer patients receiving docetaxel/cyclophosphamide chemotherapy. Support Care Cancer. 2015 Apr;23(4):1137-43.
14. Gilani GM, Kamal S, Akhter AS. A differential study of Breast Cancer Patients in Punjab, Pakistan. J Pak Med Assoc 2003;53(10):478-81.
15. Bhatty I, Shaharyar, Ibrahim M, Chaudhry ML. Complications after modified radical Mastectomy in early Breast Cancer Pak J Med Sci 2004;20(2):125-30.
16. Bokhari I, Tahir, Q Rasul S, Khan A. Early experience of sentinel lymph node biopsy in breast cancer J Surg Pak 2009;14(1):29-32.
17. Naeem M, Khan N, Aman Z, Nasir A, Samad A, Khattak A. Pattern of breast cancer: experience at Lady Reading Hospital, Peshawa J Ayub Med Coll Abottabad 2008;20(4):22-5.
18. Kazmi SIM, Mehdi SH, Umar F. Frequency and pattern of advanced breast cancer at Abbasi Shaheed Hospital Pak J Surg 2009;25(1):3-5.
19. Wang X, Fan T, Fan Z, Wang T, Xie Y, Li J, et al. Neoadjuvant chemotherapy using epirubicin, cyclophosphamide and fluorouracil: neutropenia and elevation of transaminase, and their management. Zhonghua Zhong Liu Za Zhi. 2015 Mar;37(3):204-7.
20. Nascimento TG,D Andrade M, Oliveira RA, Almeida AM. Neutropenia: occurrence and management in women with breast cancer receiving chemotherapy. Rev Lat Am Enfermagem. 2014 Mar-Apr;22(2):301-8.