Incidence of febrile neutropenia with commonly used chemotherapy regimen in localized breast cancer

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Abstract

Introduction: Breast cancer is the most frequently diagnosed cancer among the women. Most commonly used chemotherapy regimen is Doxorubicin and Cyclophosphamide (AC) which carries significant risk of febrile neutropenia. The aim of the study is to identify the incidence of febrile neutropenia and its effects on the delivery of chemotherapy in patients receiving following AC chemoregimen without primary prophylaxis. **Materials and Methods:** We retrospectively analyzed the case records of the localized breast cancer patients who were treated with AC chemoregimen without primary prophylaxis for febrile neutropenia. **Results:** Between 2013 and 2017, a total of 231 cases received AC chemoregimen. A total of 14 (6.1%) patients were found to have febrile neutropenia. All patients were recovered by day 19 and no deaths were observed. Except for ECOG performance status (P = 0.001) no significant association was found with age, co-morbidities, menopausal status, body surface area and stage of the cancer. There were no treatment delays or dose reductions because of febrile neutropenia. **Conclusion:** The incidence of FN with AC chemotherapy in breast cancer patients is relatively less in the present study. Routine primary prophylaxis is not recommended as this chemotherapy falls in to low risk category for FN but can be considered for patients with ECOG PS > 1. If the diagnosis of febrile neutropenia and institution of appropriate measures are prompt, FN did not affect the delivery of chemotherapy and thus compromise survival.

Key words: Doxorubicin and cyclophosphamide chemotherapy, febrile neutropenia, prophylaxis

Introduction

Breast cancer is the most common cancer in India and the second most common in the world, both sexes combined.[1] Over the past few decades, advances in adjuvant chemotherapy of the breast resulted in decline in mortality due to breast cancer. Sequential anthracycline followed by taxane-based regimen remains to be the gold standard when adjuvant chemotherapy is indicated in majority of cases. Doxorubicin and cyclophosphamide (AC) is the widely accepted regimen; however, it carries the potential risk of myelosuppression, leading to febrile neutropenia (FN). The efficacy of the adjuvant chemotherapy is determined by the dose density and intensity of chemotherapeutic agents, apart from other factors.[2]

FN is a serious complication, and the effects are multitude. It has the potential to cause significant morbidity to a patient, apprehension to the caretakers, economic burden to the society, and increased workload to the health-care providers, especially in resource-limited setting. Furthermore, if the patient is suffering from significant comorbidities that increase the risk of infection, it can increase mortality compromising survival.[3] FN may adversely affect the treatment outcomes as it may lead to treatment interruption, dose reductions, and even termination of chemotherapy. The cost incurred due to the hospitalization and the use of antibiotics is also significant.[4] Hence, it is important to take necessary precautions to prevent the occurrence of FN by the use of primary prophylaxis with granulocyte colony–stimulating factor (G-CSF).

On the other hand, there are problems associated with the routine use of the G-CSF which include adverse reactions and cost of the G-CSF.[5] Hence, sagacious use of G-CSF as primary prophylaxis is advised. The current recommendations guide to use primary prophylaxis with G-CSF if the risk of developing FN due to chemotherapy is >20%.[6]

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The reported risk of FN with AC chemotherapy regimen is 10%–20%. The current study is designed to study the incidence and effects of FN in localized breast cancer patients receiving AC regimen as a component of adjuvant or neoadjuvant chemotherapy.

Materials and Methods

Study design

This was a single-institutional, observational, retrospective study.

Patients

Data of all localized breast cancer patients who received AC chemotherapy as a component of either neoadjuvant or adjuvant chemotherapy between 2013 and 2017 were analyzed. AC was administered at the doses of 60 mg/m^2 and 600 mg/m^2, respectively, every three weekly. Patients who received primary prophylaxis with G-CSF for FN and patients with incomplete records were excluded from the study.

Data collection

Medical records of the patients were used to collect the data pertaining to demography, past medical history, disease characteristics, baseline laboratory values, chemotherapy details, duration of FN, and length of hospital stay, dose reductions, and treatment delays. Breast cancer staging was done according to the UICC 7th edition.

Definitions

FN is defined as single oral temperature >101°F (38.3°C) or two consecutive readings of >100.4°F (38.0°C) for 1 h and an absolute neutrophil count of <0.5 × 10^9/L or predicted to decline to ≤0.5 × 10^9/L over the next 48 h.[6] Treatment delay is defined as a delay of >3 days over the planned density and dose reduction as a reduction of >15% over the planned dose.[7]

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Statistical methods

Descriptive statistics were used to describe patient demographics, disease characteristics, chemotherapy details, and FN details. Univariate analysis was used to find association between FN and several variables.

Results

Demographic data and disease characteristics

A total of 231 patients between 2013 and 2017 who met the eligibility criteria were analyzed. All the patients were females (100%). Patient characteristics are shown in Table 1. A total of 912 cycles of chemotherapy were administered. Two hundred and twenty-five (97.8%) patients completed all four cycles of planned AC chemotherapy. Two patients defaulted after one cycle and three patients after two cycles due to reasons other than FN.

Febrile neutropenia characteristics

A total of 14 (6.1%) patients developed at least one episode of FN. Overall, 16 episodes of FN were observed as two patients suffered from FN twice. Of 225 and six patients with Eastern Co-operative Oncology Group (ECOG) performance status (PS) of ≤1 and ≥2, 11 (4.8%) and 3 (50%) patients developed FN, respectively. The incidence of FN episodes after cycle 1, 2, 3, and 4 were 10 (4.3%), 3 (1.3%), 2 (0.9%), and 1 (0.4%), respectively. The median day of onset of FN was 12 (range, day 8–15). The median day of recovery of FN was 16 (range, day 12–19). All the patients were managed on in-patient basis. Blood cultures done were sterile in all patients, and imaging done did not reveal any source of probable infection. All the patients were managed with intravenous antibiotics and G-CSF. There were no deaths due to FN and the median duration of hospital stay was 4 days (range, 2–8 days).

Impact of febrile neutropenia on chemotherapy delivery

None of the patients had either treatment delay or chemotherapy dose reduction due to FN.

Factors affecting febrile neutropenia

Age, height, weight, body mass index (BMI), body surface area, comorbidities, menopausal status, AJCC staging, and ECOG PS were analyzed using univariate analysis. None of them were found to be statistically significant in causing FN, except for the ECOG PS of ≥2 ($P = 0.0001$).

Discussion

Anthracycline and cyclophosphamide chemotherapy is generally well tolerated but, sometimes, may lead to serious and life-threatening complications including FN. The present study is a single-institutional, retrospective study which evaluated the incidence and risk factors associated with FN and its effects such as length of hospitalization, dose reduction, and treatment delay in patients with localized breast cancer treated with AC chemotherapy as part of their neoadjuvant or adjuvant chemotherapy. We believed that this study provides an informative insight into the supportive care management of the most common chemotherapy regimen used in the most common malignancy in India.

Table 1: Patient characteristics

Characteristic	Value
Median age (years)	50 (25-70)
Median BSA (m^2)	1.54 (1.15-1.93)
Comorbidities (%)	
Diabetes mellitus	54 (23.4)
Hypertension	64 (27.7)
Hypothyroidism	16 (6.9)
Others	12 (5.2)
ECOG performance status (%)	
0	122 (52.8)
1	103 (44.6)
2	5 (2.2)
3	1 (0.4)

ECOG=Eastern Co-operative Oncology Group, BSA=Body surface area

In the present study, the incidence of FN is only 6.1%, and hence, AC chemotherapy falls into low-risk category. The incidence of FN with AC chemotherapy in multi-institutional randomized controlled trials (RCTs)[8-10] and retrospective studies[7,11-13] ranged from 0.3% to 6% and 6.1% to 25.2%, respectively. Risk of FN is more in retrospective studies compared to the RCTs, the possible reason being the stringent eligibility criteria for entry into RCTs. However, in the real-world scenario, a clinician would see much more incidence of FN, which is supported by the retrospective studies. Hence, we compared the present study with other retrospective studies. In the study by Kim *et al*.,[12] FN is exceptionally higher for reasons unclear.

The present study shows that the risk of FN is less compared to other single-institutional studies. The possible explanation for this would be the differences in the demographic characteristics of the patients across various studies that have bearing on the risk of FN. Ethnic differences in hematologic toxicities which were reported for lung cancer may also have contributed for this difference in the incidence of FN.[14] Polymorphism of the hepatic enzymes involved in the metabolism of AC was also described in the literature.[15]

Factors that predispose to FN include type of chemotherapy, depth and duration of neutropenia, relative dose density, previous chemotherapy and radiotherapy, advanced age, female gender, poor PS, poor nutritional status, and presence of other comorbid conditions.[16] In the present study, the only variable that was significantly associated with the elevated risk of FN was ECOG PS. Kim *et al*.[12] reported that BMI was associated with increased risk of FN.

Maintaining relative dose intensity of >85% is of paramount importance to retain the optimal efficacy offered by the adjuvant chemotherapy.[2] There was no chemotherapy dose reduction or treatment delay in our study, whereas only a minority of patients had dose reduction and treatment delays due to FN in other studies. Dose reduction and dose delay in various studies ranged from 0% to 16.5% and 0% to 19.5%, respectively.[7,11,12] Patients who develop FN may be treated without dose reduction and delay in subsequent cycles provided that the diagnosis of FN is prompt and facilities for timely intervention with adequate supportive measures are available.

The present study has certain limitations. This was a retrospective study; however, necessary measures were taken to ensure that findings were accurate. The sample size is small but is hypothesis generating. This study was unable to correlate with any of the risk factors reported in the literature that makes patients susceptible to FN, except for ECOG PS. This highlights the importance of studies which evaluates risk factors of FN for each cancer type.

Conclusion

The incidence of FN with AC chemotherapy in breast cancer patients is relatively less in the present study. Routine primary prophylaxis is not recommended as this chemotherapy falls into low-risk category for FN but can be considered for patients with ECOG PS >1. If the diagnosis of FN and institution of appropriate measures are prompt, FN did not affect the delivery of chemotherapy and thus compromise survival.

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Conflicts of interest

There are no conflicts of interest.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A, *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Bonadonna G, Valagussa P. Dose-response effect of adjuvant chemotherapy in breast cancer. N Engl J Med 1981;304:10-5.
3. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006;106:2258-66.
4. Tai E, Guy GP, Dunbar A, Richardson LC. Cost of cancer-related neutropenia or fever hospitalizations, United States, 2012. J Oncol Pract 2017;13:e552-61.
5. Barnes G, Pathak A, Schwartzberg L. G-CSF utilization rate and prescribing patterns in United States: Associations between physician and patient factors and GCSF use. Cancer Med 2014;3:1477-84.
6. Klastersky J, de Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M, *et al.* Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. Ann Oncol 2016;27:v111-v118.
7. Chan A, Chen C, Chiang J, Tan SH, Ng R. Incidence of febrile neutropenia among early-stage breast cancer patients receiving anthracycline-based chemotherapy. Support Care Cancer 2012;20:1525-32.
8. von Minckwitz G, Raab G, Caputo A, Schütte M, Hilfrich J, Blohmer JU, *et al.* Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: The GEPARDUO study of the German breast group. J Clin Oncol 2005;23:2676-85.
9. Citron ML, Berry DA, Cirrincione C, Hudis C, Winer EP, Gradishar WJ, *et al.* Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of intergroup trial C9741/Cancer and leukemia group B trial 9741. J Clin Oncol 2003;21:1431-9.
10. Fumoleau P, Chauvin F, Namer M, Bugat R, Tubiana-Hulin M, Guastalla JP. Intensification of adjuvant chemotherapy: 5-year results of a randomized trial comparing conventional doxorubicin and cyclophosphamide with high-dose mitoxantrone and cyclophosphamide with filgrastim in operable breast cancer with 10 or more involved axillary nodes. J Clin Oncol 2001;19:612-20.
11. Leonard RC, Miles D, Thomas R, Nussey F, UK Breast Cancer Neutropenia Audit Group. Impact of neutropenia on delivering planned adjuvant chemotherapy: UK audit of primary breast cancer patients. Br J Cancer 2003;89:2062-8.
12. Kim CG, Sohn J, Chon H, Kim JH, Heo SJ, Cho H. Incidence of febrile neutropenia in Korean female breast cancer patients receiving preoperative or postoperative doxorubicin/Cyclophosphamide followed by docetaxel chemotherapy. J Breast Cancer 2016;19:76-82.
13. Kim HS, Lee SY, Kim JW, Choi YJ, Park IH, Lee KS. Incidence and predictors of febrile neutropenia among early-stage breast cancer patients receiving anthracycline-based chemotherapy in Korea. Oncology 2016;91:274-82.
14. O'Donnell PH, Dolan ME. Cancer pharmacoethnicity: Ethnic differences in susceptibility to the effects of chemotherapy. Clin Cancer Res 2009;15:4806-14.
15. Aminkeng F, Ross CJ, Rassekh SR, Hwang S, Rieder MJ, Bhavsar AP. Recommendations for genetic testing to reduce the incidence of anthracycline-induced cardiotoxicity. Br J Clin Pharmacol 2016;82:683-95.
16. Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. Crit Rev Oncol Hematol 2014;90:190-9.