International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 7; Issue 7(B); July 2018; Page No. 13977-13981
DOI: http://dx.doi.org/10.24327/ijcar.2018.13981.2517

Research Article

INCIDENCE OF FEBRILE NEUTROPENIA AMONG CANCER PATIENTS RECEIVING CHEMOTHERAPY, A SINGLE CENTER EXPERIENCE FROM PAKISTAN

Reena Kumari[1]., Ghulam Haider[2]., Sunil Kumar[3]., Jeevan Kumar[4]., Asra Tanvir[5]., Areeba Mir[6]., Madiha Ariff[7] and Adnan Anwar[8]

[1]MBBS, FCPS Medical Oncology Resident, JPMC, Karachi, Pakistan
[2]MBBS, FCPS Med, FCPS Medical Oncology, AssociateProfessor, JPMC, Karachi, Pakistan
[3]MBBS, DDerm, Dermatologist, ZiahuddinHospital, Karachi, Pakistan
[4]MBBS, FCPS Medicine Resident, BolanMedical College, Quetta, Pakistan
[5]MBBS, Medical Officer, Baqai Medical University, Karachi, Pakistan
[6]MBBS,Jinnah Medical and Dental College, Department of Medicine,Karachi,Pakistan
[7]MBBS, Dow Medical College, Karachi, Pakistan
[8]MBBS, M. Phil, AssistantProfessor, Department of Physiology, Altibri Medical College,Karachi,Pakistan

A R T I C L E I N F O

Article History:

Received 16th April, 2018
Received in revised form 4th May, 2018 Accepted 12th June, 2018
Published online 28th July, 2018

Key words:

Cancer, chemotherapy,
Febrile, neutropenia

A B S T R A C T

Objective: To determine the incidence of febrile neutropenia among cancer patients receiving chemotherapy in the Oncology Department of Jinnah Postgraduate Medical Centre, Karachi.

Material and methods: An observational study through convenient sampling technique was conducted from 1st April 2016 to Mar 30, 2017 at Department of Oncology, Jinnah Postgraduate Medical Centre, Karachi after obtaining approval from Ethical Review Committee. We included 316 cancer patients, undergoing different chemotherapy regimens for different types of tumors. Number and percentage of patients who develop febrile neutropenia and type of chemotherapy which was associated with febrile neutropenia were recorded. Febrile neutropenia defined as a single oral temperature of >38.3 ºC with absolute neutrophil count of less than 500.Patients who were known cases of diabetes, heart disease, or psychiatric illness, were excluded. Demographic variables such as age, weight, height, gender, type of cancer, chemotherapy protocol, number of days of chemotherapy, chemotherapy setting, haemoglobin, total leukocyte count, neutrophils, monocytes, platelets, were recorded. SPSS version 20.0 was used for data analysis.

Results: In the total of 316 cancer patients divided into 12 groups depending upon chemotherapeutic regimen, the overall incidence of febrile neutropenia was 164 (52%).The mean age in all groups was 42.11±14.09 years. The mean total leukocyte count recorded was 2444.46 ± 1655.35 mm3. Mean of neutrophils was 33.96 ± 21.65 %. The mean absolute neutrophil count recorded was 1058.12 ± 1237.01 mm3. The mean chemotherapy days were 10.72 ± 3.23.

Conclusion: Our study showed that among 316 of the patients on chemotherapy, half of the patients developed febrile neutropenia; this is in contrast to other studies where this frequency is 10-20%.

INTRODUCTION

Febrile Neutropenia is one of the main complication of cancer chemotherapy and a major cause of morbidity, extensive use of healthcare resources and decreased efficacy due to dose reductions and delaying in chemotherapy. Although mortality has decreased steadily but still remains significant [1]. It is estimated to be about 5% in people with solid tumors (1% among low-risk patients) and as high as about 11% in people diagnosed with hematological malignancies with worst prognosis in people with apparent bacteremia.[2] Mortality rates of 18% and 5% have been reported in patients having Gram-negative and Gram-positive bacteremia while the elderly are at a much higher risk of febrile neutropenia, which increases morbidity and mortality [3] Neutropenia is a clinical condition characterized by an abnormally low concentration of neutrophils (<500 cells/mm3).[4] They are the most numerous circulating white blood cells that are the first line of the defense for infections. [5]

Corresponding author:* **Reena Kumari
MBBS, FCPS Medical Oncology Resident, JPMC, Karachi, Pakistan

Several symptoms are related to neutropenia, and when associated with fever (≥ 38.3ºC), it is referred to as febrile neutropenia (FN) in which the occurrence of fever is typically as a result of an infection because the patients are immune-compromised and are more prone to develop infections.[6] When chemotherapy suppresses bone marrow from producing blood cells in the most commonly affected cells are the neutrophils.[7] The risk of infection as well as mortality increases with the magnitude and duration of neutropenia and the persistence of fever wherein the duration of neutropenia is mostly 7–10 days, with variations depending upon the nature and intensity of the chemotherapeutic regimen and patient's own factors, that include reserves in bone marrow, type of cancer, comorbidities and more importantly the age, all these factors are taken into consideration for treating neutropenia. The empirical antibiotics are frequently recommended and if neutropenia is associated with fever, hospital admission with intensive care isolation might be needed. [8]. Neutropenic patients show increased susceptibility to infections such as respiratory tract infection (35%–40%), bloodstream infections (15%–35%), urinary tract infections (5%–15%), gastrointestinal tract infections (5%–10%), skin infections (5%–10%), and other sites infections (5%–10%).[9] Numerous chemotherapeutic agents act on similar type of target cells division but unfortunately this mechanism of action is non-specific to the malignant cells, that result in chemotherapy associated toxicities to the healthy tissues where general effects of almost all chemotherapeutic agents are the primary limiting factor in the treatment of malignancies..[10] Risk as well as consequences of Febrile Neutropenia may slightly differ amongst cancer- and stage-specific subgroups due to systematic differences within patients, their characteristics, and treatment.[11] Patients diagnosed with metastatic disease are mostly older with comorbids and have poor performance status in comparison to the younger patients with less-severe disease. Treatment in the metastatic setting is often less aggressive, and alternative approaches to managing these toxicities such as the use of less myelosuppressive regimens or scheduled dose modifications in line of prophylaxis using colony-stimulating factors have been recommended in several literatures, especially when the intent of such care is palliative.[12-15]

Purpose of this study was to determine the incidence of febrile neutropenia among chemotherapeutic patients in order to devise an appropriate plan to better manage the patients and so help decrease mortality and morbidity as well as consequences of febrile neutropenia which may slightly differ among cancer and stage-specific patients.

MATERIAL AND METHOD

This is an observational study conducted in the department of Oncology The Jinnah Postgradute Medical center Karachi Pakistan from 1st April 2016 to 30 Mar 2017.

The Department of Oncology comprises of 54 bedded inpatient unit with 98% bed occupancy rate and 30 bedded daycare chemotherapy unit with 100% bed occupancy rate and annually registering 4500 to 5000 new cases and 31000 follow up cases in its out patientclinic. Daily admission ranges from 10-20 cases from emergency room and clinics. Patients data were collected with help of proforma using non-probability convenient sampling technique. Total 316 patients getting chemotherapy from the Oncology Department of Jinnah Postgraduate Medical Centre were included. Prior approval was taken from Ethical Review Board of the hospital.

Inclusion criteria consisted of patients age ranged from 16 years to 60 years, having histopathologically confirmed carcinoma in case of solid tumors and Bone marrow biopsy proven in case of Acute Leukemia and undergoing chemotherapy. Patients required to have adequate renal, hepatic and cardiac function before getting chemotherapy for Acute leukemia and also adequate bone marrow function for solid tumors. Febrile Neutropenia defined as any type of malignancy irrespective of stage who has received chemotherapy during previous 4 weeks and now presented with an absolute neutrophil count of less than 500/ul and fever as a single oral temperature of >38.3 ºC. Patients who were known cases of (a)uncontrolled diabetes, (b)advanced heart disease (c) psychiatric illness, (d)poor performance status (e) known source of ongoing infection and (f) not willing to give consent were excluded from the study.

Variables included, age, weight, height, and gender and body surface area, type of cancer, chemotherapy protocol, number of days of chemotherapy, chemotherapy setting and performance status, haemoglobin, total leukocyte count, neutrophils, monocytes, platelets, were recorded. Data was analysed using SPSS version 20. Patients were divided into 12 groups based on the chemotherapeutic regimen.Group 1 included patients on daunorubicin and cytarabine(3+7). Group 2 included patients on daunorubicin, vincristine, prednisone, L-asparaginase (DVPL).. Group 3 included patients on cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone (CHOP).. Group 4 included patients on adriamycin, bleomycin, vinblastine and dacarbazine (ABVD). Group 5 included patients on adriamycin and cyclophosphamide (AC). Group 6 included patients on taxotare, adriamycin and cyclophosphamide (TAC). Group 7 included patients on docetaxel. Group 8 included patients on Carboplatin plus Paclitaxel. Group 9 included patients concurrent chemoradiotherapy (CCRT) with carboplatin and paclitaxel. On Group 10 included patients on taxotare, cisplatin, flurouracil (TPF). Group 11 included patients on cisplatin and gemcitabine. Group 12 included patients on cisplatin and etoposide EP.

Descriptive statistics of Socio-demographic variables were presented as mean, standard deviation and frequency in percentages.

RESULTS

Our study comprised of 316 patients in which the mean age was 42.11 ± 14.09 years, mean weight was 57.16 ± 12.07 kg, mean height was 158.76 ± 9.99 cm, mean body surface area was 1.56 ± 0.19 m^2, mean haemoglobin 9.69 ± 1.79 gm/dl, mean platelets was 165,826.86 ± 115,070.10 cumm, mean white blood cells was 2444.46 ± 1655.35cumm, mean neutrophils was 33.96 ± 21.65 cumm, mean monocytes was 8.04 ± 8.58 cumm, mean absolute neutrophil count was 1058.12 ± 1237.01 cumm, and mean chemotherapy days were 10.72 ± 3.23 days.(Table 1) Patients were divided into 12 groups. The most frequency of febrile neutropenia was observed in groups 1 and 2 having a frequency of 43 (97.7%) and 32 (91.4%) respectively. The least frequency of febrile neutropenia was recorded in groups 4 and 11 with a frequency of 1 (9.1%) and 1 (10%) respectively. (Table 2) The overall frequency of febrile neutropenia regardless of the type of

chemotherapy was recorded to be present in 164 (52%) of the patients and absent in 152 (48%) of patients. (Figure1).

Table 1 Descriptive statistics of chemotherapeutic patients

Variable	Mean	Standard Deviation
Age (years)	42.11	14.09
Weight (kg)	57.16	12.07
Height (cm)	158.76	9.99
Body Surface Area (m^2)	1.56	0.19
Hemoglobin (mg/dl)	9.69	1.79
Platelets (mm^3)	165826.86	115070.10
Total Leucocyte Count(mm^3)	2444.46	1655.35
Neutrophils (%)	33.96	21.65
Monocytes (%)	8.04	8.58
Absolute Neutrophil Count (mm^3)	1058.12	1237.01
Chemotherapy days	10.72	3.23

Table 2 Frequency and percentage of patients based on chemotherapy protocols

n=316	Febrile Neutropenia			
	Yes		No	
	N	%	N	%
Group 1 (n=44)	43	97.7	1	2.3
Group 2 (n=35)	32	91.4	3	8.6
Group 3 (n=35)	16	45.7	19	54.3
Group 4 (n=11)	1	9.1	10	90.9
Group 5 (n=40)	6	15	34	85
Group 6 (n=12)	6	50	6	50
Group 7 (n=20)	6	30	14	70
Group 8 (n=37)	21	56.8	16	43.2
Group 9 (n=11)	2	18.2	9	81.8
Group 10 (n=43)	27	62.8	16	37.2
Group 11 (n=10)	1	10	9	90
Group 12 (n=18)	5	27.8	13	72.2

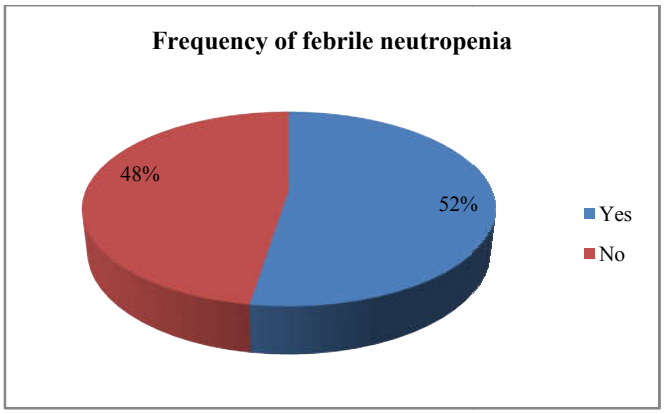

Figure 1 Frequency of febrile neutropenia among chemotherapy patients (n=316)

DISCUSSION

In our study of 316 cancer patients which were divided into 12 groups depending upon the chemotherapeutic regimen. Febrile neutropenia was found to be present in 52% of the patients in our study. In a study by Shaikh AJ, *et al*. the mean age reported in their study was 51.53 years and among the 215 patients selected for their study, 31.6% presented with febrile neutropenia. [16] In another study by, Younus J *et al*. the mean age was 61.5 years in which among total of 134 patients, 27 (20%) of patients were found to have febrile neutropenia.[17] In a study by Vandenberg T, *et al*. reported an incidence of 29% febrile neutropenia among 902 patients selected for their study.[18] In another study by Weycket D, *et al*. the mean age reported in their study was 58 years and incidence of febrile neutropenia reported ranged from 13.1% to 20.6%.[19] On the contrary in our study, the incidence of febrile neutropenia reported was 52%, which is higher than in the studies mentioned above.

Neutropenia is most commonly seen as a result of cytotoxic therapy although the Absolute Neutrophil Count of individuals can drop significantly through cancer's direct interaction with hematopoiesis (e.g. in leukemia) or the bone marrow metastatic replacement. The types of chemotherapy that can highly induce neutropenia include products such as the anthracyclines, taxanes, topoisomerase inhibitors, platinums, gemcitabine, vinorelbine, and certain alkylators like cyclophosphamide and ifosfamide. Since FN in cancer patients is usually a direct consequence of chemotherapy, an evaluation of risks factors associated with FN is necessary before any attempt to prevent the occurrence of the condition. However, medication is not the only risk factor, and the other factors should be taken into account. In the elderly patients (aged 65 and over), there is an elevated risk of FN occurrence and particular consideration should be given to this category of patients. In a study by Miller *et al* reported an incidence of 85% febrile neutropenia among the 156 cancer patients on chemotherapy. [20] In another study by Pujol *et al* of 109 patients, 91% were documented to have febrile neutropenia.[21] Quoix *et al* in their study of 38 patients reported a 57% frequency of febrile neutropenia. [22]In a study by Schiller *et al* of 402 patients, 67% were found to have febrile neutropenia. [23] Another study by Hanna *et al* reported an 86.5% incidence of febrile neutropenia among 106 patients. [24] Schmittel *et al* recorded that 51% of their 35 patients selected had febrile neutropenia. [25]In a study by Heigener *et al*, incidence of febrile neutropenia reported was 69.4% among 37 cancer patients. [26] In another study by Lara *et al* of 324 patients, 68% of the patients were found to have febrile neutropenia. [27] Zatloukal *et al* in their study of 203 patients, the range of febrile neutropenia in their study was found to be from 51-91%. [28] Our study reported164 (52%) patients to have febrile neutropenia.

The qualitative approach of our study has assured that we have observed the extensive range of chemotherapeutic agents and it effects on febrile neutropenia. However the findings might not be free from observer bias. Considering the findings of our study and to what range the different chemotherapeutic agents might be related to febrile neutropenia would be revealing to discover more facts about cancer patients on chemotherapy.

CONCLUSION

Our study indicated that febrile neutropenia is more frequent in this part of world than western part of the world. This could be because of poor nutritional status of our patients.

References

1. Clark OA, Lyman GH, Castro AA, Clark LG, Djulbegovic B. Colony-stimulating factors for

chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. *Journal of Clinical Oncology*. 2005 Jun 20;23(18):4198-214.
2. de Naurois J, Novitzky-Basso I, Gill MJ, Marti FM, Cullen MH, Roila F. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. *Annals of Oncology*. 2010;21(5):252-6.
3. Klastersky J, de Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. *Annals of Oncology*. 2016;27(5):111-8.
4. Rasmy A, Amal A, Fotih S, Selwi W. Febrile Neutropenia in Cancer Patient: Epidemiology, Microbiology, Pathophysiology and Management. *J Cancer PrevCurr Res*. 2016;5(3):165-72
5. Kristjanson M. Febrile neutropenia, the empirical strike back. *Cancer Care Manitoba*. 2015;6(25):1-6.
6. Andrès E, Mourot-Cottet R, Maloisel F, Keller O, Vogel T, Séverac F, *et al*. History and Outcome of Febrile Neutropenia Outside the Oncology Setting: A Retrospective Study of 76 Cases Related to Non-Chemotherapy Drugs. *Journal of clinical medicine*. 2017 Sep 26;6(10):92.-103
7. Lustberg MB. Management of neutropenia in cancer patients. *Clinical advances in hematology & oncology:* 2012 Dec;10(12):825-6.
8. Hoggatt J, Tate TA, Pelus LM. Role of lipegfilgrastim in the management of chemotherapy-induced neutropenia. *International Journal of Nanomedicine*. 2015 Apr 1;10:2647-52.
9. Nesher L, Rolston KV. The current spectrum of infection in cancer patients with chemotherapy related neutropenia. *Infection*. 2014 Feb 1;42(1):5-13.
10. O'Connor ML, Xiang D, Shigdar S, Macdonald J, Li Y, Wang T, *et al*. Cancer stem cells: a contentious hypothesis now moving forward. *Cancer letters*. 2014 Mar 28;344(2):180-7.
11. Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: a systematic review. Critical reviews in oncology/hematology. 2014 Jun 30;90(3):190-9.
12. DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, *et al*. Cancer treatment and survivorship statistics, 2014. CA: a cancer journal for clinicians. 2014 Jul 1;64(4):252-71.
13. Schnipper LE, Smith TJ, Raghavan D, Blayney DW, Ganz PA, Mulvey TM, *et al*. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. *Journal of Clinical Oncology*. 2012 Apr 4;30(14):1715-24.
14. Smith TJ, Hillner BE. A way forward on the medically appropriate use of white cell growth factors. *Journal of Clinical Oncology*. 2012 Feb 27;30(14):1584-7.
15. Bennett CL, Djulbegovic B, Norris LB, Armitage JO. Colony-stimulating factors for febrile neutropenia during cancer therapy. *New England Journal of Medicine*. 2013 Mar 21;368(12):1131-39.
16. Shaikh AJ, Bawany SA, Masood N, Khan AA, Abbasi AN, Niamutullah SN, *et al*. Incidence and impact of baseline electrolyte abnormalities in patients admitted with chemotherapy induced febrile neutropenia. *Journal of Cancer*. 2011;2:62-66
17. Younus J, Vandenberg T, Jawaid M, Jawaid MA. Febrile neutropenia rates with adjuvant docetaxel and cyclophosphamide chemotherapy in early breast cancer: discrepancy between published reports and community practice-an updated analysis. *Current Oncology*. 2012 Dec;19(6):332-34
18. Vandenberg T, Younus J, Al-Khayyat S. Febrile neutropenia rates with adjuvant docetaxel and cyclophosphamide chemotherapy in early breast cancer: discrepancy between published reports and community practice—a retrospective analysis. *Current Oncology*. 2010;17(2):2-3.
19. Weycker D, Li X, Edelsberg J, Barron R, Kartashov A, Xu H, *et al*. Risk and consequences of chemotherapy-induced febrile neutropenia in patients with metastatic solid tumors. *Journal of oncology practice*. 2014 Dec 9;11(1):47-54.
20. Miller AA, Herndon JE, Hollis DR, Ellerton J, Langleben A, Richards F, *et al*. Schedule dependency of 21-day oral versus 3-day intravenous etoposide in combination with intravenous cisplatin in extensive-stage small-cell lung cancer: a randomized phase III study of the Cancer and Leukemia Group B. *Journal of clinical oncology*. 1995 Aug;13(8):1871-9.
21. Pujol JL, Daures JP, Riviere A, Quoix E, Westeel V, Quantin X, *et al*. Etoposide plus cisplatin with or without the combination of 4′-epidoxorubicin plus cyclophosphamide in treatment of extensive small-cell lung cancer: a French Federation of Cancer Institutesmulticenter phase III randomized study. *Journal of the National Cancer Institute*. 2001 Feb 21;93(4):300-8.
22. Quoix E, Breton JL, Daniel C, Jacoulet P, Debieuvre D, Paillot N, Kessler R, Moreau L, Coetmeur D, Lemarié D, Lemarié D. Etoposide phosphate with carboplatin in the treatment of elderly patients with small-cell lung cancer: a phase II study. *Annals of oncology*. 2001 Jul;12(7):957-62.
23. Schiller JH, Adak S, Cella D, DeVore RF, Johnson DH. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593-a phase III trial of the Eastern Cooperative Oncology Group. *Journal of Clinical Oncology*. 2001 Apr 15;19(8):2114-22.
24. Hanna N, Bunn Jr PA, Langer C, Einhorn L, Guthrie Jr T, Beck T, *et al*. Randomized phase III trial comparing irinotecan/cisplatin withetoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *Journal of clinical oncology*. 2006 May 1;24(13):2038-43.
25. Schmittel A, von Weikersthal LF, Sebastian M, Martus P, Schulze K, Hortig P, *et al*. A randomized phase II trial of irinotecan plus carboplatin versus etoposide plus carboplatin treatment in patients with extended disease small-cell lung cancer. *Annals of oncology*. 2006 Jan 19;17(4):663-7.
26. Heigener DF, Manegold C, Jäger E, Saal JG, Zuna I, Gatzemeier U. Multicenter randomized open-label phase III study comparing efficacy, safety, and tolerability of conventional carboplatin plus etoposide versus dose-intensified carboplatin plus etoposide plus

lenograstim in small-cell lung cancer in "extensive disease" stage. *American journal of clinical oncology*. 2009 Feb 1;32(1):61-4.

27. LaraJr PN. Phase III trial of Irinotecan/Cisplatin compared with Etoposide/Cisplatin in extensive-stage small-cell lung cancer: Clinical and pharmacogenomic results from SWOG S0124. *J ClinOncol*. 2009; 27:2530-5.
28. Zatloukal P, Cardenal F, Szczesna A, Gorbunova V, Moiseyenko V, Zhang X, *et al*. A multicenter international randomized phase III study comparing cisplatin in combination with irinotecan or etoposide in previously untreated small-cell lung cancer patients with extensive disease. *Annals of oncology*. 2010 Mar 15; 21(9):1810-6.

How to cite this article:

Reena Kumari *et al* (2018) 'Incidence of Febrile Neutropenia Among Cancer Patients Receiving Chemotherapy, A Single Center Experience From Pakistan', *International Journal of Current Advanced Research,* 07(7),pp. 13977-13981.
DOI: http://dx.doi.org/10.24327/ijcar.2018.13981.2517

****