IJBC 2013;1: 3-7

Main Determinants of Severe Neutropenia in Patients with Solid Tumors Receiving Adjuvant Chemotherapy

Ghahramanfard F[1], Faranoush M [2]*, Ghorbani R [3], Rahbar M [4]

1. Assistant professor, medical hematologist oncologist, Fatemieh Hospital, Semnan University of Medical Sciences, Semnan, Iran.

2. Associate professor, pediatric hematologist oncologist, Amir al Momenin hospital, Semnan University of Medical Sciences, Iranian Blood Transfusion Organization.

3. Associate professor, Research Center for Social Determinants of Health, Department of Community Medicine Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran.

4. MD, Semnan University of Medical Sciences, Semnan, Iran.

***Corresponding Author:** Faranoush M, Email: faranoush47@aim.com*

Submitted: 15-04-2012 , Accepted: 12-07-2012

Abstract

Background:Chemotherapy-induced neutropenia as a major toxicity of systemic chemotherapy is commonly associated with substantial mortality and morbidity, and thus identifying its determinants is necessary. This study was undertaken to identify main risk factors of severe neutropenia following adjuvant chemotherapy treatment in a community-based population of patients with cancer in Semnan, Iran.

Materials and methods: This prospective study included 828 consecutive patients with histologically proven primary or metastatic solid tumors who received chemotherapy. Demographics data, disease characteristics, and co-morbidities (including current smoking and diabetes) were collected by face to face interviews with the patients and also by referring to their laboratory data and files. Patients underwent complete blood count a week after the first chemotherapy course.

Results: Based on the nadir value of the absolute neutrophil count (ANC), 30 patients (3.6%) had severe neutropenia. Multivariable logistic regression analysis showed that advanced age (OR = 5.262, p = 0.012), and the presence of diabetes mellitus (OR = 8.126, p = 0.015) were the main determinants for the appearance of severe neutropenia with the presence of demographics and studied co-morbidities as confounders.

Conclusion: We identified advanced age and the presence of diabetes as the main determinants of high-grade neutropenia in solid tumor patients receiving adjuvant chemotherapy in our study population.

Keywords: Neutropenia, solid tumor, chemotherapy.

Introduction

IChemotherapy is considered to be a complex and prolonged regimen that includes various agents given alone or in combination repeatedly, over a prolonged period e. This therapeutic regimen is usually intense and dosage reduction is seldom considered. This intensive treatment might cause serious complications namely anemia, neutropenia, and thrombocytopenia and their associated side-effects including fatigue, infection, and bleeding [1].

Chemotherapy-induced neutropenia as a major toxicity of systemic chemotherapy is commonly associated with substantial mortality and morbidity. It can necessitate hospitalization for evaluation and empiric broad-spectrum antibiotics therapy due to its concomitant morbidities such as fever and bacteremia [2]. Multiple studies over the past 30 years have demonstrated that different aspects of health-related quality of life including activities of daily living and also participation in activities that give meaning and value to a person's life are affected by the treatment-related side-effects of cancer such as neutropenia [3]. Hence, determining main risk factors for severe neutropenia is necessary to prevent its related life-threatening complications.

Review of literature indicated a wide spectrum of risk factors for severe neutropenia in various types of tumors, such as advanced age, female sex, poor performance status, poor nutritional status, and low baseline and first-cycle nadir blood cell counts along with high chemotherapy dose

intensity [4-9]. It seems that the main risk profile of severe neutropenia can be classified based on disease, patient characteristics, and the type of treatment [10-12].

This study was undertaken to identify main determinants of severe neutropenia following chemotherapy treatment in a community-based population of patients with cancer in Semnan, Iran. We especially studied the role of demographics as well as some factors such as cigarette smoking and diabetes mellitus in causing neutropenia.

Materials and methods

This prospective study included 828 consecutive patients who received chemotherapy at

the general hospitals of Semnan city from September 2006 to May 2010. All patients with histologically proven primary or metastatic solid tumors were enrolled. Informed consent was taken from patients, parents, or their guardians. Patients were treated with chemotherapy as adjuvant or for metastatic disease. All data were recorded on the first cycle of the selected chemotherapy regimen only. The study was approved by the ethics committee of the internal review board of the Semnan University of Medical Sciences. Demographics data, disease characteristics, and co-morbidities (including current smoking and diabetes) were collected by face to face interviews with the patients and from their laboratory data and files. Current cigarette smoking was defined as regular smoking a tobacco product/products one or more times per day or smoking in the 30 days prior to admission [13]. Diabetes mellitus was defined as the presence of the symptoms of diabetes plus at least one of the following criteria: plasma glucose concentration ≥11.1 mmol/l, fasting plasma glucose ≥7.0mmol/l, and 2-hpp ≥11.1 mmol/l [14]. Patients underwent complete blood count a week after the first chemotherapy course. Primary outcome including severe neutropenia (nadir value of the absolute neutrophil count (ANC) < 500/µL) was determined, and the study objective was to describe the incidence of severe neutropenia risk factors. Data were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables.

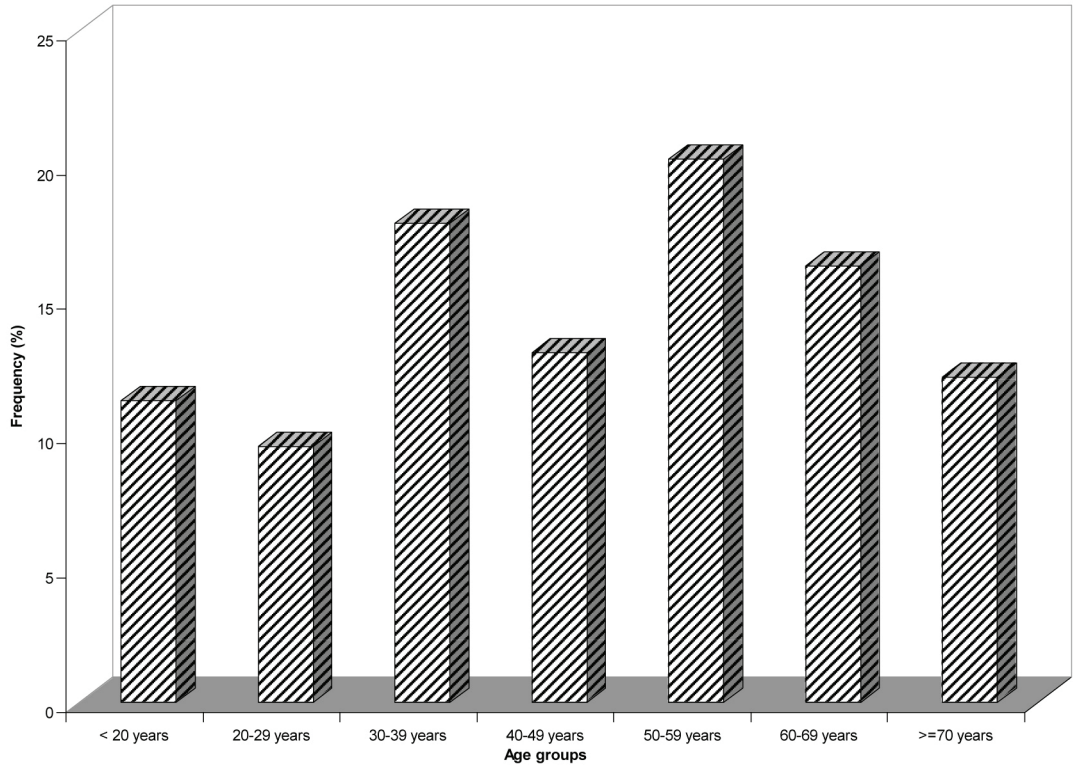

Figure 1: Age distribution of participants with different types of cancers.

Categorical variables across the study groups were compared using the Chi-square test or Fisher's exact test if required. To determine main correlates of severe neutropenia, multivariable logistic regression analysis was used adjusting for study variables. Results of this model were presented as Odds Ratio (OR) and 95% confidence intervals (95% CIs) for OR. P values of 0.05 or less were considered statistically significant. All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Age distribution of participants is shown in figure 1. Study patients with different types of cancers were more frequent in the sixth decade of life. The mean age of patients was 48.9 ± 18.7 years and 66.7% were female. Regarding the type of common malignancies, in order of frequency 35.7% of patients had breast cancer, 15.3% colorectal cancer, 7.1% Hodgkin's lymphoma 6.5% other types of lymphomas, and 4.1% had prostate cancer respectively.

Other malignancies included ovarian cancer, and lung cancer that were observed in 3.9%, and 2.3% of patients, respectively. With respect to underlying co-morbidities, 215 patients (26.0%) were current smoker and 175 cases (21.2%) had diabetes. Based on the ANC nadir value, 30 patients (3.6%) had severe neutropenia (Figure 2). The overall incidence of current cigarette smoking in patients with and without severe neutropenia was 26.3% and 16.7%, respectively. Diabetes mellitus was also reported in 21.9% of patients with severe neutropenia and only 3.3% of patients without severe neutropenia. There were significant differences in the overall incidence of current smoking and diabetes mellitus between the patients with severe neutropenia and patients without severe neutropenia.

Multivariable logistic regression analysis (Table 1) showed that advanced age (OR = 5.262, p = 0.012) and the presence of diabetes mellitus (OR = 8.126, p = 0.015) were the main determinants for the appearance of severe neutropenia with the presence of demographics and studied co-morbidities as confounders.

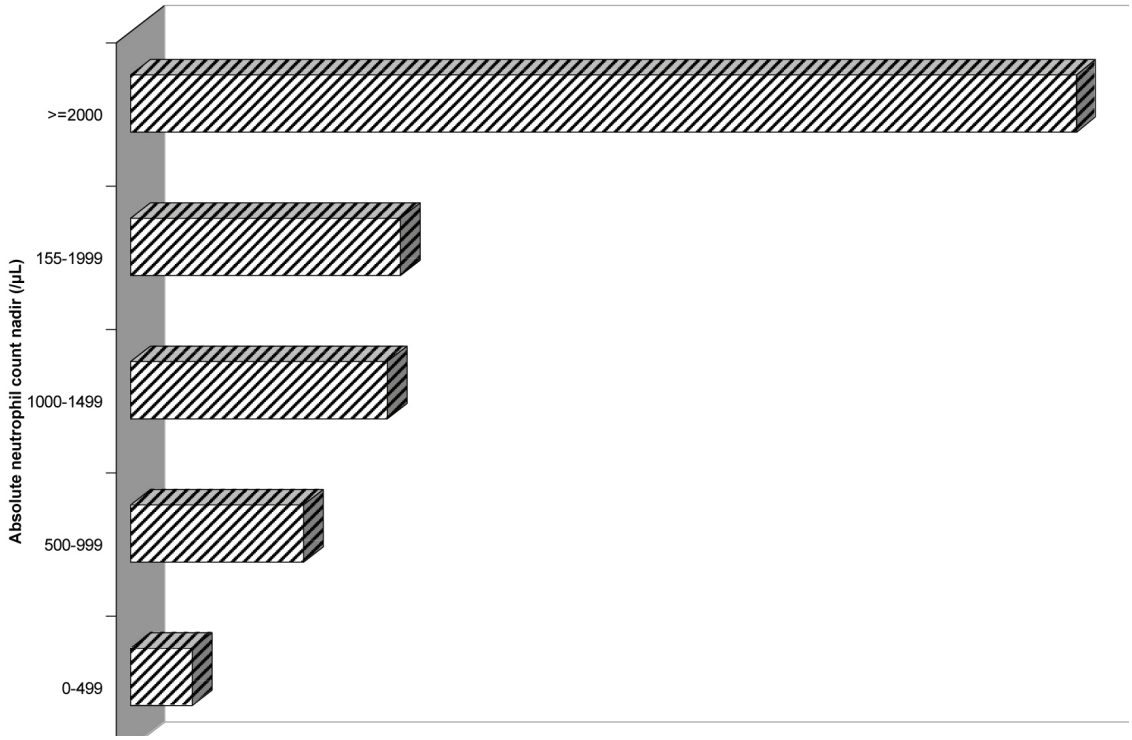

Figure 2: Neutrophil count categorization in study participants with cancer.

Discussion

Because of the reported differences in the overall incidence of neutropenia complications in solid tumors and hematologic malignancies, we decided to study the risk factors of severe neutropenia in different types of solid tumors. In our study, advanced age had a crucial role in predicting the rate of severe neutropenia following chemotherapy in malignant solid tumors.

Similar to our study, some studies have found higher age to be a general risk factor for the development of severe neutropenia[2,4,15-16], and other neutropenic complications [10, 12, 17]. Advanced age is a particularly important independent risk factor, since older patients are often treated with lower chemotherapy doses to minimize the occurrence of neutropenic complications. Since older patients with cancer can obtain the same benefit from aggressive chemotherapy as younger patients [18], effective management of the risk of neutropenia is crucial to make it possible to administer full-dose chemotherapy in this population. So the use of prophylactic agents such as myelopoietic growth factors is recommended in older individuals when the risk of chemotherapy-induced neutropenia is predicted to be considerably high.

Among co-morbidities, we only assessed the correlation of diabetes mellitus with the

appearance of severe neutropenia and thus we found its strong relationship with neutropenia in patients with solid tumors undergoing chemotherapy. The presence of co-morbid conditions with cancer has been shown to increase the risk of neutropenia and it seems that each especial type of tumors has specific clinical predicting co-morbidities.

Renal disease and heart disease have been shown to increase the risk for severe neutropenia in patients with non-Hodgkin's lymphoma [4,5]. In patients with breast cancer, liver disease along with kidney and heart disease increase the risk for severe neutropenia [6]. Similarly, some risk factors such as hypertension, chronic obstructive pulmonary disease, pneumonia, prior fungal infection, and sepsis have been shown to increase the risk for serious neutropenic complications, including prolonged hospitalizations for neutropenia and death [10, 12, 19]. Similar to our study Wolff et al showed that diabetes was a significant predictor of severe neutropenia in addition to cancer and regimen type[20]. Also, in a study by Srokowski et al., patients who had breast cancer and diabetes were at increased risk of chemotherapy-related neutropenia compared with non-diabetics who received chemotherapy and also had higher all-cause mortality [21]. In contrast, Meyerhardt et al. did not find an increased incidence of treatment-related neutropenia in diabetic versus non-diabetic patients who received adjuvant chemotherapy for colon cancer [22]. This difference may be due to the use of less-toxic chemotherapy regimens and to a younger study population in the last study.

In summary, based on our finding, clinicians must be aware that diabetic patients are more likely to experience toxicity after chemptherapy for solid tumors and should be monitored closely.

Table1: Main determinants of the appearance of severe neutropenia.

Variables	p-value	Odds Ratio (OR)	95% Confidence Interval for OR
Female gender	0.356	1.214	0.658-1.789
Age >60 years	0.012	5.262	1.243-22.276
Cigarette smoking	0.237	1.786	0.675-4.725
Diabetes mellitus	0.015	8.126	1.099-60.073

Hosmer-Lemeshow goodness of fit: Chi-Square = 12.567, p=0.128

Conclusion

We identified advanced age and the presence of diabetes as the main determinants of high-grade neutropenia in solid tumor patients receiving adjuvant chemotherapy in our study population.

References

1. Fortner B, Baldwin S, Schwartzberg L, Houts A. Validation of the cancer care monitor items for physical symptoms and treatment side effects using expert oncology nurse evaluation. Journal of Pain and Symptom Management 2006; 31(3): 207-214.
2. Lyman GH, Lyman CH, Agboola O. Risk models for predicting chemotherapyinduced neutropenia. The Oncologist 2005;10:427-37.
3. Efficace F, Novik A, Vignetti M, Mandelli F, Cleeland C. Health related quality of life and symptom assessment in clinical research of patients with hematological malignancies: Where are we now and where do we go from here? Haematologica 2007; 92(12):1596-8.
4. Lyman GH, Morrison VA, Dale DC, Crawford J, Delgado DJ, Fridman M, et al. Risk of febrile neutropenia among patients with intermediate-grade non-Hodgkin's lymphoma receiving CHOP chemotherapy. Leuk Lymphoma 2003;44(12): 2069-76.
5. Morrison VA, Picozzi V, Scott S, Pohlman B, Dickman E, Lee M, et al. The impact of age on delivered dose intensity and hospitalizations for febrile neutropenia in patients with intermediate-grade non Hodgkin's lymphoma receiving initial CHOP chemotherapy: a risk factor analysis. Clin Lymphoma 2001;2(1):47-56.
6. Morrison VA, Caggiano V, Fridman M, Delgado DJ, et al. A model to predict chemotherapy-related severe or febrile neutropenia in cycle one among breast cancer and lymphoma patients. Proc Am Soc Clin Oncol 2004;23:742. (Abstract)
7. San Matías S, Clemente M, Giner-Bosch V, Giner V. Predicting the duration of chemotherapy-induced neutropenia: new scores and validation. Ann Oncol. 2011; 22(1):181-7.
8. Szucs TD, Leonard R, Pettengell R, Paridaens R, Jackisch C, Constenla M, et al. Dose-limiting effects of neutropenic events in six European audits of adjuvant breast cancer chemotherapy. Proc Am Soc Clin Oncol 2004;24: 31. (Abstract)
9. Blay JY, Chauvin F, Le Cesne A, Anglaret B, Bouhour D, Lasset C, et al. Early lymphopenia after cytotoxic chemotherapy as a risk factor for febrile neutropenia. J Clin Oncol 1996;14(2):636-43.
10. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying lowrisk febrile neutropenic cancer patients. J Clin Oncol. 2000;18(16):3038-51.
11. Leong DC, Kinlay S, Ackland S, Bonaventura A, Stewart JF. . Low-risk febrile neutropenia in a medical oncology unit. Aust N Z J Med. 1997;27(4):403-7.
12. 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(10):2258-66.
13. Barrett-Connor E, Giardina EG, Gitt AK, Gudat U, Steinberg HO, Tschoepe D. Women and heart disease: the role of diabetes and hyperglycemia. Arch Intern Med 2004; 164(9): 934-42.
14. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2008;31 Suppl 1:S55-60.
15. Kloess M, Wunderlich A, Trumper L Pfreundschuh M, M. Loeffler M. Predicting hematotoxicity in multicycle chemotherapy. Blood 1999;94:10 (Suppl 1). (Abstract)
16. Aslani A, Smith RC, Allen BJ, Pavlakis N, Levi JA. The predictive value of body protein for chemotherapy-induced toxicity. Cancer. 2000 Feb 15;88(4):796-803.
17. Kim YJ, Rubenstein EB, Rolston KV. Colony stimulating factors (CSFs) may reduce complications and death in solid tumor patients (Pts) with fever and neutropenia. Proc Am Soc Clin Oncol 2000;19:612a. (Abstract)
18. Balducci L, Repetto L. Increased risk of myelotoxicity in elderly patients with nonHodgkin lymphoma. Cancer 2004;100(1):6-11.
19. González-Barca E, Fernández-Sevilla A, Carratalá J, Salar A, Peris J, Grañena A, et al. Prognostic factors influencing mortality in cancer patients with neutropenia and bacteremia. Eur J Clin Microbiol Infect Dis 1999;18(8):539-44.
20. Wolff DA, Crawford J, Dale DC, Poniewierski MS, Lyman GH. Risk of neutropenic complications based on a prospective nationwide registry of cancer patients initiating systemic chemotherapy. J Support Oncol. 2005;3(2)(Suppl 1):56-57.
21. Srokowski TP, Fang S, Hortobagyi GN, Giordano SH. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. J Clin Oncol.

2009;27(13):2170-6.
22. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Macdonald JS, Benson AB 3rd, Fuchs CS. Impact of diabetes mellitus on outcomes in patients with colon cancer. J Clin Oncol. 2003;21(3):433-40.