IS SERUM ALBUMIN AN INDEPENDENT PREDICTOR OF POST CHEMOTHERAPY FEBRILE NEUTROPENIA?

Lubna Saleem, Naila Anjum Zahid

Liaquat National Hospital Karachi Pakistan

ABSTRACT

Objective: To evaluate the association between serum albumin and risk of post chemotherapy febrile neutropenia.

Study Design: Cross sectional study.

Place and Duration of Study: Department of oncology, Liaquat National Hospital, from 1st Jan 2015 to 31st Dec 2016.

Material and Method: One hundred and sixty-six biopsy proven cancer patients with Eastern cooperative oncology group (ECOG) performance status <2 and without significant co-morbidities received first cycle of chemotherapy during two years study period. Different chemotherapies with moderate to severe risk of FN were used. Patient's pre-treatment serum albumin was measured and patients followed for occurrence of FN. Association between serum albumin and post chemotherapy FN was analyzed.

Results: Data of 166 patients was available for final analysis. Post chemotherapy FN was observed in 19.9% (33/166) patients. Pre-chemotherapy serum albumin level was <3.5 mg/dl in (35/166) 21.1% of patients, out of which (15/35) 42.9% developed FN. Serum albumin (p=0.0005) was highly significantly associated with a risk of FN. On analysis of other factors age, gender, body surface area (BSA) and pre-chemotherapy hemoglobin level were not significantly associated with a risk of FN while body mass index (p=0.0005) was found to be associated with risk of FN.

Conclusion: Pre-chemotherapy serum albumin levels were found to be statistically significant predictor of post-chemotherapy febrile neutropenia.

Keywords: Body mass index, Post chemotherapy febrile neutropenia, Serum albumin

INTRODUCTION

Chemotherapy induced febrile neutropenia (FN) is a common problem in cancer patients. An incidence of 7.83 neutropenic hospitalizations per 1000 cancer patients has been reported[1]. Depending on type of cancer, stage of disease and chemotherapy regimen, neutropenia has been observed in 6–50% of patients[2]. FN is associated with significant risk of life threatening infections and complications, resulting in high economic burden, reduced quality of life, and even treatment-related death, which may need dose reduction and even delays in treatment[3], thus resulting in compromised clinical outcome[4]. Mortality rate associated with grade 3 or 4 neutropenia range from 3.4-10.5%[3]. As several studies have demonstrated that risk of FN is greatest in the first cycle of chemotherapy[5], before starting chemotherapy identifying individuals who are at risk of significant myelosuppression is of considerable importance to medical oncologist.

Several studies have been done previously for identification of risk factors for myelosuppression and various risk models have been proposed. Review of these risk-models identify multiple factors which can be classified as patients specific, disease specific and regimen specific[6-10]. Patient's specific risk factors are age, measures of pretreatment nutritional status and comorbid conditions but these risk assessment models are largely based on retrospective data and have several methodological limitations such as small sample size, adjustment for different risk factors and lack of validation[6-10]. Although the

Correspondence: Dr Lubna Saleem, Dept of Oncology Liaquat National Hospital Karachi Pakistan *(Email: lubnaijlal@gmail.com)*

Received: 06 Jun 2017; revised received: 13 Jul 2017; accepted: 13 Jul 2017

dose and type of chemotherapy regimen is the most important predictor of FN[11], it could not be ignored that all patients receiving same chemotherapy regimen do not experience FN. Prophylactic use of granulocyte colony stimulating factor is recommended with those chemotherapies which have >20% risk of FN[12], but we observe that despite giving granulocyte colony-stimulating factor (GCSF), some patients develop FN and others do not, so there must be some underlying patient related factors, which need to be identified. However, it is not possible to determine the significance of each factor separately without balancing other confounding factors.

Malnutrition is highly prevalent among cancer patients due to different mechanisms[13,14]. It is significantly associated with decreased quality of life, poor response to treatment[15], increased risk of treatment related complications, lengthening the hospital stay and decreased overall survival[16,17]. The prevalence of morbidity associated with malnutrition in cancer patients range from 40-80%[18]. Various methods to assess nutritional status of cancer patients have been used previously, each with its own advantages and disadvantages. Most common of them are subjective global assessment (SGA) and laboratory measurements of serum albumin level. SGA is a subjective tool and can have inter-observer variation[19]. Serum albumin is a simple way of assessing baseline nutritional status and has been analyzed as important part of risk assessment models for FN[6,19-22]. Older age, poor performance status and co morbid conditions are the most common documented patient specific risk factors for FN[6-10]. However importance of serum albumin in predicting risk of FN has not been documented, so in order to analyze the role of serum albumin as an independent risk factor for FN we conducted this study and in order to minimize the bias for other risk factors i.e. age, poor performance status and co-morbids, we included only younger patients with good performance status and without significant co morbidities in our study. To identify those patients who are at greater risk of neutropenic complications, so that specific measures to improve nutritional status and serum albumin level can be taken to improve the treatment outcome.

MATERIAL AND METHODS

This study was approved by the ethical and scientific committee of Liaquat National Hospital, Karachi. This was a cross sectional study, and consecutive sampling technique was used. The study was conducted in oncology department of Liaquat National Hospital, Karachi. One hundred and sixty-six patients with common malignancies who had been planned for conventional chemotherapy regimens between 1st Jan 2015 to 31st Dec 2016 were included in this study and followed up to see whether they developed FN or not after first cycle of chemotherapy. FN was defined as single fever spike of >38.30C and neutrophil count <1000/mcL.

Patients with histologically confirmed common malignancies. , adult patients between 20-75 years of age and ECOG performance status of <2 were included in the study while patients with documented or suspected bone marrow infiltration by malignant cells, serious co morbid conditions, such as chronic renal failure or chronic liver disease or cardiac problems, patients who had received high dose chemotherapy followed by bone marrow transplant, patients on concurrent chemo-radiation, patients who had previously received chemotherapy and patients with an active infection or receipt of an antibiotic in the 72 hrs before chemotherapy were excluded from the study.

The purpose, procedure, risks and benefits of the study were explained to the patient and a written informed consent taken. One hundred and sixty six consecutive cancer patients who were planned for first cycle of chemotherapy regimen and who met the inclusion criteria were included in the study. Pretreatment data of all patients was collected regarding demographics and clinical variables including age, gender, height, weight, performance status, body surface

area, cancer type, disease stage and planned chemotherapy treatment including drugs, doses and schedule. The hematological evaluation comprised complete blood count, blood chemistry included serum glucose, Blood urea nitrogen (BUN), creatinine, liver function tests and serum albumin. Serum albumin levels were measured with the bromcresol purple method (Immunoturbidimetry method on Roche c501 chemistry analyzer) and levels <3.5 mg/dL of albumin were taken as hypoalbuminemia. BMI was calculated as weight (kg)/height squared (m^2). Prophylactic GCSF was given for 5 days to those patients who received chemotherapies with more than 20% risk of FN or dose dense schedules. After receiving chemotherapy these patients were observed for fever more than 38.3°C. Those patients who developed fever their blood counts were checked and if their neutrophil count came <1000/mcL they are labeled as having FN and admitted in hospital.

All data were analyzed with statistical package for the social sciences (SPSS) statistics software (version. 22). Qualitative variables were computed by frequency and percentage and quantitative variables were estimated by mean and standard deviation. The chi-square test or Fisher exact test was used to assess the relationship between the different variables. Univariate and multivariate logistic regression was applied to estimate un-adjusted and adjusted odds ratio with 95% confidence interval. A *p*-value <0.05 was considered statistically significant.

Table-I: Demographic and clinical characteristics of study patients (n=166).

Variables	Point Estimate
Age (Years)	46.97 ± 11.12
Height (cm)	154.90 ± 7.94
Weight (kg	65.94 ± 13.94
BMI (kg/m^2)	27.54 ± 5.70
BSA	1.67 ± 0.18
Gender	
Male	18 (10.8%)
Female	148 (89.2%)
Baseline CBC and LFT	
Hemoglobin(g/dl)	12.15 [11.3-13.1]
Platelet Count ()	302.5 [246-349]
Albumin (mg/dl)	4.0 [3.66-4.20]
TLC	9.1 [7.0-11.03]
LFT	20 [14-25]
Diagnosis	
Breast cancer	128 (77.1%)
Lymphoma	10 (6%)
GIT tumor	9 (5.4%)
FGT tumor	7 (4.2%)
Others	12 (7.2%)
Stage of Disease	
Stage I	8 (4.8%)
Stage 2	45 (27.1%)
Stage 3	88 (53%)
Stage 4	25 (15%)

Results are presented as mean ± SD, median (p25-p75) and n(%).
BMI, body mass index; BSA, body surface area; CBC, complete blood count; LFT, liver function test; TLC, Total leucocyte count.

RESULTS

A total of 166 biopsy proven cases of common malignancies were included in this study who have been started 1st cycle of conventional chemotherapy regimens containing approved cytotoxic agents. The average age of the patients was 46.97 ± 11.12 years. Most of the cases were female 89.2%. Average serum albumin was 4.0 (3.66-4.20). Average body mass index was 27.54 ± 5.70 and BSA was 1.67 ± 0.18.

Breast cancer was the commonest malignancy (77.1%) followed by lymphoma (10.6%), gastrointestinal tract (5.4%), female genital tract (4.2%) and others (7.2%). Most of the patients had stage III disease (53%). Baseline demographics and disease characteristics are summarized in table-I.

Most of the patients received anthracycline based chemotherapy (61%). Other regimens were taxane based (20.5%), platinum based (4.8%), RCHOP (3%), FOLFIRINOX (1.8%) and others (8.4%). Hence, a wide variety of anticancer agents were used and all the chemotherapy regimens administered were in intermediate to high risk group of neutropenia. All agents were given in the recommended dose range and when in combination at standard doses. 48.8% (81/166) patients received prophylactic GCSF, while 51.2% (85/166) did not received prophylactic GCSF. Different chemotherapy regimens and rate of FN

Table-II: Risk factors associated with febrile neutropenia in cancer patients (n=166).

Variables	n	FN(+)	FN(-)	*p*-value	Odd Ratio [95% CI]
Age Groups (Years)					
≤60 Years	104	22 (21.2%)	82 (78.8%)	0.592	Ref
>60 Years	62	11 (17.7%)	51 (82.3%)		0.804 [0.36-1.79]
Gender					
Male	18	5(27.8%)	13(72.2%)	0.532	Ref
Female	148	28(18.9%)	120(81.1%)		0.61 [0.20-1.84]
BSA					
<1.9	141	31(22%)	110(78%)	0.171	3.24 [0.72-14.51]
≥1.9	25	2(8%)	23(92%)		Ref
HB					
<12 g/dl	68	12 (17.6%)	56 (82.4%)	0.548	0.78 [0.36-1.73]
≥12 g/dl	98	21 (21.4%)	77 (78.6%)		Ref
BMI (kg/m²)					
≤ 22 kg/m²	33	12 (36.4%)	21 (63.6%)	0.020	4.08 [1.41-11.81]
22- 28 kg/m²	76	14 (18.4%)	62 (81.6%)		1.61 [0.60-4.30]
>28 kg/m²	57	7 (12.3%)	50 (87.7%)		Ref
Baseline Albumin					
≤3.5 mg/dl	35	15(42.9%)	20(57.1%)	<0.001	4.71 [2.04-10.84]
>3.5 mg/dl	131	18(13.7%)	113(86.3%)		Ref

Results are presented as n(%). FN, febrile neutropenia; HB, Hemoglobin; BMI, Body mass Index, BSA, Body surface area.

Table-III: Multivariate analysis of risk factors for febrile neutropenia in cancer patients.

Variables	Adjusted Odd Ratio	95%CI	*p*-value
Baseline albumin			
≤3.5 mg/dl	4.704	2.04-10.84	0.005
>3.5 mg/dl		Ref	

Febrile neutropenia is an outcome variable. Model Accuracy = 80%
Other independent variables are excluded from the model due to insignificant effect.

after different chemotherapy regimen is shown in table-IV and V.

Post chemotherapy FN was observed in 19.9% (33/166) patients. Pre-chemotherapy serum albumin level was <3.5 mg/dl in (35/166) 21.1% of patients, out of which (15/35) 42.9% developed FN. Serum albumin (p=0.0005) was highly significantly associated with a risk of FN in univariate analysis as observed in table-II. Risk of FN was 5 times more likely in those patients who had albumin ≤3.5 mg/dl (OR=4.71; 95%CI: 2.04-1.0.84). Stepwise multivaraite logistic regression was performed and observes, FN was also significantly associated with albumin. Adjusted odd ratio showed that risk of FN was 5 times more likely in Albumin ≤3.5 mg/dl as shown in table-III. On sub analysis of other factors age, gender, BSA and pre-chemotherapy haemoglobin (HB) were not significantly associated with a risk of FN while body mass index (p=0.0005) found to be associated with risk of FN and risk of FN was 4 times more likely in those patients who had BMI ≤ 22 kg/m^2 (OR=4.08; 95%CI: 1.41-11.81).

Table-IV: Different chemotherapy regimens and febrile neutropenia (n=166).

Chemotherapy regimen	FN(+)	FN(-)	*p*-value
Anthracycline based chemotherapy (61.4%)	19(18.6%)	83(81.4%)	0.378
Taxanes based chemotherapy (20.5%)	8(23.5%)	26(76.5%)	
Platinum based chemotherapy (4.8%)	0(0%)	8(100%)	
RCHOP (3%)	1(20%)	4(80%)	
Folfirinox (1.8%)	0(0%)	3(100%)	
Others (8.4%)	5(35.7%)	9(64.3%)	

Results are presented as n (%) FN, febrile neutropenia.

Table-V: Prophylactic Granulocyte Colony-Stimulating Factor (GCSF).

		Frequency	Percent	FN +	FN -	*p*-value
Prophylactic GCSF	Given	81	48.8	20	61	0.129
				24.7%	75.3%	
	Not Given	85	51.2	13	72	
				15.3%	84.7%	
Total		166	100	33	133	

DISCUSSION

FN is one of the common side effects of chemotherapy. Multiple risk models have been identified to stratify one's risk of having FN before starting chemotherapy so that in high risk patients certain important decision regarding selection of chemotherapeutic agent with less toxicity, dose reduction or prophylactic GCSF could be made to prevent this life threatening condition developing.

Serum albumin concentration is the most commonly used biochemical marker of nutritional status[21]. Because of long half-life and broad distribution of albumin in the body acute changes in nutritional status do not readily reflect in serum albumin concentration[22]. Several mechanisms for increased risk of FN because of hypoalbumenimia have been proposed. The most important of these is bioavailability of more free form of chemotherapy in blood stream because of low albumin binding, thus altering pharmacokinetics of many anticancer agents resulting in more toxicity[14]. In our study we found that 21.1% patients had serum albumin <3.5 mg/dl. We found that patients who had normal albumin levels benefited in terms of less incidence of FN after first cycle of chemotherapy, in comparison with patients who had serum albumin levels below 3.5 mg/dL.

Our results are consistent with previous studies which also identified serum albumin as an important part of risk models for predicting post chemotherapy risk of FN, such as in non-hodgkin lymphoma patients, hypoalbuminemia

was identified as a risk factor and correlated with a higher incidence of FN[6,22]. Additionally, in non-small cell lung cancer patients treated with paclitaxel and cisplatin, low serum albumin was associated with severe cytotoxicity and FN. Also there was a possible association between serum albumin and overall survival among patients treated with docetaxel chemotherapy for castration-resistant prostate cancer (CRPC)[16].

We used different chemotherapies in our study, all with moderate to severe risk of neutropenia, so that we can justify that serum albumin is a predictive parameter of FN that is applicable to any chemotherapy regimen. In our study BMI <22 kg/m^2 was significantly associated with risk of FN. As BMI is a widely used parameter of nutritional assessement, therefore in additon to serum albumin BMI should also be incorporated in pre-chemotherapy nutritional assessements. In our study we did not find any association between any specific chemotherapy regimen and FN. The failure to identify association between any particular chemotherapy regimens causing FN and hypoalbuminemia is possibly because of small sample size. Theoretically the drugs which bind to serum albumin may have greater toxicity in patients with hypoalbuminemia which can be further confirmed by estimating serum levels of these chemotherapeutic agents in hypoal-buminemic patients but this was beyond the scope of our study. In our study 48.8% patients received prophylactic GCSF but despite giving GCSF 24.7% patients developed febrile neutropenia, among them half had serum albumin <3.5mg/dl. So the role of prophylactic GCSF in preventing FN only because of hypoalbuminemia remained unclear in our study.

CONCLUSION

Hypoalbuminemia is therefore an important risk factor for FN. We suggest that pretreatment nutritional assessment by serum albumin should be taken into account when deciding about type of chemotherapy and dosage modification of chemotherapies. As hypoalbuminemia is an important predisposing factor for FN prophylactic GCSF should be considered in hypoalbuminemic patients.

AUTHORS CONTRIBUTIONS

Dr Lubna Saleem: Worked on study concept and design, collection of Data, analysis and interpretation.

Dr Naila Zahid: Worked on study concept, analysis and interpretation of results, revised article critically for important intellectual content.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Chelenz S, Giles D, Abdallah SE. Pidemiology, management and economic impact of febrile neutropenia in oncology patients receiving route care at a regional UK cancer centre. Ann Oncol 2012; 23(7): 1889-93.
2. Smith TJ, Bohlke K, Lyman GH. Recommendations for the use of WBC growth factors: American Society of clinical oncology clinical practice guideline update. J Clin Oncol 2015; 33(28): 3199-212.
3. Pathak R, Giri S, Aryal MR, Karmacharya P, Bhatt VR, Martin M, et al. Mortality, length of stay and health care costs of febrile neutropenia-related hospitalizations among patients with breast cancer in united states. Support Care Cancer 2015; 23(3): 615-17.
4. Lyman GH. Impact of chemotherapy dose intensity on cancer patient outcomes. J Natl Compr Canc Netw 2009; 7: 99-108.
5. Culakova E, Thota R, Poniewierski MS, Kuderer NM, Wogu AF. Patterns of nation-wide prospective cohort. Cancer Med 2014; 3(2): 434-44.
6. 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.
7. Takumi F, Hirotsugu K, Tateaki N, Takahisa K. The incidence and risk factors of febrile neutropenia in chemotherapy-naïve lung cancer patients receiving etoposide plus platinum. Cancer Chemotherpy and Pharmacology 2017; 79: 1229-37.
8. Jenkins P, Scaife J, Freeman S. Validation of a predictive model that identifies patients at high risk of developing febrile neutropaenia following chemotherapy for breast cancer. Ann Oncol 2012; 23: 1766–71.
9. Eva C, Marek SP, Debra AW, David CD, Crawford J, Lyman GH, et al. The impact of chemotherapy dose intensity and supportive care on the risk of febrile neutropenia in patients with early stage breast cancer: A prospective cohort study. Springer plus 2015; 4: 396.
10. Thomas J, Smith TJ, Bohlke K, Lyman GH, Kenneth R, Crawford J, et al. Recommendations for the use of WBC Growth factors: American society of clinical oncology clinical practice guideline update. J Clin Oncol 2015; 33(28): 3199-3212.

11. Suzuki H, Asakawa A, Amitani H, Nakamura N, Inui A. Cancer cachexia--pathophysiology and management. J Gastroenterol 2013; 48(5): 574–94.
12. Trobec K, Kerec Kos M, Von Haehling S, Springer J, Anker SD. Pharmacokinetics of drugs in cachectic patients: A systematic review. PLoS ONE 2013; 8(11): e79603.
13. Andrea N, Paola F, Maria CM, Milena F, Stefania P. Malnutrition, anorexia and cachexia in cancer patients: A mini-review on pathogenesis and treatment. Biomedicine & Pharmacotherapy 2013; 67(8): 807-17.
14. Linton A, Pond G, Clarke S, Vardy J, Galsky M, Sonpavde G. Glasgow prognostic score as a prognostic factor in metastatic castration resistant prostate cancer treated with docetaxel based chemotherapy. Clin Genitourin Cancer 2013; 11: 423–30.
15. Ga WY, Kyung JE, Sang WK, EunJi N, Young TK. Malnutrition identified by the nutritional risk index and poor prognosis in advanced epithelial ovarian carcinoma. Nutrition and Cancer 2016; 68, 772-79.
16. Barret M, Malka D, Aparicio T, Dalban C, Locher C, Sabate JM, et al. Nutritional status affects treatment tolerability and survival in metastatic colorectal cancer patients: results of an AGEO prospective multicenter study. Oncology 2011; 81(5-6): 395–402.
17. Phippen NT, Lowery WJ, Barnett JC, Hall LA, Landt C, Leath CA. Evaluation of the patient-generated subjective global assessment (PG-SGA) as a predictor of febrile neutropenia in gynecologic cancer patients receiving combination chemotherapy: a pilot study. Gynecol Oncol 2011; 123: 360-4.
18. Yong WC, Seong HJ, Mi SA, Hyun WL. Patterns of neutropenia and risk factors for febrile neutropenia of diffuse large B-Cell lymphoma patients treated with rituximab-CHOP. J Korean Med Sci 2014; 29(11): 1493-1500.
19. Alexandre J, Gross-Goupil M, Falissard B, Nguyen ML, Gornet JM, Misset JL, et al. Evaluation of the nutritional and inflammatory status in cancer patients for the risk assessment of severe haematological toxicity following chemotherapy. Ann Oncol 2003; 14: 36-41.
20. Shiota M, Yokomizo A, Takeuchi A, Kiyoshima K, Inokuchi J. Risk factors for febrile neutropenia in patients receiving docetaxel chemotherapy for castration-resistant prostate cancer. Support Care Cancer 2014; 22(12): 3219-26.
21. Santarpia L, Contaldo F, Pasanisi F. Nutritional screening and early treatment of malnutrition in cancer patients. J Cachex Sarcopenia Muscle 2011; 2(1): 27-35.
22. Arrieta O, Ortega MRM, Rodríguez VG, SernaThomé MG, Flores-Estrada D. Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-smal cell lung cancer treated with Paclitaxel cisplatin chemotherapy: a prospective study. BMC Cancer 2010; 10: 50.

.....