Original Article

Non Hodgkin's Lymphoma

Frequency of Chemotherapy Induced Neutropenia in Patients of Non Hodgkin's Lymphoma

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ABSTRACT

Objective: The aim of the study is to see the frequency and severity of neutropenia after first or subsequent cycles of chemotherapy in patients of Non Hodgkin's lymphoma (NHL).

Study Design: Descriptive cross sectional study.

Place and Duration of Study: This study was carried in the Radiotherpay & Oncology Department, Bolan Medical Complex Hospital, Quetta, from March 2010 to February 2012.

Patients and Methods: Forty two patients of different types of NHL diagnosed on lymph node biopsy presenting for the first time at Radiotherapy & Oncology Department in collaboration with Haematology Section (Pathology Deptt:), Bolan Medical Complex Hospital, Quetta, were included. They were admitted in the ward and evaluated with history, physical examination and for staging investigations. Patients were then planned for chemotherapy comprising cyclophosphamide, doxorubicin, and vincristine with prednisolon (CHOP) and with rituximab (R-CHOP). After the first cycle of chemotherapy they were monitored for expected neutropenia in the ward. The neutrophil counts were repeated on days 7 and 10 following chemotherapy. Neutropenia was graded as defined in the operational definition and all the data were entered on a designed data sheet.

Results: Forty two patients of NHL were included in this study, of which 34 patients received CHOP, and 08 patients R-CHOP, from march, 2010 to February, 2012. According to WHO classification, 24(57.1%) patients were of Diffuse large B-cell lymphoma (DLBCL), 08(19.0%) were follicular lymphoma (FL) and 04(9.5%) patients were Mantle cell lymphoma (MCL) and remaining 06(1430) are other types of NHL's. 2(4.7%) of patients suffered from grage IV neutropenia (absolute neutrophil count of <0.5 x 10^9/L), 3(7.1%) had grade III Neutropenia (absolute. Neutrophil count of 0.5 x 10^9/L-0.9 x 10^9/L),3(7.1%) had Grade II neutropenia (absolute netrophil count 1.5 x 10^9 /L-1.4 x 10^9/L) and 5(11.9%) had Grad I neutropenia (absolute netrophil count 1.5 x 10^9/L-1.9x10^9/L). Other risk factors noted, i.e., cardiac, Liver and Renal comorbidities in 3(7.1%), 5(11.9%) and 4(9.5%) of patients respectively.

Conclusion: Overall 30.8% of patients of NHL's suffered from neutropenia of all grades post first cycle of chemotherapy comprising CHOP and R-CHOP.

Key Words: Non Hodgkin's lymphoma, Neutropenia

INTRODUCTION

Chemoherapy induced neutropenia (CIN), is serious doselimiting toxicities that occur frequently during the first or subsequent cycles of chemotherapy. Identifying patients most at risk of developing CIN might help physicians to target prophylactic treatment with Granulocyte Colony-stimulating factor (G-CSF), in order to decrease the incidence, or duration of myelosuppression and facilitate delivery of chemotherapy as planned.

Myelosuppression represents a major toxicity of systemic cancer chemotherapy associated with considerable morbidity, mortality, and costs.[1] Such complications also result in dose reductions or treatment delays, which may compromise clinical outcomes[2,3] Previous studies have demonstrated that the risk of an initial episode of chemotherapy induced febrile neutropenia (FN) is greatest during the first cycle of treatment when most patients are receiving full dose intensity often without prophylactic measures.[4,5] The standard CHOP chemotherapy may produce severe neutropenia in first cycle which may compel for dose modification and early termination of therapy.[6] While several studies have suggested that standard therapy may improve the outcome of patients, the requirement for dose reductions (from any cause) has been associated with lower response and survival rates.[7] The addition of rituximab to the CHOP regimen (R-CHOP) has further improved patient outcomes.[8,9]

CIN is a frequent and potentially serious adverse effect of cancer treatment[10]. Lymphoma patients with CIN who develop frbrile neutropenia are typically hospitalized and treated with intravenous antibiotics[11,12,13]. A commom response to CIN is to reduce or delay delivery of chemotherapy treatment[10]. National Comprehensive Cancer Network Inc, 2008a, confirmed R-CHOP the current standard of *care*[14].

CHOP-like chemotherapy carries a significant risk of FN (17-50%)[15,16,17]. In addition to the risk associated with the chemotherapy regimen, other risk factors should be considered in order to determine the patient's overall FN risk[14,15]. Several retrospective studies have identified potential risk factors for FN in lymphoma patients, including older age, low baseline blood cell counts, low serum albumin, anaemia, abnormal bone marrow, increased lactate dehydrogenase (LDH), co-morbid renal, cardiovascular of hepatic disease, full or high-risk planned chemotherapy regimen, and lack of G-CSF prophylaxis[18,19].

CIN is an important reason for not maintaining the desired dose intensity of CHOP therapy. A large percentage of neutropenia related deaths occurring within the initial (first 2) cycles of therapy has been described in several studies which emphasize the importance and severity of these events[20]. Patients surviving these initial events may experience repeated events during their future course of treatment. This early neutropenic complication may impact the total length of hospitalization and thus influence not only economic factor but also the patients compliance to further chematherapy[21].

The present study was planned with a view to determine the frequency and severity of neutropenia in patients with NHL. These studies may help to target high-risk patients for prophylactic treatment in order to decrease the incidence of myelosuppression and enable full-dose chemotherapy to be delivered on schedule.

MATERIALS AND METHODS

This was a descriptive cross sectional study, conducted at Radiotherapy & Oncology Department in collaboration with Haematology Section (Pathology Deptt:), Bolan Medical Complex Hospital, Quetta, from march 2010 to February 2012.

42 patients of NHL diagnosed on lymph node biopsy presenting for the first time were studied. Convenience (non probability) sampling technique was used. All new patients of NHL diagnosed on lymph node biopsy who have not received any chemotherapy previously and age between 26-62 years were included. Patients with diabetes mellitus or on steroid therapy for any other reason were excluded. Patients with ischemic heart disease and cardiac dysfunction with an ejection fraction of less than 50% were also excluded.

RESULTS

On presentation the patients were admitted and a detailed history was recorded, followed by through physical examination especially emphasizing on evidence of lymphadenopathy and hepatospleno-mengaly recording the size of each. Patients height and weight were recorded and body surface area was calculated using standard tables. This was followed by the base line investigations and staging investigations including Blood complete picture and platelets counts, serum urea and creatinine, Liver function tests, chest X-Ray PA view/CT scan, Ultrasound abdomen/CT scan, Bone marrow aspiration and trephine examination, Blood sugar random, serum uric acid, electrocardiogram (ECG) and echocardiogram in case of any ECG abnormality showing a suspicion of ischemic heart disease. Patients were then planned for first cycle of chemotherapy comprising CHOP or R-CHOP the doses of chemotherapy were calculated using the body surface area as Inj.

Table No.1: Patients and Baseline Disease Characteristics (n=42)

Age (years), mean ± SD (range)	38 ± 15 (26-62)
Gender, n(%)	
Male	36 (85.7)
Female	06 (14.2)
Height (cm), mean ± SD (range)	169.9±9(145-194)
Weight(kg), mean±SD(range)	75±16(41-176)
BSA m^2, mean±SD (range)	1.8±0.2(1.3-2.4)
WHO classification, n(%)	
Diffuse large Cell	24 (57.1)
Follicular	08 (19.0)
Mantle Cell	04 (9.5)
Others	06 (14.2)
Ann Arbor Staging, n(%)	
I	04 (9.5)
II	08 (19.0)
III	12 (28.5)
IV	18 (42.8)
Regimen, n(%)	
CHOP	34 (80.9)
CHOP-R	08 (19.0)
Neutropenia Grading, n (%)	
Grade I	05 (11.9)
Grade II	03 (7.1)
Grade III	03 (7.1)
Grade IV	02 (4.7)
No of comorbidities,	
Mean ± SD (ragne)	2.1±2.1(0-11)
Cardiac Comorbidity n(%)	03 (7.1)
Liver comorbidity n(%)	5 (11.9)
Renal Comorbidity n(%)	04 (9.5)
Baseline albumin<3.5g/dl, n(%)	06 (14.2)
LDH>1000mg/dL, n(%)	7 (16.6)
BSA Body surface area,	
WHO World health organization,	
SD Standard deviation	

Cyclophosphamide 750 mg/m^2, injection Doxorubicin 50 mg/m2, and Inj. Vincristine 1.4 mg/m^2 (maximum

dose 2.0 mg). all of these drugs were given slowly intravenously via the wide bore canula on day 1 of therapy together with Tables Prednisolon 60-100 mg/m^2 orally from day 1 to day 5. After the first cycle of chemotherapy the patients were monitored for expected bone marrow suppression for next 10 days. Colony-stimulating factors were not given prophylactically. The neutrophil counts were repeated on days 7 and 10 following chemotherapy. All the blood samples were sent to the Haematology laboratory where these sample were analysed on Hematology Analyzer (Medonic 20) through standard protocol. The reports showing neutropenia were also assessed by haematopathologist to reduce the chances of error.

All data were entered on the data entry sheet. The data was analysed using SPSS. Neutrophil count (ANC) was noted after first and subsequent cycles of chemotherapy. Fig 1: shows that 2(4.7%) of patients suffered from grade IV.

Neutropenia (absolute neutrophil count of <0.5 x 10^9/L), 3(7.1%) had grade III neutropenia (absolute neutrophil count of 0.5 x 10^9/L-1.4x10^9/L) (Table-1). Overall 30.8% of patients suffered from neutropenia of all grades post 1st and second cycles of chemotherapy. LDH was high in 7(16.6%) of patients, other risk factors noted, i.e., are cardiac, liver and renal comorbidities in 3(7.1%), 5(11.9%) and 4(9.5%) of patients respectively.

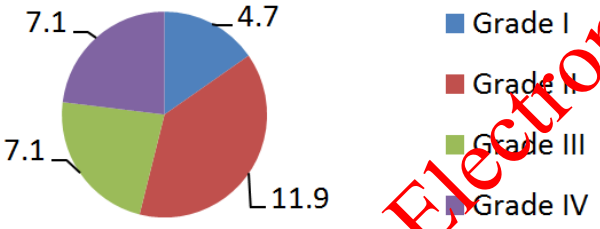

Figure No. 1: Grading of Neutropenia

DISCUSSION

The use of chemotherapy may improve tumor response rates in cancer patients, the prognosis for patients may be compromised by myelosuyppression and its compolications, including neutropenia and subsequent infective complications, often resulting in reduced chemotherapy dose intensity due to dose delays or reductions.

In this present study we treated NHL patients with standard chemotherapy regimens CHOP and R-CHOP and we observed the severity of neutropenia, found that overall 30.8% of patients suffered from all grades of neutropenia after first and second cycle of chemotherapy. The management of this neuropenia and its associated fever/infection costs are substantial and are likely to be an important cost driver especially in under developed countries. This fact was shown in a study from Germany by Herold et al[22]. Moreover in the management of NHL with CHOP or R-CHOP chemotherapy, neutropenia after first and subsequent cycles may compel for dose modification and early termination of therapy. In this study several risk factors were found to be associated with febrile neutropenia amoung patients with NHL who were treated with CHOP-R-CHOP. The greatest risk of febrile neutropenia occurred during chemotherapy cycles 1 and and 2 an increased risk was significantly associated with factors. i.e, age 56 years or older, baseline serum albumin level less than or equal to 3.5g/dL, ANC less than 1.5 x 10^9 at the time of presentationk, and the presence of hepatic disease. The finding that the majority of initial hospitalizations for FN occur within the first 2 cycles of chemotherapy is consistent with a previous study in which 83% of these events occurred by cycle 3[23]. The early time of onset is important because of the potential impact of resulting treatment delays or dose reductions on the overall dose inte4nsity in patients with responsive and potentially curable. Malignancies such as NHL[24,25,26]. These concerns are further confirmed by recent data, suggesting that patients hospitalized for FN in cycle 1 were 4.4 times more likely to prematurely discountinue CHOP chemotherapy, 19. Moreover in the management of NHL with CHOP, neutropenia after first cycle may compel for dose modification and early termination of therapy. This has an impact on survivial also. As shown in a study by elizabeth at al the first-cycle FN hosptialisation and age≥60 years were associated with premature termination of CHOP therapy and thus compromising survival[27]. Abnormal bone marrow, BSA less than 1.9 m2, serum albumin level less than 3.5g/dL, and LDH level greater than 1000/dL have all been identified as predictors of an increased risk for neutropenia in this patient population[28,29].

In another sutdy from James P Wilmot Cancer centre, out of 577 patients receiving CHOP chemotherapy 160 patients experienced neutropenic events, i.e., 27% which was significantly associated with age more than or euqal to 65 years[30,31]. They further observed that first febrile neutropenic event occurred by day 14 of cycle 1 in one half of patients experiencing FN. In these studies the slightly higher percentage of patients experienceing the FN events may have occurred due to the relatively higher age group population[32]. However these events did affect the plan of chemotherapy that is early termination of chemotherapy. Longer lengths of stay and increased mortality rates have been associated with hospitalizations for older patients, possible because of comorbidities that are more common among the elderly[33,34].

CONCLUSION

The current study suggests that patients with NHL receiving CHOP or R-CHOP chemotherapy regimens who are at increased risk of hospitalziation for febrile

neutropenia can be indetified. This may permit a more rational-targeted application of supportive care measures, such as the hamatopoietic growth factors, toward the patients at greatest risk and most likely to benefit.

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