

ORIGINAL ARTICLE

FREQUENCY AND SEVERITY OF NEUTROPENIA IN DIFFUSE LARGE B-CELL NON HODGKIN'S LYMPHOMA AFTER FIRST CYCLE OF CHEMOTHERAPY COMPRISING CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE WITH PREDNISOLON

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Background: Chemotherapy used for malignant diseases may produce severe neutropenia in first cycle which may compel for dose modification and early termination of therapy. This descriptive cross sectional study was planned to see the frequency and severity of neutropenia after first cycle of chemotherapy comprising cyclophosphamide, doxorubicin, vincristine with prednisolon in patients of diffuse large B-cell non Hodgkin's lymphoma presenting at Oncology Department Combined Military Hospital Rawalpindi from August 2009 to July 2010. **Methods:** Thirty patients of diffuse large B-cell non Hodgkin's lymphoma diagnosed on lymph node biopsy presenting for the first time at Oncology Department Combined Military Hospital Rawalpindi were included. They were admitted in the ward and evaluated with history, physical examination and staging investigations. Patients were then planned for first cycle of chemotherapy comprising cyclophosphamide, doxorubicin, and vincristine with prednisolon. 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 was entered on a specially designed data card. **Results:** As much as 3.3% of patients suffered from grade IV neutropenia (absolute neutrophil count of $<0.5 \times 10^9/L$), 3.3% had grade III neutropenia (absolute neutrophil count of $0.5 \times 10^9/L - 0.9 \times 10^9/L$), 6.6% had Grade II neutropenia (absolute neutrophil count $1.0 \times 10^9/L - 1.4 \times 10^9/L$ and 10% had Grade I neutropenia (absolute neutrophil count $1.5 \times 10^9/L - 1.9 \times 10^9/L$). **Conclusion:** Overall 23.2% suffered from neutropenia of all grades post 1st cycle of chemotherapy comprising cyclophosphamide, doxorubicin, vincristine with prednisolon in diffuse large B-cell non Hodgkin's lymphoma. Further studies are required to find the risk factors to predict this complication in our population.

Keywords: Non Hodgkin's lymphoma, CHOP chemotherapy, Neutropenia

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is defined as a neoplasm of transformed large B-cells with prominent nucleoli and basophilic cytoplasm with a diffuse growth pattern and a high (greater than 40%) proliferation fraction.¹ Historically CHOP therapy consisting of Cyclophosphamide 750 mg/m^2 , Doxorubicin 50 mg/m^2 , and Vincristine 1.4 mg/m^2 with Prednisolon $60-100 \text{ mg/m}^2$ administered every 21 days for 6-8 cycles remains the standard curative treatment of this lymphoma type.² The standard CHOP chemotherapy may produce severe neutropenia in first cycle which may compel for dose modification and early termination of therapy.² 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.³

More recently using the combination of Rituximab (chimeric monoclonal anti CD-20 antibody) with the standard CHOP leads to significant improvement of the outcome and survival benefit.⁴ However because of the very high cost of Rituximab, majority of the patients cannot afford this option and

standard CHOP remains the economical and effective treatment for patients with diffuse large B-cell non Hodgkin's lymphoma.

Chemotherapy induced neutropenia 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 emphasise the importance and severity of these events.^{4,5} 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 hospitalisation and thus influence not only economic factor but also the patients compliance to further chemotherapy.⁵ Severity of neutropenia absolute is based upon neutrophil count (band and segmented forms):

Table-1: Grades of neutropenia⁶

Grade	Absolute neutrophil count
Grade-I	$1.5 \times 10^9/L - 1.9 \times 10^9/L$
Grade-II	$1.0 \times 10^9/L - 1.4 \times 10^9/L$
Grade-III	$0.5 \times 10^9/L - 0.9 \times 10^9/L$
Grade-IV	$<0.5 \times 10^9/L$

The present study was planned with a view to determine the frequency and severity of neutropenia in patients with diffuse large B-cell non Hodgkin's lymphoma after first cycle of CHOP chemotherapy in our population as no local or regional study is available so far on this subject.

PATIENTS AND METHODS

This was a descriptive (cross sectional) study, conducted at Oncology Department Combined Military Hospital Rawalpindi from August 2009 to July 2010. Thirty patients of diffuse large B-cell non Hodgkin's lymphoma diagnosed on lymph node biopsy presenting for the first time were studied. Convenience (non-probability) sampling technique was used.

All new patients with diffuse large B-cell lymphoma diagnosed on lymph node biopsy who have not received any chemotherapy previously and age between 18–60 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.

On presentation the patients were admitted, and a detailed history was recorded, followed by thorough physical examination specially emphasising on evidence of lymphadenopathy and hepatosplenomegaly recording the size of each. Patient's 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 count, 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, 12 lead standard electrocardiogram and 2-dimensional echocardiogram in case of any ECG abnormality showing a suspicion of ischemic heart disease.

Patients were then planned for first cycle of chemotherapy comprising cyclophosphamide, doxorubicin, and vincristine with prednisolon. For this purpose a wide bore cannula was passed in a large arm vein. The doses of chemotherapy were calculated using the body surface area as Inj. Cyclophosphamide 750 mg/m², Injection Doxorubicin 50 mg/m², and Inj. Vincristine 1.4 mg/m² (maximum dose 2.0 mg). All of these drugs were given slowly intravenously via the wide bore cannula on day 1 of therapy together with Tablet Prednisolon 60–100 mg/m² 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 same hospital laboratory where these samples were analysed on Hematology Analyser through standard protocol. The reports showing neutropenia were later seen by pathologist also to reduce the chances of error. Neutropenia was monitored and graded as defined in Table-1. All data was entered on the data entry card. No ethical issue was encountered in this study.

The data was analysed using SPSS-16. Means and standard deviation were calculated for numerical variables like age and body surface area. Frequencies (percentages) were calculated for categorical variables like gender, stage of disease and frequency and severity of neutropenia.

RESULTS

At day 7 after chemotherapy the mean nadir neutrophil count was 4.1×10⁹/L. At day 10 mean nadir neutrophil count was 3×10⁹/L. As much as 3.3% of patients suffered from grade IV neutropenia (absolute neutrophil count of <0.5×10⁹/L), 3.3% had grade III neutropenia (absolute neutrophil count of 0.5×10⁹/L– 0.9×10⁹/L), 6.6% had Grade II neutropenia (absolute neutrophil count 1.0×10⁹/L– 1.4×10⁹/L) and 10% had Grade I neutropenia (absolute neutrophil count 1.5×10⁹/L–1.9×10⁹/L) (Table-2). Overall 23.2% suffered from neutropenia of all grades post 1st cycle of chemotherapy comprising cyclophosphamide, doxorubicin, vincristine with prednisolon in diffuse large B-cell non Hodgkin's lymphoma.

Out of 30 patients selected for study 22 (73.3%) were males and 8 (26.6%) were females. The mean age of the patients was 38±15.0 years. The mean body surface area was 1.7±0.18 m². On clinical and radiological evaluation 4 (13.3%) had Clinical Stage (CS) I, 8 (26.6%) had CS II, 12 (40%) had CS III and 6 (20%) had CS IV (Table-3). Bone marrow was the extra-nodal site in CS IV disease.

Table-2: Frequency and severity of neutropenia (n=30)

Grades	Number	Percentage
I	1	3.3
2	1	3.3
3	2	6.6
4	3	10.0
Total	7	23.2

Table-3: Diffuse large B-cell lymphoma (n=30)

Stage	Number	Percentage
I	4	13.3
II	8	26.6
III	12	40.0
IV	6	20.0
Total	30	100

DISCUSSION

Chemotherapy is a promising option with curative potential in the management of lymphomas. However chemotherapy has its own limitations. One of the major dose-limiting toxicity of chemotherapy is neutropenia and subsequent infective complications. In the present study overall 23.2% suffered from any grade of neutropenia post first-cycle of chemotherapy comprising cyclophosphamide, doxorubicin, vincristine with prednisolon in diffuse large B-cell non Hodgkin's lymphoma. The management of this neutropenia 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.*⁷ Moreover in the management of diffuse large B-cell non Hodgkin's lymphoma with historical CHOP therapy consisting of Cyclophosphamide, Doxorubicin, and Vincristine with Prednisolon, neutropenia after first cycle may compel for dose modification and early termination of therapy. This has an impact on survival also. As shown in a study by Elizabeth *et al* the first-cycle febrile neutropenic hospitalisation and age ≥ 60 years were associated with premature termination of CHOP therapy and thus compromising survival.⁸ They also showed that this association between completing a full course of therapy and survival differed by age group. They showed that out of the 25 patients who received less than 6 cycles of CHOP chemotherapy the febrile neutropenic hospitalisation after cycle 1 had occurred in 8 patients, i.e., 32%. While those who received full course of chemotherapy the febrile neutropenic hospitalisation after cycle 1 had occurred in 9 out of 99 patients, i.e., 9%. So the febrile neutropenic hospitalisation after first cycle CHOP was an independent factor to impact on completing full course CHOP and thus effecting survival. They have not commented on the grades of neutropenia rather they studied the hospitalisation because of febrile neutropenia. Our study has shown a total of 23.2% of neutropenic events. But in our results this 23.2% represents all grades of neutropenia and that we had not studied the febrile episodes and hospitalisations associated with these events. In another study 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 equal to 65 years.⁹ They further observed that first febrile neutropenic event occurred by day 14 of cycle 1 in one-half of patients experiencing febrile neutropenia. Picozzi *et al* in their study showed that 24% patients were hospitalised for febrile neutropenia after receiving CHOP chemotherapy.¹⁰ In these two studies the slightly higher percentage of patients experiencing the febrile neutropenic events may have occurred due to the

relatively higher age group population than ours. However these events did affect the plan of chemotherapy that is early termination of chemotherapy. Two other studies showing the incidence of neutropenia post cycle one CHOP therapy in lymphoma were from Rabinowitz *et al* from the Lehey clinic. In one study they showed that cycle one neutropenia may serve as a warning sign for increased risk of premature death. In that study 29.4% patients suffered from cycle 1 severe neutropenia.¹¹ In the other study from the same authors a predictive model was suggested to predict the neutropenia post cycle 1 CHOP.¹² In that study Fifty-three percent of patients (47–89) had severe neutropenia, with 70% of first episodes occurring during cycle 1. Eighty-two percent of first-cycle, severe neutropenia events occurred in patients more than or equal to 65 years of age. The study results suggest that data obtained before initiating CHOP-based chemotherapy can be used to identify those patients who are at risk for severe neutropenia in cycle 1. These two studies showed a higher percentage of patients experiencing cycle 1 neutropenia than our study as their population had advanced age than ours. Our centre caters for the army personnel who are relatively in younger age group however a certain percentage of dependants including parents are also provided with treatment at our centre. This leads to a relatively younger age group being represented in our study than in the literature cited above. Since the risk of neutropenia increases with age as is shown in various studies the percentage of patients experiencing neutropenia also varies among our study and these studies.

Among the regional studies, one study from India showed that 83% of patients receiving CHOP therapy experienced toxicities.¹³ Haematological toxicities were observed in 47% patients. They grouped grade III and IV haematological toxicities together, i.e., neutropenia, anaemia and thrombocytopenia. In their study this factor leads to a delay in treatment and even a high dropout rate. The median age in their study was 55.5 years. Since they grouped all haematological toxicities together therefore the figure of 47% does not represent neutropenia alone and cannot be compared with our study in which we had studied neutropenia alone in haematological toxicity occurring at the frequency of 23.2%. Another interesting finding was the frequency of different stages of lymphoma in that study. They showed that among their population the frequency of different stages were 34% for stage I and II, 13% for stage III and 53% for stage IV. They also showed that extra nodal presentation was seen in 24% patients. However the problem while interpreting these statistics is that they had grouped all lymphomas as one group and these frequencies are not representative for DLBC lymphoma only. We have studied DLBCL and the

frequency for various stages is 22.8% for stage I, 34.2% for stage II, 25.7% for stage III and 17.1% for stage IV disease. They also found that complete staging was not possible in a significant number of patients due to financial constraints. The most common investigations left out were whole body CT scans and bone marrow examination. Our centre caters for that group of general population that has a sponsored health care facility and therefore getting the staging investigations was not a major issue in our study. In another regional study from Thailand¹⁴, 145 patients were studied to propose a predictive model for life threatening neutropenia and febrile neutropenia after the first course of CHOP chemotherapy with aggressive non-Hodgkin's lymphoma. They showed that 39% of the patients had life threatening neutropenia and 33% develop febrile neutropenia after first cycle CHOP. However, the population did not consist of diffuse large B-cell histology uniformly but other aggressive histologies were also included. Moreover various grades of neutropenia were not mentioned. These frequencies of neutropenic events are higher than in our study. Their population had a mean age of 47 years and 48% were in stage III and IV. However, the mean age in our population was 38 years and 40% were in stage III and 6% were in stage IV. The slightly higher age group and advanced stage might have contributed to the increased incidence of these neutropenic events.

CONCLUSION

Neutropenia post chemotherapy is an important complication of any chemotherapy leading not only to increased morbidity and mortality but it is also an important cost driver in any setting. This study had shown an overall frequency of 23.2% neutropenic events after first cycle of CHOP chemotherapy with varying severity. Age is an important risk factor for neutropenia post chemotherapy, not focused in the present study. Further studies should be done to determine the important risk factors to predict these events especially the impact of increasing age on the occurrence of neutropenic events after chemotherapy in our population.

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