NEUTRROPHIL TOXICITY AND PRIMARY PROPHYLAXIS IN DIFFUSE LARGE B CELL LYMPHOMA TREATED WITH R-CHOP

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ABSTRACT

Objective: To identify the risk of neutrophil toxicity in patients of advanced stage Diffuse Large B Cell Lymphoma (DLBCL) patients with low to intermediate-risk International prognostic index (IPI) treated with three weekly R-CHOP therapy.

Study design: Quasi-experimental study.

Place and duration of study: Combined Military Hospital Rawalpindi on 50 patients of advanced stage DLBCL from 1st Jan 2009 to 31st Dec 2009.

Patients and Methods: Patients were observed for occurrence of significant neutrophil toxicity defined as grade 4 neutropenia between day 7 and 10 post therapy, febrile neutropenia and grade 2 or more neutrophil toxicity persisting on day 1 of next cycle. NCI Common Toxicity Criteria version 3.0 was used for grading toxicity. Patients with WHO Performance status scale 4, on immunosuppressive drugs, abnormal hepatic or renal functions and inadequate hematological values were excluded.

Results: Fourteen (28%) patients had poor performance status (WHO ≥2) and amongst them grade 4 neutrophil toxicity was seen in 8(57%) and 3 got complicated with febrile neutropenia. In the remaining 36 (72%) patients with good performance status (WHO 0 or 1) only 2(5.5%) developed grade 4 toxicity none getting complicated with febrile neutropenia.

Conclusion: Frequency of neutrophil toxicity was 20% in Non Hodgkin's Diffuse Large B Cell Lymphomas (Low and Intermediate IPI) patients treated with 3 weekly R-CHOP. Patients with WHO performance status scale ≥ 2 are high-risk for developing significant neutrophil toxicity and therefore require primary neutropenia prophylaxis.

Keywords: Colony stimulating factors, Diffuse Large B Cell Lymphoma, Neutropenia, Primary prophylaxis

INTRODUCTION

A major change in the 2006 American Society of Clinical Oncology (ASCO) guidelines for white-cell growth factors was to recommend their use when the risk of febrile neutropenia (FN) is approximately 20% rather than 40% as in pervious guidelines[1]. The National Comprehensive Cancer Center Network (NCCN) also revised their guidelines in favor of 20% FN threshold for a definite indication of colony stimulating factors (CSF) prophylaxis and 10% to 20% FN threshold range indicating optional CSF prophylaxis[2].

Diffuse Large B cell Lymphomas (DLBCL) are commonly diagnosed malignancies and is treated with curative intent. The standard treatment for low to intermediate International Prognostic Index (IPI) is R-CHOP. This therapy is considered to have an intermediate risk of FN (10-20%)[3]. Routine CSFs prophylaxis is not recommended in the NCCN guidelines for intermediate risk conditions except in the presence of patient related risk factors[4,5].

The cost benefit implications are major issues in the treatment of malignancies in developing countries and therefore more selective use of CSFs is required due to cost constraints[6]. This needs identifying the high-risk groups. The aim of this study was to identify the risk of neutrrophil toxicity patients of Diffuse Large B Cell Lymphoma (DLBCL) with low to intermediate IPI when excluded for risk factors and treated with standard dosage R-CHOP therapy with curative intent.

PATIENTS AND METHODS

This quasi-experimental study was carried out in a specialized oncology unit of Combined Military Hospital, Rawalpindi from 1st Jan 2009

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to 31st Dec 2009. It was conducted in accordance with the ethical standards of Helsinki declaration, 1983 and approved by the institutional review board.

Fifty patients of Diffuse Large B-Cell Non Hodgkin Lymphoma (CD20 positive), low and intermediate IPI treated with R-CHOP combination therapy were enrolled and observed for neutrophil toxicity and febrile neutropenia. Eligible patients were required to meet the following criteria: age > 18 < 60; Ann Arbor stage II to IV; no previous treatment; adequate hematological values (absolute neutrophil count ≥1500 cells/μL, hemoglobin ≥ 10 g/dl, and platelet count ≥ 100,000/μL); normal renal and hepatic functions; no preexisting infections or recent surgery, no concomitant medications including phenothiazines, diuretics or other immunosuppressive agents. Patients with WHO performance status scale 4 were excluded. All patients provided written informed consent. Patients were given standard dosage R-CHOP chemotherapy at three weekly intervals for six to eight cycles. The NCI Common Toxicity Criteria version 3.0 was used for grading neutrophil toxicity and febrile neutropenia. Patients were monitored for hematological toxicity between days 7 and 10 and before beginning of each treatment cycle. Dose modification and primary prophylaxis for neutropenia was not allowed however secondary prevention with colony stimulating factors were permitted in subsequent cycles in case of significant neutrophil toxicity defined as grade 4 neutrophil toxicity between days 7 and 10, any single episode of febrile neutropenia or persisting neutropenia grade 2 or more on day 1 of next cycle.

Data was analyzed using SPSS version 15. Descriptive statistics were used to describe the data. Chi-square test was applied to study the comparison of performance status with neutrophil toxicity and febril neutropenia. A *p*-value <0.05 was considered significant.

RESULTS

A total of 50 patients of CD20 positive DLBCL meeting the protocol eligibility requirement were enrolled. Among these patients, 38 (76%) were male and 12 (24%) were females, and the age range was 28 to 58 years with median age of 45 years. Ten (20%) patients of Ann Arbor stage II, 26 (52%) with stage III and 14 (28%) of stage IV were enrolled. Twenty four (48%) patients were scored as Low International Prognostic Index group and 26 (52%) in the Intermediate group. All patients received R-CHOP at 3 weekly intervals. Patients were investigated and graded for neutrophil toxicity and for occurrence of febrile neutropenia.

Significant neutrophil toxicity was observed in 10 (20%) patients developing between days 7 and 10 of treatment cycle (Table-1). Six developed grade 4 neutrophil toxicity after the first therapy, 2 after second therapy and another 2 in the following cycles. Three of these 10 patients got complicated with febrile neutropenia all recovered with empirical antibiotic therapy and growth factors support. Fourteen (28%) patients had poor performance status (WHO ≥2) and amongst them grade 4 neutrophil toxicity was seen in 8(57%) and 3 (21.4%) got complicated with febrile neutropenia. In the remaining 36(72%) patients with good performance status (WHO 0 or 1) only 2 (5.5%) developed grade 4 toxicity none getting complicated with febrile neutropenia (Table-2).

Results show that frequencies of neutrrophil toxicity and febrile neutropenia was significiantly higher in WHO performance status ≥ 2.

DISCUSSION

Chemotherapy induced neutropenia and febrile neutropenia can be a cause of substantial morbidity, mortality and cost. Occurrence of the FN may delay the subsequent chemotherapy course or result in dose reduction that may compromise treatment outcomes. Febrile neutropenia also increases diagnostic and treatment cost and often leads to prolonged hospitalization. This realization led to change in risk threshold for febrile neutropenia from 40% to approximately 20%. The prophylactic use of CSFs can reduce this risk, despite this CSFs are not administered to

Table-1: Description of Significant Neutrophil Toxicity: 10 patients (20%).

Neutrophil toxicity	After 1st therapy	After 2nd therapy	In following therapies
Grade 4	6	2	2
Febrile Neutropenia	2	1	Nil
Grade 2 or more toxicity on day 1 of next cycle	Nil	Nil	Nil

Table-2: Toxicity distribution with reference to performance status of the patients

	Performance Status		
	Good (0 to 1) (n=36)	**Poor (≥2) (n=14)**	***p*-value**
Neutrrophil Toxicity	2 (5.5%)	8 (57.1%)	<0.05
Febrile Neutropenia	0(0%)	3(21.4%)	<0.05

all patients receiving chemotherapy because of cost associated with their routine use.

The risk of severe and febrile neutropenia is usually based on the treatment regimen and delivered dose intensity[7,8]. The rates of myelosuppression with the same and similar regimens vary greatly, making it difficult to determine the actual risk for neutropenic complications associated with common therapeutic regimens like R-CHOP[9]. Differences in the reported rates may relate to differences in study patient populations or delivered dose intensity[1,10].

Administration of CSFs results in a 50% risk reduction of developing FN. Based on both, type of chemotherapy and patient related risk factors, the patient is assigned to a high risk group (>20% risk of FN), an intermediate group (10-20% risk) and low risk (<10% risk). In addition to patient and treatment-related risk, consideration is given to the intent of treatment. Non Hodgkin Lymphomas treated with standard dosage R-CHOP regimen are treated with a curative intent and are defined in intermediate risk group. Primary prophylaxis with CSFs in these intermediate risk patients is recommended in special situations defined in the NCCN guidelines and grouped under the headings: patient factors, comorbidities, disease and treatment related factors. Poor functional status is recognized as a comorbidity predisposing the patient to myelosuppression and neutropenia however it remains undefined in terms of scale.

CONCLUSION

This study shows that the good performance status (0 or 1) patients have a low risk for febrile neutropenia and WHO performance scale ≥ 2 is a major independent determinant for considering primary prophylaxis with CSFs in DLBCL(Low to Intermediate IPI) patients treated with 3 weekly standard dosage R-CHOP regimen with curative intent.

REFERENCES

1. Smith TJ, Khatcheressian J, Lyman GH: 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based, clinical practice guideline. J Clin Oncol 24:3187-3205.
2. NCCN Releases New Myeloid Growth Factors Clinical Practice Guidelines. http://www.nccn.org/about/news/newsinfo.asp?NewsID=50
3. Lyman G, Delegado DJ. Risk of febrile neutropenia among patients with intermediate-grade non-Hodgkin's lymphoma receiving CHOP chemotherapy. Leukemia & Lymphoma 2003;44(12):2069-2076
4. Dale D, McCarter GC, Crawford J, Luman GH. Chemotherapy-induced neutropenia and associated complications in randomized clinical trials: an evidence based review. J Nat Compr Canc Netw 2003;1:440-454.
5. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer. 2004 Jan 15;100(2):228-37
6. Lyman GH, Kuderer NM. The economics of the colony stimulating factors in the prevention and treatment of FN. Crit Rev Oncol Hematol 2004;50(2):129-46
7. Crawford J, Wolff D, Dale Dcet al. Assessment of neutropenic risk in cancer patients receiving systemic chemotherapy: results of aprospective nationwide registry (abstract). Support Care Cancer 2004;12(6):374 Abstract A-29
8. Komrokji RS, Lyman GH. The colony-stimulating factors: use to prevent and treat neutropenia and its complications. Expert Opin Biol Ther 2004;4(12):228-37
9. Lyman G, Delgado DJ. Risks of febrile neutropenia among patients with intermediate-grade non-Hogkin's lymphoma receiving CHOP chemotherapy. Leukemia & Lymphoma 2003;44(12):2069-2076
10. Lyman GH, Kuderer NM, Crawford J, Wolf DA, Culakova E.poriewierski MS et al. Prospective validation of a risk model for the first cycle neutropenic complications in patients receiving cancer chemotherapy. J Clin Oncol 2006; 24(18S):8561