Detection of the Incidence of HBV, HCV Infection and Febrile Neutropenia Associated With CHOP With or Without Rituximab in Diffuse Large B-Cell Lymphoma–Treated Patients

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Abstract

Background: Reactivation of hepatitis B virus (HBV) and hepatitis C virus (HCV) and febrile neutropenia (FN) are common in diffuse large B-cell lymphoma (DLBCL) patients undergoing cyclophosphamide, hydroxyrubicin, Oncovin, and prednisolone (CHOP) or cyclophosphamide, hydroxyrubicin, Oncovin, prednisolone - rituximab containing (R-CHOP) chemotherapy. This ultimately leads to delaying the therapy, increasing hospital stay, and raising the pharmacoeconomic burden on patients. **Aim and Objective:** The aim of this study was to determine the incidence of HBV and HCV infection and febrile neutropenia in DLBCL patients treated with R-CHOP and CHOP. **Methodology:** This was an institutional approved study in which patient records from a private hospital, specialized in hematology and oncology (Karachi, Pakistan), were reviewed retrospectively from 2014 to 2016. Patients aged above 18 years with known diagnosis of DLBCL who underwent CHOP-21 or R-CHOP-21 chemotherapy regimen were included. Baseline blood chemistry and liver function tests along with the data regarding HBV (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [anti-HBs]), HCV (antibody anti-HCV), and febrile neutropenia were collected from patient records. **Results:** In total, 35 cases of DLBCL were treated during a 3-year period (ie, from 2014 to 2016), of which 16 were on CHOP-21 regimen whereas 19 were treated with R-CHOP-21. Of the 19 patients who underwent R-CHOP chemotherapy, only 2 (10%) patients were HBsAg reactive. Before commencing the second cycle, 2 (10%) patients reported to hospital with fever and had hematological (low neutrophil count) and microbiological (*Escherichia coli*) proven febrile neutropenia. The incidence of HBV infection post treatment was lower in group treated with CHOP (1 patient showed HBsAg reactivity).

Keywords

intravenous therapy, medication safety, monitoring drug therapy, oncology, outcomes research

Introduction

Diffuse large B-cell lymphoma (DLBCL) is one of the most common histological subtypes of non-Hodgkin lymphoma (NHL) found in adults. Annually, it accounts for approximately 32.5% of NHL cases diagnosed. Currently, cyclophosphamide, hydroxyrubicin, Oncovin, prednisolone - rituximab (R-CHOP) is the standard treatment for DLBCL. Rituximab (Rituxan) is a chimeric human-mouse monoclonal antibody (IgG1) that has a propensity to react specifically with CD20 antigen present on almost all the normal and malignant B cells.¹⁻³ It also has substantive involvement with cells/components involved in complement-mediated and antibody-dependent cellular cytotoxicity.⁴ Growing body of evidence on Rituximab (R) supports the notion that besides its effects

on B cell, it causes immunosuppression through several other mechanisms such as influencing T-cell immunity, causing delayed-onset cytopenia, particularly neutropenia and hypogammaglobulinemia, especially when administered for long periods, eg, in maintenance therapy. The incorporation of

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rituximab to standard cytotoxic therapy for DLBCL has improved the outcome at the expense of reactivating hepatitis B virus (HBV) in lymphoma patients.⁵⁻⁷ Not only has the reactivation of HBV been reported; rather, there are case reports and case series suggesting that rituximab (R) also increases the risk of viral infections. HBV infection is a global infective condition affecting almost one-third of the world's population. Seventy-five percent of 350 million people who have chronic HBV infection live in Southeast Asia and the Western Pacific regions.⁸⁻¹⁰ It is endemic in Pakistan affecting approximately 9 million people and the rate of infection is steadily increasing.¹¹

The clinical picture and outcome are further compromised by febrile neutropenia (FN). FN is one of the major toxicity reported in DLBCL patients treated with R-CHOP. It is reported in number of studies that most cases of FN occur during the first cycle of R-CHOP.¹² According to National Comprehensive Cancer Network (NCCN) and European Organization for Research and Treatment of Cancer (EORTC) guidelines, R-CHOP is an intermediate risk for FN. The guidelines also recommended that patient's own factors, chemotherapy regimen, and prophylactic treatment with granulocyte colony-stimulating factor (G-CSF) should also be taken into the equation of risk assessment for FN.^{9,10,13}

The aim of this study was to determine the incidence of HBV and hepatitis C virus (HCV) infection and FN in DLBCL patients treated with R-CHOP and to compare it with the patients receiving the conventional cytotoxic treatment, ie, cyclophosphamide, hydroxyrubicin, Oncovin, and prednisolone (CHOP). We also aimed to establish the relationship between the incidence of viral infection (ie, HBV or HCV) and FN.

Method

This was an institutional approved study in which patient records from a private hospital, specialized in hematology and oncology (Karachi, Pakistan), were reviewed retrospectively from 2014 to 2016. Patients aged above 18 years with known diagnosis of DLBCL who underwent CHOP-21 or R-CHOP-21 chemotherapy regimen were included. Baseline blood chemistry and liver function tests along with the data regarding HBV (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [anti-HBs]), HCV (antibody anti-HCV), and FN were collected from patient records. The collected data were subjected to statistical analysis using SPSS.

Results

In total, 35 cases of DLBCL were treated during a 3-year period (ie, from 2014 to 2016), of which 16 were on CHOP-21 regimen whereas 19 were treated with R-CHOP-21. Mean age of the patients on either treatment was 53.15 ± 13 years. Twenty-five patients out of 35 were male. From the data, it

was gathered that patient were followed up for 6 months post treatment. Blood chemistry and liver function test were done both pretreatment and on the beginning of every cycle (Table 1). However, none of the patients neither had their baseline viral screening done nor were they given G-CSF within 7 days after the administration of chemotherapy, which is a recommended international practice.

Of the 19 patients who underwent R-CHOP chemotherapy, only 2 (10%) patients were HBsAg reactive. Before commencing the second cycle, 2 (10%) cases reported to hospital with fever and had hematological (low neutrophil count) and microbiological (*Escherichia coli*) proven FN. The incidence of HBV infection post treatment was lower in group treated with CHOP (1 patient showed HBsAg reactivity). The prevalence of both HBV infection and FN was 8.57% in our cohort. HCV reactivity was not found in either group (Table 2). The baseline and posttreatment blood chemistry showed no significant difference except for alkaline phosphatase ($P < .002$).

Discussion

To the best of our knowledge, this was one of its kind studies performed to investigate the incidence of HBV, HCV, and FN in DLBCL patient on CHOP or R-CHOP therapy. The research was conducted in a specialty tertiary care center offering therapeutic services in heme-oncology. Reactivation of HBV is commonly reported in HBsAg-positive patients undergoing immunosuppressive anticancer therapy. It is strongly recommended in literature to routinely screen NHL patients for HBsAg who are residing in HBV endemic areas before commencing cytotoxic chemotherapy. The screening recommendation is to identify the high-risk patient for prophylactic antiviral treatment and to reduce the incidence and morbidity associated with reactivation of HBV.¹⁴

The findings of the study revealed that incorporation of rituximab significantly increased the incidence of HBV, whereas HCV incidence was reported in none. Fifty-four percent (19 of 35) of patients enrolled in the study were on R-CHOP and 45.7% (16 of 35) were on CHOP treatment. Of the 19, 2 (10.5%) showed reactivity for HBsAg, whereas 6.25% (1 of 16) had substantive antibody titers for HBsAg to show positive reactivity. At present, no screening or prophylactic antiviral treatment is recommended in our practice. However, our study finding strongly warrants not only revision of the institutional policy in this regard; rather, it requires conducting the study more thoroughly with ample sample size to confirm our present findings.

Neutropenia with fever is one of the complications of myelosuppressive chemotherapy which accounts for considerable morbidity and mortality and also results in hospitalization. According to the current guideline, chemotherapy regimens with occurrence rate of FN are classified as high (>20%), intermediate (10%-20%), and lower (<10%). Though these classifications of chemotherapy regimens are

Table 1. Baseline Investigation of CHOP and R-CHOP.

	R-CHOP (n = 19)		CHOP (n = 16)	
	M/F = 15/4		M/F = 10/6	
	Age (mean $\pm$ SD) years = 52.5 $\pm$ 13		Age (mean $\pm$ SD) years = 53.8 $\pm$ 14	
	Mean $\pm$ SD	P value	Mean $\pm$ SD	P value
Creatinine–baseline	0.69 $\pm$ 0.17	.41	0.748 $\pm$ 0.18	.39
Creatinine–post	0.743 $\pm$ 0.21		1.21 $\pm$ 2.08	
Urea–baseline	24.26 $\pm$ 19.20	.74	22.37 $\pm$ 7.95	.11
Urea–post	25.84 $\pm$ 10.02		25.50 $\pm$ 7.90	
Sodium–baseline	135.26 $\pm$ 3.94	.20	133.06 $\pm$ 3.29	.83
Sodium–post	134.0 $\pm$ 4.10		132.81 $\pm$ 3.18	
Chloride–baseline	101.21 $\pm$ 4.77	.59	100.50 $\pm$ 3.70	.04
Chloride–post	101.73 $\pm$ 4.59		103.62 $\pm$ 3.63	
Bicarbonate–baseline	25.57 $\pm$ 1.80	.87	24.56 $\pm$ 1.15	.89
Bicarbonate–post	25.47 $\pm$ 2.65		24.62 $\pm$ 1.54	
Bilirubin_total–baseline	0.74 $\pm$ 0.33	.34	0.812 $\pm$ 0.84	.63
Bilirubin_total–post	0.65 $\pm$ 0.33		0.69 $\pm$ 0.33	
Bilirubin_direct–baseline	0.38 $\pm$ 0.25	.31	0.85 $\pm$ 1.39	.88
Bilirubin_direct–post	0.31 $\pm$ 0.20		0.92 $\pm$ 1.21	
Alkaline phosphatase–baseline	228.0 $\pm$ 82.91	.700	196.48 $\pm$ 71.62	.002
Alkaline phosphatase–post	220.84 $\pm$ 75.41		288.88 $\pm$ 73.03	

Table 2. Outcomes of DLBCL patients treated with CHOP and R-CHOP.

Variables	CHOP (n = 16)	R-CHOP (n = 19)
Demographic characteristics	53.8 $\pm$ 14 years	52.5 $\pm$ 13 years
Male preponderance	10 (62%)	15 (78%)
Female preponderance	6 (37%)	4 (21%)
Anti-HBs reactive	1 (6.25%)	2 (10%)
Anti-HBs nonreactive	15 (93.33%)	17 (89%)
Febrile neutropenia	1 (6.25%)	2 (10%)
Anti-HCV reactive	—	—
Anti-HCV nonreactive	—	—

Note. Viral markers were performed by a Roche Cobas E-411. DLBCL = diffuse large B-cell lymphoma; HBs = hepatitis B surface; HCV = hepatitis C virus; CHOP=cyclophosphamide, hydroxyrubicin, Oncovin, and prednisolone; R-CHOP=cyclophosphamide, hydroxyrubicin, Oncovin, prednisolone - rituximab..

deduced on the basis of several clinical trials of eligible patients, unfortunately, hematological toxicities are often underreported in these highly selected patients. EORTC and NCCN guidelines considers R-CHOP regimen as an intermediate risk for FN.¹⁵ Several observational studies report that occurrence of FN during R-CHOP regimen in patient including those who had received primary prophylaxis of G-CSF was 17% to 22%, whereas 1 study reports that 23.8% of those with no prophylaxis of G-CSF experienced at least 1 episode of FN.¹² Evidences in the scientific literature suggest

that in real clinical situations the practicing hematology oncologist should consider R-CHOP regimen as a high risk for FN. In the light of cited evidences in the literature, the EORTC and NCCN guidelines do not seem to be in agreement regarding the risk classification of R-CHOP; however, a number of clinical trials have suggested considering a variety of patient- and disease-related risk factors like older age, advanced disease, comorbidities, poor performance status, low baseline blood cell count, and low body surface area/body mass index. Older age group (>60 or 65 years) has been reported to be a more consistent risk factor; both advance age and poor performance status were substantiated to be an independent risk factor for development of FN in NHL patients on R-CHOP regimen.^{11, 16}

In this study, 10% (2 of 19) of DLBCL patients on R-CHOP developed FN, whereas 6.25% (1 of 16) on CHOP developed FN (Table 2); taken together, 8.57% (3 of 35) suffered from FN. In our practice, none received G-CSF either as prophylaxis or after development of FN. Moreover, patients presenting to our center with DLBCL had an average age of 54 years, which does not increase the risk for FN. Due to limitation of sample size, it is difficult to establish any substantive relationship between neither the FN or HBV and DLBCL patients on R-CHOP therapy nor other risk factors can be taken into account. The limitation of sample size is attributed to the fact that only 1 center was taken into consideration. Furthermore, comprehensive and elaborate study is required to explore the casual relationship and establish the

risk assessment criteria for patients on either R-CHOP or CHOP in Pakistan.

Conclusion

The study highlighted the incidence of HBV and FN in DLBCL patient receiving either CHOP or R-CHOP therapy. All the patients undergoing either treatment should be screened for HBV (HBcAg, HBsAg, and HBsAg titer) to establish their pretreatment status. Besides, this screening will help to decide about prophylactic antiviral therapy and will also help to delineate between the patients who had reactivation of HBV or had acquired de novo new infection as a result of chemotherapy. Moreover, prophylactic treatment with G-CSF should also be taken into the equation after evaluating all the risk factor reported to increase the incidence of FN in DLBCL patients on either treatment regimen. Unfortunately, this is not the practice in our setup. Hopefully, our study will help to improve the current management practices for DLBCL patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Ganem D, Prince AM. Hepatitis B virus infection—natural history and clinical consequences. *N Engl J Med*. 2004;350(11):1118-1129.
2. Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology*. 2007;45(2):507-539.
3. Lok AS, Lai CL, Wu PC, Wong VC, Yeoh EK, Lin HJ. Hepatitis B virus infection in Chinese families in Hong Kong. *Am J Epidemiol*. 1987;126(3):492-499.
4. Rehermann B, Ferrari C, Pasquinelli C, Chisari FV. The hepatitis B virus persists for decades after patients' recovery from acute viral hepatitis despite active maintenance of a cytotoxic T-lymphocyte response. *Nat Med*. 1996;2(10):1104-1118.
5. Coiffier B, Lepage E, Brière J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346(4):235-242.
6. Pfreundschuh M, Trümper L, Österborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2006;7(5):379-391.
7. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol*. 2006;24(19):3121-3127.
8. Aksoy S, Harputluoglu H, Kilickap S, et al. Rituximab-related viral infections in lymphoma patients. *Leuk Lymphoma*. 2007;48(7):1307-1312.
9. Targhetta C, Cabras MG, Mamusa AM, Mascia G, Angelucci E. Hepatitis B virus-related liver disease in isolated anti-hepatitis B-core positive lymphoma patients receiving chemo-or chemo-immune therapy. *Haematologica*. 2008;93(6):951-952.
10. Niscola P, Del Principe MI, Maurillo L, et al. Fulminant B hepatitis in a surface antigen-negative patient with B-cell chronic lymphocytic leukaemia after rituximab therapy. *Leukemia*. 2005;19(10):1840-1841.
11. Salar A, Haioun C, Rossi FG, et al. Febrile neutropenia risk assessment and granulocyte-colony stimulating factor support in patients with diffuse large B cell lymphoma receiving R-CHOP regimens.
12. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management [published correction appears in *Cancer*. 2004;100(9):1993-1994]. *Cancer*. 2004;100(2):228-237.
13. Perceau G, Diris N, Estines O, Derancourt C, Lévy S, Bernard P. Late lethal hepatitis B virus reactivation after rituximab treatment of low-grade cutaneous B-cell lymphoma. *Br J Dermatol*. 2006;155(5):1053-1056.
14. Yeo W, Chan TC, Leung NW, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol*. 2008;27(4):605-611.
15. Choi YW, Jeong SH, Ahn MS, et al. 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.
16. Lanini S, Molloy AC, Fine PE, Prentice AG, Ippolito G, Kibbler CC. Risk of infection in patients with lymphoma receiving rituximab: systematic review and meta-analysis. *BMC Med*. 2011;9(1):36.