RESEARCH ARTICLE

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Clinical Response to CHOP vs. R-CHOP in Adult Patients with Diffuse Large B-Cell Lymphomas

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Abstract

Purpose: The purpose of this study was to address the question of "superiority of R-CHOP versus CHOP", with addition of Rituximab to CHOP, regarding survival of patients suffering from DLBCL. **Patients and methods:** A cohort retrospective design was used to conduct this study in a tertiary care hospital. A total of 100 patients (50 in each group) were randomly selected. The primary and secondary end points were EFS, OS, PFS and DFS. Kaplan Meier survival curve analysis (log rank, Breslow and Tarone ware tests) was employed to compare probability of survival for the two groups (CHOP/ R-CHOP). **Results:** The mean primary and secondary clinical indicators were estimated for each group (EFS, 1.7; 3.09 with a p value P=0.02), (OS, 0.60; 0.43 with a p value P=0.40), (PFS, 1.73; 3.57 with a p value P=0.002), (DFS, 0.02; 0.48 with a p value of P=0.00). **Conclusion:** The results for differences in clinical response were statistically significant in favor of the R-CHOP group.

Keywords: CHOP- RCHOP- clinical response evaluation- DLBCL

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Introduction

Diffuse large B-cell lymphoma, is the most frequent subtype of lymphoma (non-Hodgkin's lymphoma) in which B lymphocytes have potential to grow and proliferate abnormally (Gatter andPezzella, 2010; Tariq et al., 2015). Lymph node and outside of the lymphatic system are main arising points for development of DLBCL (LeBien andTedder, 2008; Psyrri et al., 2008). Large mass of B cells, B symptoms and extranodal sites are the main features of DLBCL (Rosenwald et al., 2003; Pfreundschuh et al., 2006). In Pakistan, DLBCL reaches to an epidemic proportion (Naz et al., 2011; Tariq et al., 2015). For more than twenty five years, the cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) regimen has been considered the gold standard treatment for patients with DLBCL (Feugier et al., 2005; Johnson et al., 2012). Later on several studies have proved that addition of rituximab (chimeric human/murine immunoglobulin) in to CHOP considerably enhances the complete response rate, decreasing the relapse rate and improve the EFS, OS (Feugier et al., 2005; Sehn et al., 2007). It has been demonstrated in phase II studies that rituximab has ascertained efficacy in DLBCL alone and in combination with the CHOP regimen (Feugier et al., 2005; Persky et al., 2008; Link et al., 2011).

Materials and Methods

Patients

This study was carried out in adult cancer patients (age >18) having confirmed diagnoses of DLBCL. This retrospective study was conducted by employing hospital information system to find the previous 8 years patient's data. Patients with previously untreated for advanced stage DLBCL should be treated with LYCHOP-R, Patients had not got any other chemo protocol for DLBCL, Adult patients of both genders, Patients had got more than 4 cycles of CHOP/R-CHOP were eligible for this study. While the patients having any severe co-morbidity like cardiac dysfunction, had received any other chemo protocol for any stage of DLBCL, Patients with age less than eighteen were not included in this study. The mean age of selected population was found to be ˷39 years.

Method

Patients were identified using hospital information system (HIS) of SKMCH &RC. Shaukat Khanum cancer registry was searched for the previous 8 years registered cases of DLBCL, who did' t receive any other chemo protocol except CHOP/ R-CHOP and had advanced stage disease (III or IV; stage I or II with "B"

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symptoms). One hundred patients of diffuse large beta cell lymphoma were randomly selected from hospital information system and then stratified in to two groups. In group 150 patients were included who had received only CHOP protocol while in group 2, those patients were included who had received only R-CHOP protocol. This cohort retrospective study was conducted to collect and record all the required demographic information, lab investigations (CBCs, LFTs), patient's performance status (ECOG and Karnofsky's Scale), start date of chemo therapy, date of negative scan, and date of relapse for each patients. From this base line information, parameters of clinical response evaluation were estimated to compare both chemo protocols (CHOP/ R-CHOP). So, in this study we had followed the DLBCL patients up to eighth cycle of chemo protocols to find out the final clinical outcome.

Outcome measures

Primary clinical indicator used in this study was Event free survival (EFS) of patients with DLBCL after chemo therapy (CHOP/R-CHOP). EFS may be defined as "The lapse of time that pursues treatment for a tumor or the malignant disease, during which no impartial signs of recurrence are present. Secondary clinical indicators assessed at the end of chemo protocols were overall survival (OS), progression free survival (PFS), disease free survival (DFS) for each patient that was included in this study. The OS is the % age of people who are able to still alive for definite time period after they were clinically diagnosed with certain disease like cancer or started therapy for that disease. The PFS is the period of time during treatment and after the management of a malignant disease like cancer, patient lives with the disease but it does not get worse. In DFS, we estimate the number of people who are alive and free from the signs of cancer after a certain number of years.

Statistical data analysis

The SPSS version 16 was employed to evaluate the results obtained from this study. Independent samples t-test and Kaplan Meier survival curve analysis (log rank, Breslow and Tarone ware tests) were employed to compare the means and probability of survival for the two groups of cases (CHOP/ R-CHOP) to find any difference in response due to treatment protocols. The Kaplan-Meier method is a nonparametric method used to estimate the probability of survival past given time points (i.e., it calculates a survival distribution). All three tests of survival (log rank, Breslow and Tarone ware tests) compare a weighted difference between the observed number of events and the number of expected events at every time point, but differ in how they calculate the weight. The Log-Rank Test tends to perform best towards the right side of the survival curves. The Breslow Test tends to perform best on the left side of the survival curves and the Tarone-Ware Test tends to perform best in the middle of the survival curve. A p-value of <0.05 was considered as significant with confidence interval of 95%.

Results

Determination of clinical indicators

At the time of inclusion, mean age of patients in group 1 and 2 were 36.7 yrs and 41.9 yrs respectively with

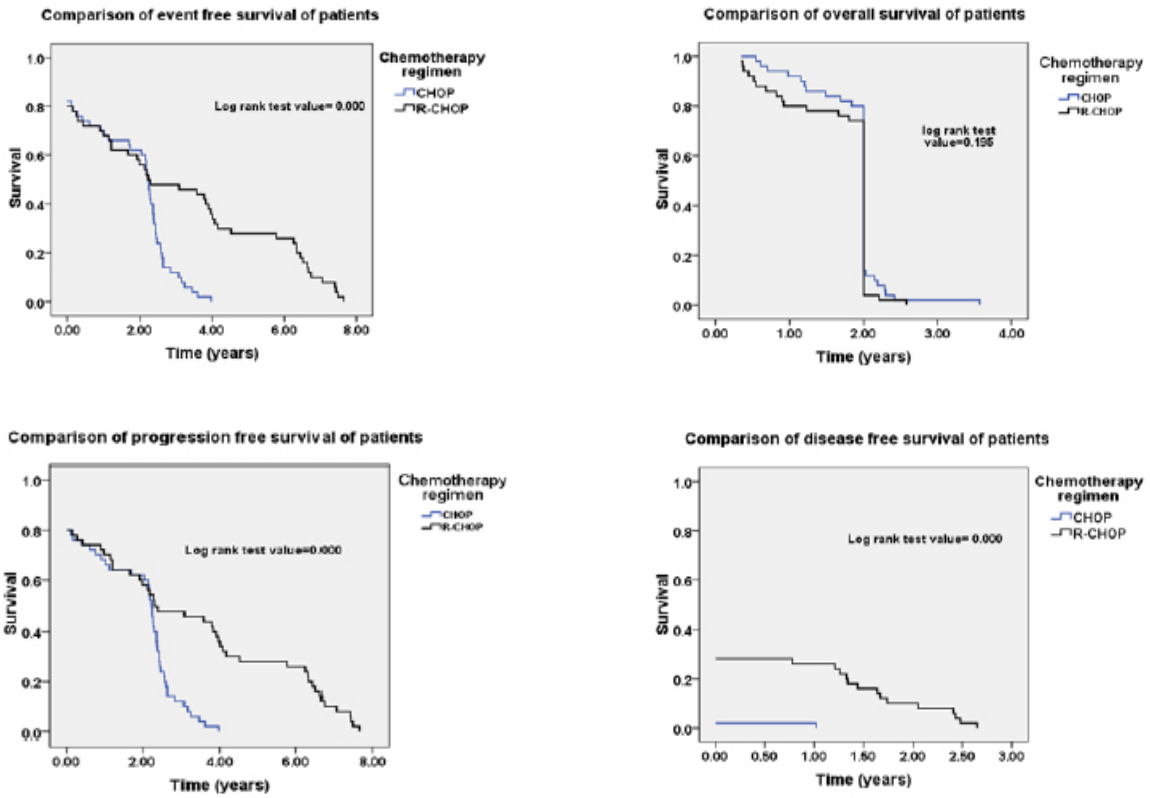

Figure 1. Kaplan Meier Survival Plots for Overall Survival, Event Free Survival, Progression Free Survival, Disease Free Survival

Table 1. Patients Characteristics

Characteristics	Group 1(CHOP) N=50	Group 2(R-CHOP) N=50	P-value
Mean Age (years)	36.7 yrs	41.9yrs	0.029
ECOG performance status			
0	26	36	0.035
1	21	13	
2	3	1	
Karnofsky's performance status			0.310
100	26	36	
90	16	3	
80	5	10	
≤70	3	1	
Stage			0.431
I	7	7	
II	17	16	
III	17	11	
IV	9	16	

Table 2. Comparison of Outcome Measures of CHOP and R-CHOP

Clinical indicator	Chemotherapy regimen	Total number of patients	Mean	Standard Deviation	T-test P- value	Log rank test P-value	Breslow test P-value	Tarone- ware test P-value
Event free survival of patient	CHOP	50	1.7642	±1.17802	0.002	0.000	0.068	0.007
	R-CHOP	50	3.0934	±2.69613				
Overall Survival	CHOP	50	0.6076	±.93736	0.404	0.195	0.110	0.126
	R-CHOP	50	0.4390	±1.06928				
Progression free survival	CHOP	50	1.7392	±1.19389	0.002	0.000	0.035	0.003
	R-CHOP	50	3.5704	±3.97340				
Disease free survival	CHOP	50	0.0204	±.14425	0.000	0.000	0.000	0.000
	R-CHOP	50	0.4886	±.84463				

p value of (P= 0.029). The characteristics of 100 patients selected for this study are summarized in the following Table 1.

Firstly, the p-value of the independent sample t-test was calculated from the overall mean values of EFS, OS, PFS and DFS. The mean EFS with standard deviation for CHOP and R-CHOP was estimated as 1.7yr (SD±1.17) and 3.09 yrs (SD± 2.69) with P= 0.002. In case of overall survival, mean calculated values for CHOP and R-CHOP, with SD were 0.607± 0.93 and 0.439 ± 1.06 having p value P=0.404. The mean value of progression free survival were found to be (CHOP=1.73 yrs ±1.19) and (R-CHOP= 3.5 yrs ±3.9) having p=0.002. At the end, disease free survival was calculated (CHOP= 0.02 yrs ±0.14) and (R-CHOP=0.488 ±0.84) with P= 0.000.

Discussion

Secondly, the Kaplan Meier survival curve analysis (log rank, Breslow and Tarone ware tests) was employed to compare probability of survival for the two groups of cases (CHOP/ R-CHOP). In case of EFS, PFS and DFS significant result were obtained in all three tests because the p value is less than 0.05 which showed that patients of group 2(R-CHOP) had higher survival time than patients of group 1(CHOP) (Table 2). However, In case of OS statistical insignificant results was found in all three tests because p value is greater than 0.05 (Figure 1).

In conclusion, our study depicted that the results of three clinical indicators like event free survival (P=0.002), progression free survival (P=0.002) and disease free survival (P=0.000) were in favor of R-CHOP chemoprotocol but there is no difference in the overall survival (P=0.404) of both group of patients who had received CHOP or R-CHOP. So the DLBCL patients of the CHOP chemoprotocol receiving group had been survived for same duration as the group of patients who received R-CHOP but their survival was not event, progression and disease free. So, It is concluded that event free survival, progression free survival, and disease free survival rates were higher in 2nd group (R-CHOP), and statistically significant. However, only one clinical indicator, overall survival, showed no difference between two regimens.

References

Feugier P, Van Hoof A, Sebban C, et al (2005). Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*, **23**, 4117-26.

Gatter K ,Pezzella F (2010). Diffuse large B-cell lymphoma. *Diagn Histopathol*, **16**, 69-81.

Johnson NA, Slack GW, Savage KJ, et al (2012). Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol*, **30**, 3452-9.

LeBien TW ,Tedder TF (2008). B lymphocytes: how they develop and function. *Blood*, **112**, 1570-80.

Link BK, Brooks J, Wright K, et al (2011). Diffuse large B-cell lymphoma in the elderly: diffusion of treatment

with rituximab and survival advances with and without anthracyclines. *Leuk Lymphoma*, **52**, 994-1002.
Naz E, Mirza T, Danish F (2011). Clinicopathologic evaluation of subgroups of diffuse large B cell lymphoma by immunohistochemistry. *Asian Pac J Cancer Prev*, **12**, 3335-9.
Persky DO, Unger JM, Spier CM, et al (2008). Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. *J Clin Oncol*, **26**, 2258-63.
Pfreundschuh M, Trümper L, Österborg A, et al (2006). 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*, **7**, 379-91.
Psyrri A, Papageorgiou S ,Economopoulos T (2008). Primary extranodal lymphomas of stomach: clinical presentation, diagnostic pitfalls and management. *Ann Oncol*, **19**, 1992-9.
Rosenwald A, Wright G, Leroy K, et al (2003). Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. *J Exp Med*, **198**, 851-62.
Sehn LH, Berry B, Chhanabhai M, et al (2007). The revised international prognostic index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood*, **109**, 1857-61.
Tariq A, Khurshid A, Mehmood Y (2015). Potential risk factors and prevalence trend of diffuse large beta cell lymphoma in Pakistani population. *Int J Pharm Res Allied Sci*, **4**, 75-85.