ORIGINAL ARTICLE

CHARACTERISTICS AND OUTCOME OF PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA-TREATED WITH CHEMOTHERAPY OR CHEMO-IMMUNOTHERAPY

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Background: Diffuse large-B-cell lymphoma, is the most common subtype of Non-Hodgkin lymphoma. Aim of this study was to look at the characteristics and outcome of DLBCL patients who were treated with chemotherapy or chemotherapy plus rituximab at our institution. **Methods:** Data of 750 patients, who got registered at our institute between 2007 and 2014, was reviewed retrospectively. After appropriate exclusions, 337 were included. Disease free survival (DFS) and overall survival (OS) were compared between patients who received rituximab plus CHOP (Cyclophosphamide, Doxorubicine, Vincristine, Prednisolon) (R-Ch) and standard chemotherapy-CHOP (S-Ch). **Results:** Males and females were 216 (64%) and 121 (36%) respectively, with median age 38 years (Range 18–80 yrs.). R-Ch and S.Ch was received by 129(38.3%) and 197(58.4%) patients, respectively. Complete remission (CR) was achieved by 81 (62.8%) vs. 105 (53.3%) patients in R-Ch vs. S-Ch cohorts, respectively. In subset analysis CR was seen in 34 (63.0%) and 45 (58.4%) (p=0.01) in R-Ch/XRT and S-Ch/XRT, respectively. At three years, DFS was 85.3% vs. 74% (p=0.04) and OS was 82.2% vs. 72.6% (p=0.02) in R-Ch and S-Ch cohorts respectively. Deaths observed were 9 Vs.13 in R-Ch/XRT and S-Ch/XRT, respectively. **Conclusion:** Based on our study, onset of DLBCL is at younger age in our population with male predominance. Addition of rituximab to CHOP resulted in better DFS and OS in patients with DLBCL. In developing countries, due to cost, large number of patients do not have access to rituximab. Efforts should be made to reduce the price of targeted therapies so that more and more patients are benefitted from these newer agents.

Keywords: DLBCL, CHOP, Rituximab, DFS, OS

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INTRODUCTION

Diffuse large-B-cell lymphoma, is the most common subtype of Non-Hodgkin lymphoma (NHL). It accounts for up to 40% of all NHL cases.[1] Onset is usually in the 6th decade of life with male predominance. Morphological, clinical and biological variation of DLBCL confirms the coexistence of several subtypes of the disease with distinct behaviour of each type. Based on gene expression profile, three basic subgroups of DLBCL were defined; (i) germinal centre B-cell (GCB)-characterized by expression of genes typically expressed in germinal centre centroblasts, (ii) Activated B-cell (ABC) -derived from post-germinal B cells expressing genes characteristic for in vitro activated B cells, (iii) Primary mediastinal B-cell lymphoma (PMBL)- with gene expression completely different from those in the previous two subtypes.[2,3] Clinical presentation depends upon the site of involvement and stage of the disease. Ann Arbor staging system is widely used to evaluate the cases of non-Hodgkin's lymphoma (NHL). International prognostic index (IPI) is a prognostic tool for patients with DLBCL.[4] Revised International prognostic index (R-IPI) was introduced in the era of rituximab and is currently used to predict prognosis in patients treated with rituximab based regimens.[5]

Treatment of DLBCL has improved significantly over the past 40 years. This was contributed by deeper understanding into disease pathophysiology, better diagnostic capabilities, improved staging, development of useful prognostic indices and effective therapies. CHOP regimen has been standard of care for more than 25 years.[6] Several other intensive chemo regimens were developed in an attempt to improve the disease end points but none proved to be more efficacious and safe as compared to CHOP.[7] Dose intense and high dose therapy followed by autologous stem cell transplant is proved to prolong survival in subgroup of patients with high risk features.[8] Addition of Rituximab to chemotherapy in the first line treatment of DLBCL has revolutionized the outcomes in all categories of DLBCL.[9] Long term follow up has proved that addition of rituximab to standard chemotherapy (CHOP) decreased rates of treatment failure, relapse and increased event free survival (EFS) and overall survival (OS).[10] CD 20 antigen is expressed by more than 90% of B cell lymphomas. Rituximab is a chimeric human murine immunoglobulin that binds to CD20 positive B

cells.[11] Initially it was approved for the indolent lymphomas.[12] Rituximab causes destruction of CD 20+ve cells through various mechanisms including, induction of apoptosis, complement dependent cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC).[12] Although there are various effective ways through which rituximab causes cell destruction, after treatment with R-CHOP not all the patients respond to therapy. Treatment unresponsiveness is probably because of rituximab resistance. Hypothesized mechanisms of resistance include low serum levels, rapid metabolism, heavy disease burden, impaired complement dependent cytotoxicity and poor cell surface CD 20 expression.[13,14] Although, addition of rituximab has significantly improved outcomes; however, a significant number of patient will have early treatment failure or disease relapse. More work needs to be done, to develop novel agents to treat patients with relapsed/refractory disease.

Rituximab along with standard chemotherapy is considered to be standard of care in developed world. Due to high cost of this agent, many patients in developing world cannot afford treatment with rituximab. Published data about the outcome of patients treated with rituximab based regimens remain sparse from this region. In this study, we looked at the characteristics and outcome of DLBCL patients who were treated with chemotherapy or chemotherapy plus rituximab at our institution.

MATERIAL AND METHODS

We retrospectively studied 750 patients with diagnosis of diffuse large B-cell lymphoma (DLBCL), T-cell/histiocyte-rich B cell lymphoma (TCRBCL), or plasmablastic lymphoma (PL).

All patients were diagnosed and treated at our institute between 2007 and 2014 at Shaukat Khanum Memorial Cancer Hospital & Research Centre. This study was approved by hospital ethical committee. Data were collected from hospital information system (HIS). The selection criteria were the availability of pathological diagnosis, detailed information on treatment and follow up. Biopsy specimens were available in all cases and were reviewed by two pathologists, who confirmed that all cases were de novo DLBCL/ TCRBCL/ PL according to the 2008 WHO lymphoma classification. Disagreements were resolved by mutual consensus by reanalysis of the immunohistochemical staining.

The extent of disease was determined at first presentation by physical examination, serum lactate dehydrogenase (LDH) concentration, bone marrow biopsy and computed tomography (CT) or positron emission tomography–computed tomography (PET-CT). CT scan or magnetic resonance imaging (MRI) of the brain was done where central nervous system (CNS) involvement was suspected. For each patient, the following characteristics were noted from the medical records: date of first clinical visit, age at diagnosis, gender, Ann Arbor stage, LDH, CNS involvement, type of chemotherapy, radiotherapy and date of last clinical visit or death where applicable. Response to therapy was assessed by reviewing CT or PET/CT reports done after 3–4 cycles of chemotherapy. Different chemotherapy regimens were used. Intrathecal chemotherapy was given to the patients with high risk of CNS relapse.

Disease status - remission or relapse and patient status - dead or alive, at three years, was recorded. Patients with no or incomplete initial staging work-up, missing data and those who lost to follow-up or died before receiving three cycles of chemotherapy were excluded from the study. Cases who transformed from low grade to high grade lymphoma were also in exclusion group.

The clinical and radiological response criterion of non-Hodgkin's lymphomas was applied to determine the occurrence of complete remission (CR), partial remission (PR), stable disease (SD), or progressive disease (PD). Disease status at three years was categorized as remission, partial remission, or relapse as concluded from both clinical examination and CT or PET-CT scan reports. Overall survival (OS) was measured from the date of first consultant visit to last follow up or death from any cause. Disease-free survival (DFS) was determined as an interval between the date of remission and relapse or death.

Disease-free survival and OS were assessed by Kaplan-Meier graphs. Fischer's exact test was used to identify significant correlations between variables. The *p*-values for these analyses are based on the log-rank test. Cox proportional hazard multivariate analysis was performed to compare the prognostic importance of the different variables. SPSS 19.0 for Windows software was used for all assessments.

RESULTS

This is a single centre retrospective study done in a tertiary level cancer centre in Pakistan. Patients registered from 2007 to 2014 with a proven diagnosis of DLBCL were enrolled. After making appropriate exclusions, 337 patients were included in the final analysis. Patients with age of 18 years or above were included. The median age was 38years (Range18–80 years). Majority of the patients 321 (95.2%) were less than 65yr of age. There were 216 (64%) males and 121 (36%) females. The follow up period ranged from 24 months to 83 months (median 58 months). Number of patients with stage I–IV was 64 (19%), 97 (28.8%), 60 (17.8%) and 113 (33.5%), respectively. Abnormal high LDH was noted in 177 (52.5%) patients. Seventeen (5%) patients were noted to have CNS involvement. Intrathecal chemotherapy was given to 93 (27.6%)

patients as primary CNS prophylaxis. Indications for intrathecal chemotherapy were bone marrow, nasopharyngeal, more than one extra nodal site with high LDH, Para spinal, renal, bone and breast involvement. Disease and patients characteristic are given in table-1. RCHOP regimen was given to 129 (38.3 % of) the patients while 197(58.5%) were treated with CHOP. There were 11 (3.3%) patients who were treated with other chemotherapy regimens including HCVAD/CVP/RCVP, table-2. There were 133 (39.5 %) patients treated with radiation therapy along with different chemotherapy regimens. The indication for radiation therapy was either localized disease or bulky disease at the outset, or being the only site of active disease at the end of treatment. Bulky disease was defined as >10 cm mass in the mediastinum and >6 cm at sites other than mediastinum. There were 81 (62.8%) patients in RCHOP cohort who achieved CR on end of treatment (EOT) scan as compared to 105 (53.3%) in CHOP group, p=0.3. Patients with PR, SD and PD in RCHOP and CHOP groups were 18(14%), 9 (7%), 9 (7%) and 37 (18.8%), 14 (7.1%), 25 (12.7%), respectively.

Relapse rate at three years was lower in RCHOP (14.7%) than CHOP (26%). Disease free survival (DFS) at three years was better in RCHOP group compared to CHOP, 85.3% vs 74%, respectively, p=0.04 (Figure-1). Less number of deaths was recorded in RCHOP compared to CHOP group, 23 (17.8%) and 54 (27.4%), respectively. The overall survival (OS) at three years was 82.2% and 72.6% in both arms, respectively, p=0.02.

The difference was statistically significant as shown in the Kaplan-Meier graph (Figure-2). These two treatment combinations were also analysed for responses in the presence of radiotherapy. Complete remission on EOT scan was noticed in 34 (63.0%) in RCHOP with XRT as compared to 45 (58.4%) in CHOP with XRT, p=0.01. There were less number of deaths in RCHOP/XRT regimen than CHOP/XRT, 9 and 13, respectively.

Table-1: Patients and disease characteristics.

Patient Characteristics	Parameters	Percent %	Number (n)
Age	Less than 65	95.2	321
	More than 65	4.74	16
Gender	Male	64	216
	Female	36	121
LDH	Normal	46.6	157
	Abnormal	52.5	177
	N/A	0.9	3
Stage	I	19	64
	II	28.8	97
	III	17.8	60
	IV	33.5	113
	N/A	0.9	3
CNS involvement	Yes	5	17
	No	95	320
Intrathecal chemotherapy	Given	27.6	93
	Not given	72.4	244
Radiotherapy	Yes	39.5	133
	No	60.5	204

Table-2: Type of chemotherapy regimens

Chemotherapy Type	Number of patients	Percent (%)
RCHOP	129	38.3
CHOP	197	58.5
HCVAD	2	.6
CVP	1	.3
RCVP	1	.3
OTHER	7	2.1
Total	337	100.0

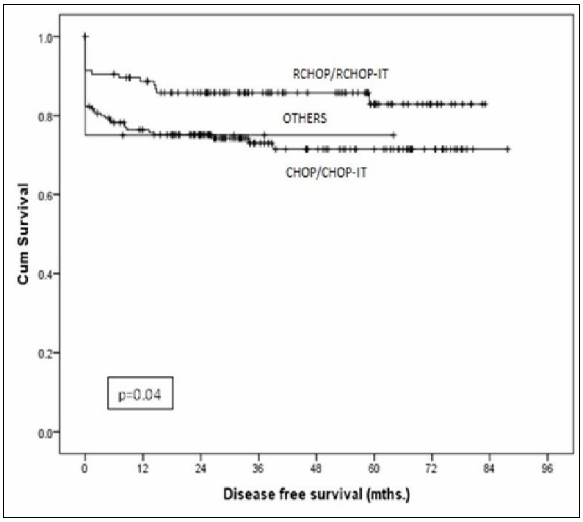

Figure-1: Disease Free Survival (DFS)

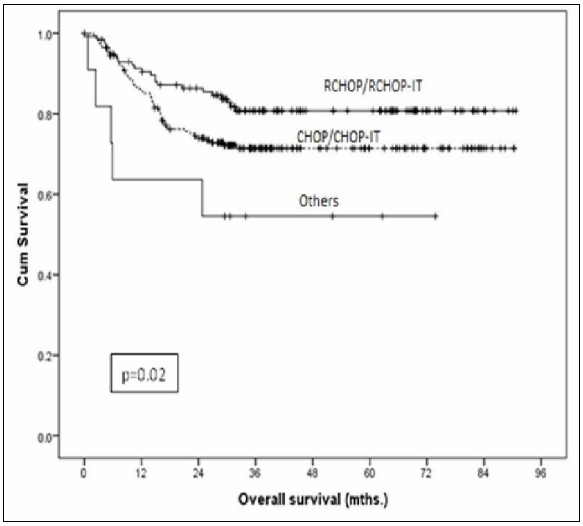

Figure-2: Overall Survival

DISCUSSION

Diffuse large B cell lymphoma is the commonest type of NHL. Treatment paradigm has changed since the addition of rituximab to historic standard of care CHOP.[15] A significant number of DLBCL patients are cured with RCHOP regimen. To improve things further, number of different agents had been used in clinical trials but no RCHOP successor been found.

In our study, mean age was lower compared to Caucasian population. However, was consistent

with the fact that onset of NHL in Asian patients is in relatively at younger age compared to western world. In addition, same findings have been noticed in previous studies from this region.[15]

There were more males than females. Almost equal number of patients presented with high or normal LDH and stage I/II and III/IV. Some studies have shown that in developed countries the presentation was more commonly with high LDH and advanced stage disease.[16] Data are sparse from our region addressing the issue of stage and LDH in these patients. In our study, because of the cost issue, most patients could not get rituximab. The majority of patients were treated with CHOP and less than 40% of patients received RCHOP regimen. As far as response rate was concerned, there were more CR/PR and less PD in RCHOP group. Although, this difference was not statistically significant but there was trend towards better CR rates, it may be due to small number of patients. There were more relapses in CHOP group when compared to RCHOP, leading to better DFS in later group. With a median follow up of 3 years, less number of deaths was noticed in RCHOP arm than CHOP (17.8 vs. 27.4, respectively, p=0.02). This resulted in better OS in RCHOP group, again consistent with established evidence.[10] Better OS also points to important fact that more patients in RCHOP regimen were salvaged on relapse as compared to CHOP group. Some studies have shown better results on second line therapy if patient had rituximab in frontline therapy.[16]

CNS disease was found in about 5% of patients at diagnosis. These patients were treated with standard chemotherapy plus intrathecal chemotherapy (IT) and high dose methotrexate. About one fourth of total patients had intrathecal methotrexate as primary CNS prophylaxis to high risk group including patients with >1 extranodal sites with high LDH, kidney, breast, marrow and testis involvement and patients with oropharyngeal or paraspinal masses. The evidence regarding benefit of primary CNS prophylaxis is rather conflicting however, as many studies showed the less CNS relapse risk with prophylaxis, so we continue to give Intrathecal chemotherapy to high risk population.[17,18] There is a need for more clinical trials to have clear guidelines on this issue.

In our analysis, a significant number of patients were treated with radiotherapy in addition to different chemotherapy regimens. In our institution, most of low risk disease patients receive 3 cycles of planned chemotherapeutic agents followed by IFRT. In addition, patients with advanced stage disease with residual lesions or bulky disease were also given consolidative XRT after discussion in MDT. Patients who had XRT in RCHOP group they did better in regards to response rate on EOT scan, PFS and OS than CHOP/XRT group. In this study, we did not look at the outcome of patients who did not have XRT. Overall, our results are in keeping with established fact that DFS and OS are better with chemoimmunotherapy compared to chemo alone.[10]

The limitations of this study include:

- Retrospective nature
- Adverse events with both regimens were not mentioned
- A single centre study
- No details of CNS relapses despite of primary CNS prophylaxis

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CONCLUSION

Based on our study, onset of DLBCL is at younger age in our population with male predominance. Addition of rituximab to CHOP resulted in better DFS and OS in patients with DLBCL. In developing countries, due to cost, large number of patients do not have access to rituximab. Efforts should be made to reduce the price of targeted therapies so that more and more patients are benefitted from these newer agents.

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AUTHOR'S CONTRIBUTION

All authors contributed equally to the preparation of the manuscript.

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