

Impact of Rituximab and IPI on survival in diffuse large B cell Lymphoma patients treated at a tertiary level cancer centre in Pakistan: A single-centre experience

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Abstract

Objective: To determine the impact of Rituximab and international prognostic index score on survival in diffuse large B-cell lymphoma patients.

Method: The retrospective study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, from January to May 2013 and comprised record of patients with diffuse large B-cell lymphoma who were treated from 2007 to 2010. Baseline international prognostic index score, stage at presentation were noted and the records were divided into two groups A and B on the basis of the type of chemotherapy. SPSS 19 was used for statistical analysis.

Results: Of the 93 patients in the study whose records were reviewed, 54(58%) were men. Overall median age was 43 years (range: 18-76). Stages at presentation were stage-I 14 (15.1%), stage-II 41 (44.1%), stage-III 20 (21.5%) and stage-IV 18 (19.4%). International prognostic index risk categorisation was low risk 59(63.4%), low intermediate risk 23(24.7%), high intermediate risk 10(10.8%) and high risk 1(1.1%). There were 31(33%) patients in Group A and 62(67%) in Group B. Median follow-up was 3.9 years (range: 1.2-6.1). Overall survival at 4 years was 66.4%; for Group A 65.3% and for Group B 66.7% ($p < 0.4$). On the basis of risk categories, overall survival was statistically significant ($p < 0.001$) between the groups..

Conclusion: International prognostic index risk categorisation had statistically significant impact on survival. However, there was no evidence of a significant survival benefit between types of chemotherapy. Further controlled trials are needed in this regard.

Keywords: Diffuse large B cell lymphoma, Rituximab, Outcome, Survival, Chemotherapy, Extranodal. (JPMA 65: 170; 2015)

Introduction

Diffuse large B cell lymphoma (DLBCL) is a heterogeneous disease in terms of morphology, behaviour and genetics. It is the commonest histological subtype of Non Hodgkin lymphoma (NHL), accounting for 25-40% of all NHL cases.¹⁻³ It is classified as an aggressive type of lymphoma.¹ Median age at presentation is 64 years with slight male predominance. Clinical presentation is variable and dependent on the site of involvement. Most patients present with nodal enlargement and B symptoms (weight-loss, fever, drenching night sweats).^{2,4}

Extranodal disease (gastro-intestinal, liver, lung, breast) is present in 40% cases.⁵⁻⁷ Most cases (60%) present with advanced stage (i.e. cannot be contained in one radiation field), with bone marrow involvement in 30% of cases and can present with discordant histology like follicular lymphoma.⁸ DLBCL arises from mature B cell resembling centroblasts or immunoblasts with presence of B cell

antigens on immunohistochemistry i.e. (CD19, CD20, CD22, and CD79a) as well as CD45 on tumour cells. Using gene expression profiling (GEP) by means of deoxyribonucleic acid (DNA) microarray technology, DLBCL has been subdivided into germinal centre DLBCL and non-germinal centre DLBCL.⁹

In 1993, International prognostic index (IPI) was proposed which predicts the survival of patients with NHL. It consists of five factors: age > 60 years, serum lactate dehydrogenase (S.LDH), performance status > 2 , extranodal sites > 1 , and stage of disease III-IV. Using IPI, four prognostic groups are formed depending on the number of risk factors present, low-risk group (LR) with 0-1 prognostic factors, low intermediate risk group (LIR) with 2 prognostic factors, high intermediate risk group (HIR) with 3 factors, and high risk group (HR) with 4-5 factors. Five-year survival using the IPI prognostic groups has been reported to be: 73%, 51%, 43% and 26% for the four groups respectively.¹⁰

Age-adjusted IPI is used for patients with age < 60 years in which all the above factors are included except age and extranodal sites. One point is given to each factor so the

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total score ranges from 0 to 3 with LR score 0, LIR score 1, HIR 2, and HR score 3. Five-year overall survival (OS) is 83%, 96%, 46% and 32% respectively.¹⁰

Recently, enhanced IPI — National Comprehensive Cancer Network-IPI (NCCN-IPI) has been proposed in which all factors which were part of original IPI were used but further characterization of age, lactate dehydrogenase (LDH) and extranodal sites are proposed.¹¹ First change was in age group i.e. <40y 0 point, 41-60y 1 point, 61-75y 2 points and >75y 3 points. Second change was in the LDH ratio (LDH-R) i.e. LDH-R <1 0 score, LDH-R >1-3 score 1, LDH-R >3 score 2. Third change was in extranodal sites with 1 score being given to lymphomatous involvement in bone marrow, central nervous system (CNS) liver, gastrointestinal (GI) tract and lung. The risk groups, as such, are: LR (0-1 score), LIR (2-3 score), HIR (4-5 score) and HR >6. Five-year OS for the four groups has been reported to be 96%, 82%, 64% and 33% respectively.¹¹

Poor survival in patients with age >60 could be due to multiple co-morbidities, and poor tolerance to chemotherapy. Moreover, a recent study showed that activated B cell (ABC) DLBCL is more prevalent in old age which carries poor prognosis.¹²

Over-expression of c-MYC and B-cell lymphoma 2 (BCL-2) by immunohistochemistry has shown poor survival after being treated with Rituximab-based chemotherapy.¹³ Moreover, mutation in p53 also results in poor OS.¹⁴ A study has proposed two gene score (TGS) using expression of tumour cell biomarker LIM domain only 2 (LMO2) with micro environment marker tumour necrosis factor (TNF) receptor superfamily member 9 (TNFRSF9) to predict outcome in DLBCL, but this needs further validation.¹⁵

Chemotherapy with or without radiation was the standard of care for the treatment of DLBCL before the addition of Rituximab anti-CD20 antibody in the management of this disease. DLBCL is treated with combination of treatment modality i.e. chemotherapy and radiation therapy depending upon the disease extent. Anthracyclin-based chemotherapy consisting of Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone (CHOP) is the most widely used and recommended treatment for DLBCL with 3-year OS of 52%.¹⁶ After the introduction of anti-CD20 monoclonal antibody, Rituximab is used in combination with chemotherapy (Chemoimmunotherapy R-CHOP). Studies from Western world suggest that survival of patients with DLBCL has improved significantly and chemoimmunotherapy is the current standard of care.¹⁷

Patients and Methods

The retrospective study was conducted at Shaukat

Khanum Memorial Cancer Hospital and Research Centre, Lahore, from January to May 2013 after approval was obtained from the institutional review board and comprised record of patients with DLBCL who were treated from 2007 to 2010. Data collection was done through the computerised database system. Patient's medical record number, age and gender were recorded. Baseline pathology reports, computed tomography (CT) scan reports and bone marrow biopsy were reviewed. Ann Arbor staging was used to stage the disease. Serum LDH, performance status, bone marrow involvement and type of chemotherapy were also recorded. On the basis of data, IPI risk categorisation was done.

Data was analysed using SPSS 19. OS was calculated from the date of registration to the last date of follow-up or death. OS was estimated using Kaplan Meier survival curves which were compared using the log-rank test.^{18,19}

Results

Of the 93 patients in the study whose records were

Table-1: Clinicopathological characteristics of patients with DLBCL.

Characteristic's	Total number of patients n= 93 Numbers	Percentages
Median Age	43 years (range 18-76)	
Gender M	54	58
F	39	42
Current status		
Alive	63	67.7
Dead	18	19.4
Lost to follow up	12	12.9
Stage at presentation		
I	14	15.1
II	41	44.1
III	20	21.5
IV	18	19.4
Bone marrow involvement		
Yes	4	4.3
No	89	95.7
IPI Risk Group		
Low risk	59	63.4
Low Intermediate risk	23	24.7
High intermediate risk	10	10.8
High risk	1	1.1
Type of chemotherapy		
CHOP (group 1)	31	33
R-CHOP (group 2)	62	67
Response to chemotherapy		
CR	74	79.6
PR	9	9.7
SD	3	3.2
PD	7	7.5

CR: Complete Remission. PR: Partial Recovery. SD: Stable Disease. PD: Progressive Disease.

Table-2: Characteristic of group 1 and group 2.

Type of chemotherapy	CHOP (group 1)	R-CHOP (group 2)
Stage at presentation		
Localized	18 (58.0%)	37 (59.67%)
Advanced	13 (41.93%)	25 (40.31%)
IPI at presentation		
Low risk	18 (58.0%)	41 (66.1%)
Low intermediate risk	08 (25.0%)	15 (24.1%)
High intermediate risk	04 (12.9%)	06 (9.6%)
High risk	01 (3.2%)	00 (0%)
Response to chemotherapy		
CR	24 (77.4%)	50 (80.6%)
PR	03 (9.6%)	06 (9.6%)
SD	00 (0%)	03 (4.8%)
PD	04 (12.9%)	03 (4.8%)

Response Criteria²⁷

- ◆ Complete Remission (CR): Disappearance of all evidence of measurable disease.
- ◆ Partial Response (PR): Regression of measurable disease (>50%) and no new sites of disease.
- ◆ Stable Disease (SD): Failure to attain CR/PR or PD
- ◆ Progressive Disease: Any new lesion or increase by ? 50% of previously involved sites from nadir.

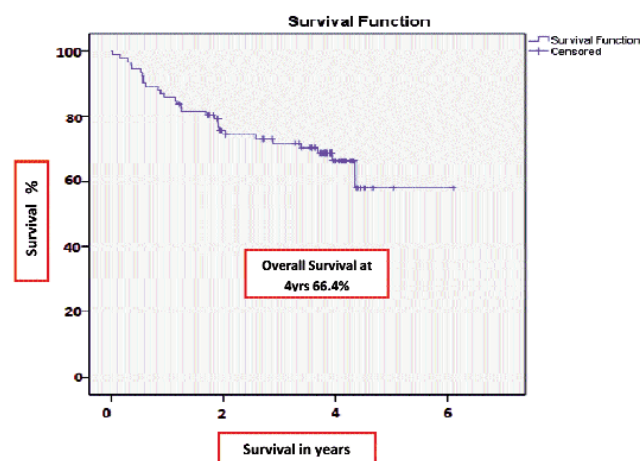


Figure-1: Overall Survival at 4 years.

reviewed, 54(58%) were men. Overall median age was 43 years (range: 18-76). Stages at presentation were stage-I 14 (15.1%), stage-II 41 (44.1%), stage-III 20 (21.5%) and stage-IV 18 (19.4%). IPI risk categorisation was LR 59(63.4%), LIR 23(24.7%), HIR 10(10.8%) and HR 1(1.1%). CHOP chemotherapy Group A had 31(33%) patients, while R-CHOP Group B had 62(67%) (Table-1).

According to IPI scores in Group A, there were 18(58.06%), 8(25.80%), 4(12.90%) and 1(3.2%) patients in LR, LIR, HIR and HR category respectively. In Group B, there were 41(66.12%) patients in LR, 15(24.19%) in LIR, 6(9.6%) in

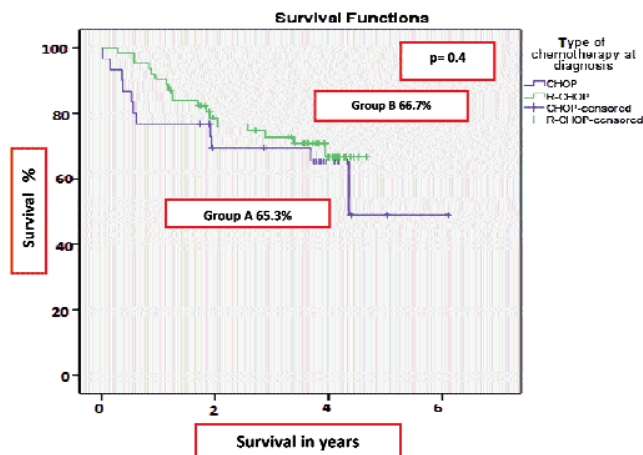


Figure-2: Overall survival at 4 years for Group A and Group B.

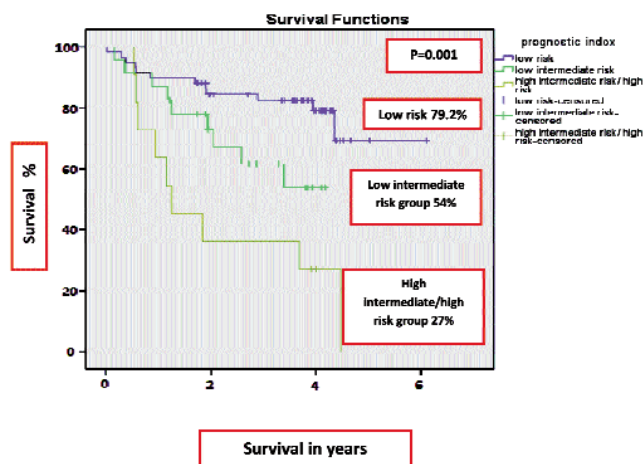


Figure-3: Overall Survival according to IPI (International Prognostic Index) risk group at 4 years.

HIR, while there was no patient with HR characteristics (Table-2). Consolidative radiation therapy was used in 15(16%) patients; 7(46.66%) in R-CHOP group and 8(53.33%) in the CHOP group. Patients were given minimum four and maximum eight cycles of chemotherapy.

Median follow-up was 3.9 years (range: 1.2-6.1). At the time of analysis, 63(68%) were alive, 18(19%) were dead and 12(12.9%) had been lost to follow-up. Median survival for all patients was not reached. Kaplan Meir estimated OS at 4 years in both group was 66.4% (Figure-1). At 4 years, OS for Group A and Group B were 66.3% and 66.7% (p=0.4) (Figure-2). At 4 years, OS for LR, LIR, HIR/HR groups were 79.2%, 54% and 27%, respectively and it was statistically significant (p<0.001) (Figure-3).

Discussion

The retrospective study added to knowledge available on DLBCL, which is the most common type of NHL worldwide and there is some concern about rising number of patients with this aggressive nature of disease in our population.²⁰ CHOP chemotherapy has been the standard first-line chemotherapy for several decades with complete response rate (CRR) of 41%, 3-year disease-free survival (DFS) of 41% and 3-year OS of 54%.¹⁶

In GELA trial, combination of anti-CD20 antibody and CHOP chemotherapy showed survival advantage in patient with age >60 years with 5-year OS of 58% in R-CHOP vs 45% in CHOP alone, with no clinical significant toxicity upon adding Rituximab with CHOP chemotherapy.^{21,22}

In 2006, MInT trial was conducted in younger patient age <60 years. Adding Rituximab to CHOP chemotherapy resulted in increase of 3-year event-free survival (EFS) to 79% in R-CHOP group and 50% in CHOP group. Similarly, 3-year OS was 93% in R-CHOP vs 84% in CHOP. The update result for MInT trial has been published in 2011, which shows better 6-year EFS in patients treated with R-CHOP i.e. 74.3% vs 55.8% in CHOP group.²³

The role of maintenance Rituximab after R-CHOP combination was addressed in 2006, and showed no improvement in failure-free survival (FFS). However, FFS was improved by using maintenance Rituximab after CHOP chemotherapy.²⁴

IPI has been validated to predict survival in patients with DLBCL in pre-Rituximab era. A study to evaluate utility of IPI during Rituximab era analysed data from three trials and found that IPI still remains an important tool to predict EFS, DFS and OS in all four groups, while Rituximab significantly improves outcome in all groups of IPI.²⁵

In our study, median age at presentation was 43 years, which is younger than the Western world with male predominance of 58% which was similar to Western data.^{2,26} In this analysis, only 8(8.6%) patients were >60 years of age. Literature shows 30-40% patients present with localised disease, while 60-70% patients present with advanced disease.²⁷ In our cohort 59% patients presented with localised disease, while 41% presented with advanced disease. Since the majority of patients belonged to low to low intermediate group, treating these patients with R-CHOP did not give survival benefit in our study. The retrospective nature and its small sample size are the main limitations of the study.

Conclusion

IPI remains an important tool to predict survival. R-CHOP

is the standard of care for CD20 positive NHL, but in under-resourced countries CHOP alone may be used in low-risk patients, while R-CHOP can be used in the high-risk group. Further prospective studies are required to validate these results.

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