The Impact of Bulky Mass on Treatment Response and Overall Survival in Patients with Diffuse Large B-Cell Lymphoma in Rituximab Era

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ABSTRACT

We aim to evaluate the prognostic value of the presence of bulky mass at the time of diagnosis in patients with diffuse large B cell lymphoma (DLBCL) receiving R-CHOP chemotherapy. The data of 86 patients were analyzed retrospectively. The patients were divided into 2 groups according to the presence of bulky mass. The impact of bulky disease on treatment response and overall survival (OS) in patients receiving R-CHOP therapy was assessed. Twenty five (28.7%) patients had bulky disease. Sixteen of 25 patients (64%) with bulky mass achieved CR, whereas 53 of 59 patients (90%) without bulky mass achieved CR (p= 0.015). Within a median 17 months (range, 3-86) of follow up period, 16 (18.6%) of the patients died. Among them, 9 patients had bulky disease. The probability of OS at the end of follow-up time was 54% in patients with bulky disease and 87% in patients without bulky disease (p= 0.007). Cox regression analysis showed that the presence of bulky disease had a negative impact on OS (p= 0.012); however this effect was not independent of IPI (p= 0.078). We found that the presence of bulky mass is a poor prognostic factor in DLBCL patients treated with R-CHOP regimen.

Keywords: Diffuse large B cell lymphoma, Bulky mass, Rituximab

ÖZET

Rituksimab Çağında Diffüz Büyük B Hücreli Lenfoma Hastalarında Bulky Kitlenin Tedavi Yanıtı ve Genel Sağkalıma Etkisi

Bu çalışmada R-CHOP kemoterapisi alan diffüz büyük B hücreli lenfoma (DBBHL) hastalarında tanı anında bulky kitle varlığının prognostik değerini incelemeyi amaçladık. 86 hastanın verileri retrospektif olarak analiz edildi. Hastalar bulky kitle varlığına göre iki gruba ayrıldı. R-CHOP tedavisi alan hastalarda bulky hastalığın tedavi yanıtı ve genel sağkalım (GS) üzerindeki etkileri değerlendirildi. Yirmi beş (%28.7) hastada bulky kitle bulunmaktaydı. Bulky kitlesi olan 25 hastanın 16'sında (%64) tam yanıt (TY) elde edilirken bulky kitlesi olmayan 59 hastanın 53'ünde (%90) TY elde edildi (p= 0.015). Medyan 17 aylık (3-86) takip süresinde 16 hasta (%18.6) öldü. Bu hastaların 9'unda bulky hastalık bulunmaktaydı. Takip süresinin sonunda GS olasılığı bulky kitlesi olan hastalarda %54 iken bulky kitlesi olmayanlarda %87 idi (p= 0.007). Cox regresyon analizi bulky hastalık varlığının GS üzerine olumsuz etkisi olduğunu gösterse de (p= 0.012), bu etki IPI skorundan bağımsız değildi (p= 0.078). Çalışmamızın sonucunda R-CHOP rejimi ile tedavi edilen DBBHL hastalar ında bulky kitle varlığının kötü prognostik bir belirteç olduğunu saptadık.

Anahtar Kelimeler: Diffüz büyük B hücreli lenfoma, Bulky kitle, Rituksimab

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL), representing approximately 30%-58% of all Non-Hodgkin lymphomas (NHL), is the most frequently-encountered subtype of NHLs.[1-4] The major prognostic factor in DLBCL is the cell of origin and accordingly, the prognosis of tumors with germinal center phenotype is superior to the ones with B-cell phenotype. In addition, International Prognostic Index (IPI) score, which is calculated by using patient's age, serum lactate dehydrogenase (LDH) level, disease stage, performance status and presence of extranodal involvement, has been used widespread to predict prognosis in DLBCL patients. Currently, the first-line treatment of DLBCL with a worldwide consensus is cyclophosphamide, doxorubicin, vincristine and prednisone in combination with monoclonal antibody rituximab (R-CHOP).[1-4] Combining rituximab with CHOP regimen was shown to improve progression-free survival (PFS) and overall survival (OS) in DLBCL patients with either early stage or advanced stage disease in Southwest Oncology Group (SWOG) 0014, Groupe d'Etude des Lymphoma de l'Adulte (GELA) (LNH 98-5) and RICOVER-60 studies.[5-7]

Although the presence of bulky mass has not been used in risk stratification of DLBCL patients, it was previously demonstrated that the presence of bulky mass was associated with aggressive disease in the pre-rituximab era.[8-10] However, there is a conflict whether the presence of bulky mass is a poor prognostic factor or not in DLBCL patients in the rituximab era.[6,11-13] In this retrospective study, we aimed to evaluate the prognostic value of the presence of bulky mass at the time of diagnosis in patients with DLBCL receiving R-CHOP chemotherapy.

METHOD

The data of 86 DLBCL patients, who were diagnosed and followed at the University of Health Sciences, Istanbul Training and Research Hospital, Department of Hematology, between January 2010 and November 2017, was analyzed retrospectively. The data including gender, age, lactate dehydrogenase (LDH) level, presence of extranodal involvement, B symptoms, bulky mass, bone marrow involvement, liver involvement and spleen involvement, IPI score, Eastern Cooperative Oncology Group (ECOG) score and treatment regimens of the patients, were reviewed from the database of the hematology department. Bulky mass was defined as any mass measuring > 7.5 cm by any imaging study.[2] The patients were staged according to the Ann Arbor Classification.[14] Staging procedure comprised the search for B symptoms, computed tomography (CT) scans or Positron Emission Tomography (PET)-CT scans. Treatment response was evaluated according to Lugano response criteria for Non-Hodgkin lymphoma. On a 5-Point Scale, scores 1, 2 and 3 with or without residual mass on control PET-CT scan were considered as complete response (CR). Scores 4-5 with reduced FDG uptake compared with baseline without new lesions were considered as partial response (PR). Scores 4-5 with no significant changes in uptake from baseline were considered as non-response (NR) or stable disease (SD), whereas scores 4-5 with increased uptake in comparison to baseline or development of new lesions were considered as progressive disease (PD).[15] The study protocol was approved by the local ethical committee.

Statistical Analysis

Statistical evaluation was made by using SPSS 24 package program. Data were described as numbers and percentage or median and range, when appropriate. x2 Fisher's exact test was used for evaluating categorical values and Mann-Whitney U test for continuous values in patient groups. Kaplan-Meier test with log rank analysis and Cox regression analysis were used for survival analysis. OS was calculated from initial diagnosis to death from any causes. All p-values were 2-sided with statistical significance at 0.05 alpha levels.

RESULTS

The characteristics of 86 patients are presented in Table 1. The median age of the patients was 57 years (range, 17-82). Thirty five (40%) patients were female and 52 (60%) were male. LDH was elevated in 52 (60%) of the patients. Twenty-five (29%) patients were at stage I-II and 61 (71%) patients at stage III-IV. Thirty (35%) patients had

Table 1. Patient characteristics

Characteristics	N= 86
Gender, n, (%)	
Female	34 (40 %)
Male	52 (60 %)
Age, years, median (range)	57 (17-82)
LDH level, n (%)	
Normal	52 (60 %)
Elevated	34 (40 %)
Stage, n (%)	
Stage I-II	25 (29 %)
Stage III-IV	61 (71 %)
Bulky mass, n (%)	
Present	25 (29 %)
Absent	61 (71 %)
B symptoms, n (%)	
Present	30 (35 %)
Absent	56 (65 %)
Bone marrow involvement, n (%)	
Present	6 (7 %)
Absent	80 (93 %)
Liver involvement, n (%)	
Present	2 (2.3 %)
Absent	84 (97.7 %)
Spleen involvement, n (%)	
Present	7 (8 %)
Absent	79 (92 %)
Extranodal involvement, n (%)	
Present	38 (44 %)
Absent	48 (56 %)
ECOG, n (%)	
0-1	68 (79 %)
2-4	18 (21 %)
IPI score, n (%)	
0-1	37 (44 %)
2-3	41 (50 %)
4-5	5 (6 %)
Radiotherapy	
Present	19 (22 %)
Absent	67 (78 %)
Response to treatment, n (%)	
CR	69 (80 %)
PR	6 (7 %)
NR	9 (11 %)
Unknown	2 (2 %)

LDH= lactate dehydrogenase, ECOG= Eastern Cooperative Oncology Group, IPI= International Prognostic Index, CR= complete Response, PR= partial response, NR= non-response

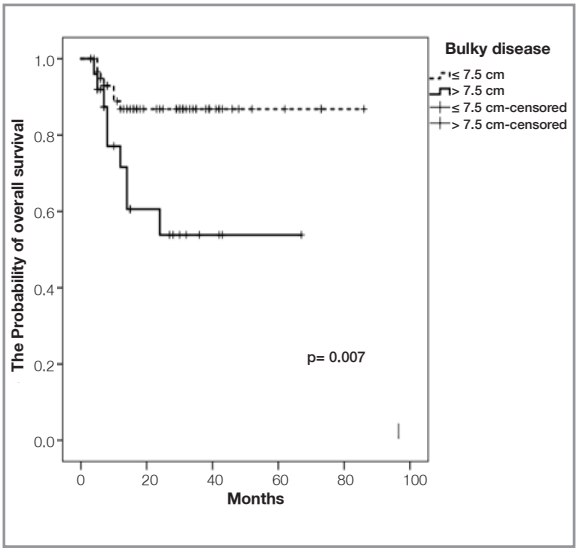

Figure 1. The overall survival of patients with and without bulky disease

B symptoms; 6 (7%) patients had bone marrow involvement; 2 (2.3%) patients had liver involvement, 7 (8%) patients had spleen involvement and 38 (44%) patients had extranodal involvement. ECOG score was 0-1 in 68 (79%) patients and 2-4 in 18 (21%) patients. IPI score was 0-1 in 37 (44%) patients, 2-3 in 41 (50%) patients and 4-5 in 5 (6%) patients. All patients were applied R-CHOP chemotherapy regimen at initial treatment. Radiotherapy was applied to 19 (22%) patients. After treatment, 69 patients (80%) achieved CR, 6 patients (7%) achieved PR while 9 patients (11%) had NR.

The patients were divided into 2 groups according to the presence of bulky disease. 25 (28.7%) patients had bulky disease. The patients with or without bulky disease were comparable in terms of gender, age, LDH level, stage, presence of B symptoms, bone marrow involvement, spleen involvement, extranodal involvement, ECOG and IPI scores (p> 0.05). Among patients with bulky mass, 16 patients (64%) achieved CR; 3 patients (12%) achieved PR and 6 patients (24%) had no response. Among patients without bulky mass, 53 out of 59 patients (90%) achieved CR; 3 patients (5%) achieved PR and 3 patients (5%) had no response (p= 0.015) (Table 2).

The median follow-up was 17 months (range, 3-86) and 16 (18.6%) patients died at the end of follow-up time. Among them, 9 patients had bulky

Table 2. Comparison of patients with and without bulky mass

Characteristics	Patients without bulky disease (n= 61)	Patients with bulky mass (n= 25)	p-value
Gender, n, (%)			
Female	25 (41 %)	9 (36 %)	0.809
Male	36 (59 %)	16 (64 %)	
Age, years, median (range)	57 (17-82)	55 (18-75)	0.842
LDH level, n (%)			
Normal	40 (66 %)	12 (48 %)	0.151
Elevated	21 (34 %)	13 (52 %)	
Stage, n (%)			
Stage I-II	18 (29 %)	7 (28 %)	1.0
Stage III-IV	43 (71 %)	18 (72 %)	
B symptoms, n (%)			
Present	38 (62 %)	18 (72 %)	0.461
Absent	23 (38 %)	7 (28 %)	
Bone marrow involvement, n (%)			
Present	6 (10 %)	0 (0 %)	0.175
Absent	55 (90 %)	25 (100 %)	
Liver involvement, n (%)			
Present	1 (1.6 %)	1 (4 %)	0.499
Absent	60 (98.4 %)	24 (96 %)	
Spleen involvement, n (%)			
Present	4 (7 %)	3 (12 %)	0.409
Absent	57 (93 %)	22 (88 %)	
Extranodal involvement, n (%)			
Present	25 (41 %)	13 (52 %)	0.474
Absent	36 (59 %)	12 (48 %)	
ECOG, n (%)			
0-1	51 (84 %)	17 (68 %)	0.144
2-4	10 (16 %)	8 (32 %)	
IPI score, n (%)			
0-1	30 (51 %)	7 (29 %)	0.195
2-3	26 (44 %)	15 (62 %)	
4-5	3 (5 %)	2 (9 %)	
Radiotherapy			
Present	11 (18 %)	8 (32 %)	0.166
Absent	50 (82 %)	17 (68 %)	
Response to treatment, n (%)			
CR	53 (90 %)	16 (64 %)	0.015
PR	3 (5 %)	3 (12 %)	
NR	3 (5 %)	6 (24 %)	

LDH= lactate dehydrogenase, ECOG= Eastern Cooperative Oncology Group, IPI= International Prognostic Index, CR= complete Response, PR= partial response, NR= non-response

disease. The probability of OS at the end of follow-up time was 54% in patients with bulky disease and 87% in patients without bulky disease (p= 0.007) (Figure 1). Cox regression analysis showed that the presence of bulky disease had a negative impact on OS (p= 0.012); however this effect was not independent of IPI score (p= 0.078) (Table 3). The number of patients who progressed after achieving CR was 6/69, 3 of which had bulky disease. The number of patients was too low to make an analysis for PFS.

DISCUSSION

Although the course of DLBCL has been improved considerably with the introduction of rituximab therapy[1-3], new attempts such as addition of either bortezomib[16] or ibrutinib[17] to R-CHOP regimen

Table 3. Univariate and multivariate analysis including IPI score and presence of bulky disease

Variable	P value (univariate)	P value (multivariate)	HR	95% CI
IPI				
Score I	0.002	0.080	1	–
Score II	0.008	0.134	3.317	0.692-15.908
Score III	0.001	0.003	13.409	2.365-76.017
Presence of bulky disease	0.012	0.078	2.646	0.896-7.809

CI= Confidence interval, HR= Hazard ratio, IPI= Internatioanal prognostic index

have come into question to provide even better results, especially in patients with poor prognostic factors. Also, upfront autologous stem cell transplantation (ASCT) consolidation after first complete response (CR1) has been a controversial topic in recent years.[3,18] Yet, such important modifications in the treatment of DLBCL require a well-defined high risk group of patients; and the presence of bulky mass could be a candidate in risk evaluation of those patients.

Even though the presence of bulky mass is not employed in risk stratification of DLBCL including IPI in daily practice, it has been described as a poor prognostic factor in a number of studies.[8,9,12,19] In pre-rituximab era, The International Non-Hodgkin's Lymphoma Prognostic Factors Project demonstrated that post-treatment CR rate was lower and OS was shorter in patients who had a tumor size larger than 10 cm at the time of diagnosis.[8] Similarly, Coiffier et al. showed that patients with tumor size > 10 cm had shorter survival.[9] On the other hand, Cowan et al. found that bulky mass was only associated with lower CR, however they used a cutoff of 5 cm in the definition of bulky mass.[10] Although there has been no debate about the unfavourable influence of bulky mass in DLBCL in pre-rituximab era, such certainty has not been established in rituximab era. While Coiffer et al.[6] and Takasaki et al.[20] demonstrated that the presence of bulky mass was not a prognostic factor, Pfreundschuh et al.[12] found that combining CHOP chemotherapy with rituximab decreased but did not eliminate the negative prognostic impact of bulky mass. Regarding extranodal DLBCL, Moo-Kon Song et al revealed that OS and PFS were significantly lower in extranodal DLBCL with bulky mass.[19] Similarly, we found that both response rate and OS were substantially inferior in DLBCL patients with bulky mass. However, the negative effect of bulky mass on OS was not independent of IPI. The inconsistency between our study and the previous reports might have been created due to the use of different cutoffs used for the definition of bulky disease in the rituximab era, and also due to the lack of the standardization in radiotherapy application to the patients in our study.

The present study shows that the presence of bulky mass is a poor prognostic factor in DLBCL patients treated with R-CHOP regimen. Although, rituximab is a milestone in the treatment of DLBCL, it seems that its effect might not be valid for bulky mass in DLBCL. However, we can not give a precise conclusion due to the limitations of this study which are; its retrospective nature, relatively small sample size and presence of patients who were not applied radiation therapy despite the presence of bulky disease. Thus, further studies with larger sample size and prospective design are warranted to clarify the impact of bulky mass in DLBCL in rituximab era.

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