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The Obesity Controversy: Does It Impact Treatment Response in Diffuse Large B-Cell Lymphoma?

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ABSTRACT

Background: We aimed to investigate the association of body mass index (BMI) with treatment response in patients with DLBCL

Material and Methods: Seventy-nine DLBCL subjects were included in this study. Data about patient age, sex, serum LDH level, presence of B symptoms, IPI score, ECOG performance score, disease stage, extranodal involvement, and BMI values at diagnosis were retrieved by retrospective patient record review. Patients were staged according to Ann Arbor classification using CT and/or PET/CT findings, and the presence of B symptoms. Body mass index was calculated by dividing weight in kilograms by height in meters squared (kg/m^2). Patients were divided into groups according to their BMI as underweight (BMI≤ 18.5 kg/m^2), normal weight (BMI 18.5-25 kg/m^2), overweight (BMI 25-30 kg/m^2), and obese (BMI≥ 30 kg/m^2), as defined by the World Health Organization.

Results: Patients were divided into four groups according to their BMIs, but because there was only one patient in the underweight group, comparisons were performed between normal-weight, overweight, and obese patients. There was no statistically significant difference between these groups in terms of age, sex, serum LDH level, disease stage, presence of B symptoms, extranodal involvement, ECOG performance score, IPI score and treatment response (p= 0.070, 0.704, 0.325, 0.464, 0.254, 0.152, 0.658, 0.620, and 0.947, respectively)

Conclusion: In our study, we showed that BMI has no significant impact on treatment response in patients with DLBCL.

Keywords: Diffuse large B-cell Lymphoma; Obesity; Body mass index

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphomas (NHL), accounting for 35 to 40% of all NHL cases[1]. It can affect patients of all age groups and present with various clinical scenarios. Most patients respond to treatment with rituximab, which isan anti-CD20 monoclonal antibody, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) given for 6 to 8 cycles. However, 10-15% are remain refractory to treatment and 20-30% relapse in the future [2-4]. In order to predict diagnosis, patients are divided into risk groups as low, low-intermediate, high-intermediate and high, according to their IPI scores, which is calculated based on age, serum lactate dehydrogenase (LDH) levels, Eastern Cooperative Oncology Group (ECOG) performance status, disease stage and the number of extranodal sites[5]. Besides high IPI score, other risk factors

indicating poor prognosis include the presence of bulky mass, tumor originating from active B cells, presence of MYC rearrangement along with BCL2 and/or BCL6 rearrangement, and TP53 mutation or overexpression[6-10].

Obesity is considered as a risk factor for many malignancies because it changes endogenous hormone metabolism and disorients cell proliferation, differentiation and apoptosis as well as altering immune response and chronic inflammatory response [11-13]. Certain metanalyses also indicate that obesity may be associated with increased risk of DLCBL[14, 15]. However, whether obesity affects survival and treatment response in patients with DLCBL remains. Even though there are studies showing an association between obesity and shorter survival in DLBCL, studies implying improved survival with obesity are also reported [16, 17]. In this study, we aimed to investigate the association of body mass index (BMI) with treatment response in patients with DLBCL.

MTERIALS AND METHODS

Patients diagnosed with DLBCL by excisional lymph node biopsy and were given R-CHOP chemoimmunotherapy in the University of Health Sciences Cemil Taşçıoğlu City Hospital Hematology Clinic between December 2005 and March 2019 were included in the study. Data about patient age, sex, serum LDH level, presence of B symptoms, IPI score, ECOG performance score, disease stage, extranodal involvement and BMI values at diagnosis were retrieved by retrospective patient record review. Patients were staged according to Ann Arbor classification using CT and/or PET/CT findings and the presence of B symptoms [18]. Body mass index was calculated by dividing weight in kilograms by height in meters squared (kg/m^2). Patients were divided into groups according to their BMI as underweight (BMI≤ 18.5 kg/m^2), normal weight (BMI 18.5-25 kg/m^2), overweight (BMI 25-30 kg/m^2) and obese (BMI≥ 30 kg/m^2), as defined by the World Health Organization (WHO) [19]. 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) [20].

The study protocol was approved by the institute's Ethics Committee on clinical research.

Statistical analysis

Data were analyzed with SPSS software for Windows (v21.0; IBM, Armonk, NY,USA). Data were also described as numbers and percentage or median and range, when appropriate

RESULTS

Data of 79 patients with diffuse large B cell lymphoma are summarized in Table 1. Among 79 patients included, 31 patients (39.2%) were female and 48 (60.8%) were male. Median age was 60 years (range: 23-84). Serum LDH level was elevated in 40 (50.6%) patients. Eight (10.1%) patients had stage I, 24 (30.4%) patients had stage II, 13 (16.5%) patients had stage III and 34 (43.0%) patients had stage IV disease. Thirty-one (39.2%) patients had B symptoms. Extranodal involvement was present in 47 (59.8%) patients. ECOG score was 0-1 in 66 (83.5%) patients, and 2-4 in 13 (16.5%) patients. IPI score was 0 in 7 (8.9%) patients,1 in 15 (19.0%) patients, 2 in 22 (27.8%) patients, 3 in 18 (22.8%) patients, 4 in 13 (16.5%) patients and 5 in 4 (5.1%) patients. One patient (1.3%) was underweight (BMI< 18.5 kg/m^2), 26 patients (32.9%) were normal weight (BMI 18.5-25 kg/m^2), 34 (43.0%) were overweight (BMI 25-30 kg/m^2) and 18 (22.8%) were obese (BMI≥ 30 kg/m^2). After treatment, 67 patients (84.8%) achieved complete response(CR), 2 patients (2.5%) achieved partial response (PR), while 10 patients (12.7%) had no response (NR).

Patients were divided into four groups according to their BMIs, but because there was only one patient in the underweight group, comparisons were performed between normal-weight, overweight and obese patients. There was no statistically significant

difference between these groups in terms of age, sex, serum LDH level, disease stage, presence of B symptoms, extranodal involvement, ECOG performance score, IPI score and treatment response and response distributions within stage subgroups (p >0.05) (Table 2).

Table 1: Patient characteristics

Characteristics	N= 79
Gender, n, (%)	
Female	31 (39.2%)
Male	48 (60.8%)
Age, years, median (range)	60 (23-84)
BMI, median (range)	25.93 (17.92-46.6)
Serum LDH level, n (%)	
Normal	39 (49.4%)
Elevated	40 (50.6%)
Stage, n (%)	
Stage I	8 (10.1%)
Stage II	24 (30.4%)
Stage III	13 (16.5%)
Stage IV	34 (43.0%)
B symptoms, n (%)	
Present	31 (39.2%)
Absent	48 (60.8%)
Extranodal involvement, n (%)	
Present	47 (59.5%)
Absent	32 (40.5%)
ECOG, n (%)	
0-1	66 (83.5%)
2-4	13 (16.5%)
IPI score, n (%)	
0	7 (8.9%)
1	15 (19%)
2	22 (27.8%)
3	18 (22.8%)
4	13 (16.5%)
5	4 (5.1%)
Response to treatment, n (%)	
CR	67 (84.8%)
PR	2 (2.5%)
NR	10 (12.7%)
BMI, n (%)	
Underweight	1 (1.3%)
Normal	26 (32.9%)
Overweight	34 (43.0%)
Obese	18 (22.8%)

LDH: lactate dehydrogenase, ECOG: Eastern Cooperative Oncology Group, IPI: International Prognostic Index, CR: complete Response, PR: partial response, NR: non-response, BMI: body mass index

Table 2: Comparison of patient characteristics according to BMI groups

Characteristics	Normal Weight (n=26)	Overweight (n=34)	Obese (n=18)	p
Gender, n, (%)				
Female	11 (42.3%)	9 (26.5%)	11 (61.1%)	0.070
Male	15 (57.7%)	25 (73.5%)	7 (38.9%)	
Age, years, median (range)	54 (28-83)	58.5 (34-84)	61.5 (23-78)	0.704
LDH level, n (%)				
Normal	16 (61.5%)	15 (44.1%)	8 (44.4%)	0.325
Elevated	10 (38.5%)	19 (55.9%)	10 (55.6%)	
Stage, n (%)				
Stage I	2 (7.7%)	4 (11.8%)	1 (5.5%)	
Stage II	6 (23.1%)	11 (32.3%)	7 (38.9%)	
Stage III	3 (11.5%)	7 (20.6%)	3 (16.7%)	0.464
Stage IV	15 (57.7%)	12 (35.3%)	7 (38.9%)	
Stage, n (%)				
Stage I				
CR	2 (7.7%)	4 (11.8%)	1 (5.5%)	
PR/NR	0 (0%)	0 (0%)	0 (0%)	
Stage II				
CR	6 (23.1%)	10 (29.5%)	6 (33.3%)	
PR/NR	0 (0%)	1 (2.9%)	1 (5.5%)	
Stage III				
CR	3 (11.5%)	7 (20.6%)	3 (16.8%)	
PR/NR	0 (0%)	0 (0%)	0 (0%)	
Stage IV				
CR	11 (42.5%)	11 (32.3%)	7 (38.9%)	
PR/NR	4 (15.4%)	1 (%2.9)	0 (0%)	p>0.05
B symptoms, n (%)				
Present	13 (50%)	11 (32.4%)	6 (33.3%)	0.254
Absent	13 (50%)	23 (67.6%)	12 (66.7%)	
Extranodal involvement, n (%)				
Present				
Absent	19 (73.1%)	16 (47%)	11 (61.1%)	0.152
	7 (26.9%)	18 (53%)	7 (38.9%)	
ECOG, n (%)				
0-1	20 (77%)	29 (85.3%)	16 (88.9%)	0.658
2-4	6 (23%)	5 (14.7%)	2 (11.1%)	
IPI score, n (%)				
0	1 (3.9%)	5 (14.7%)	1 (5.5%)	
1	5 (19.2%)	6 (17.6%)	4 (22.2%)	
2	7 (26.9%)	11 (32.3%)	3 (16.7%)	
3	7 (26.9%)	5 (14.7%)	6 (33.4%)	0.620
4	6 (23.1%)	4 (11.7%)	3 (16.7%)	
5	0 (0%)	3 (9%)	1 (5.5%)	
Response to treatment, n (%)				
CR				
PR/NR	22 (84.6%)	29 (85.3%)	15 (83.3%)	0.947
	4 (15.4%)	5 (14.7%)	3 (16.7%)	

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

DISCUSSION

Along with altering immune response and chronic inflammatory response, obesity changes endogenous hormone metabolism and disrupts cell proliferation, differentiation, and apoptosis[11-13]. Therefore, it has been associated with hematological malignancies including lymphoma, multiple myeloma, and leukemia, as well as various solid tumors [21]. Two large metanalyses have shown that the risk of DLBCL is increased in patients with higher BMI. Castilo et al. found that overweight and obese individuals have respectively 15% and 30% increased risk for DLBCL when compared to normal-weight population. Similarly, Larsson et al. reported that every 5 kg/m^2 increase in BMI is associated with a 14% increased risk for DLBCL [14, 15.]

Even though studies have shown that obesity increases the risk for DLBCL, whether obesity affects survival and treatment response in these patients remains controversial. In their study, Geyer et al. found that patients with higher BMI have shorter survival. Authors attributed this finding to obesity being a proinflammatory state causing TNF-alpha release, as well as overweight patients potentially receiving lower doses of chemotherapy [16]. On the other hand, Carson et al. reported increased survival in patients with higher BMI. The researchers emphasized the pharmacokinetic differences between patients with higher and lower BMI, germinal center phenotype being more dominant in the higher BMI group, and that patients with higher BMI better tolerate treatment and receive higher doses [17]. Boyle et al.; however, showed that obesity had no impact on survival in patients with DLBCL [22]. In the current study, we found no significant difference between normal weight, overweight and obese DLBCL patients, who had comparable age, sex, and prognostic factors, in terms of treatment response.

The dose of treatment given to patients with DLBCL is determined according to the body surface area calculated using the patient's weight and height. Depending on patient's height, body surface area of a patient with higher BMI may be lower, compared to a patient with normal BMI. Therefore, a patient being in the obese or overweight range does not always imply receiving higher doses of chemotherapy. As a result, observing no significant difference in treatment response between different BMI groups is a predictable outcome. However, it should be noted that when calculating chemotherapy doses, actual weight should be preferred in obese patients rather than the ideal weight. Especially in morbid obese patients, there are substantial differences in treatment doses calculated according to ideal weight or actual weight. Miyahara et al. found that the rate of grade 3-4 hematologic toxicity is not different in patients with a hematological malignancy whose treatment doses are calculated using either actual weight or ideal weight [23]. Similarly, in their metanalysis, Hourdequin et al. proved that toxic effects of chemotherapy were similar between obese patients, who receive treatment based on their actual weight, and normal-weight patients [24].

In our study, we showed that BMI has no significant impact on treatment response in patients with DLBCL. However, our study has several limitations including its retrospective nature, and relatively small sample size. Thus, further studies with larger sample size and prospective design are warranted to clarify the impact of BMI on treatment response for DLBCL patients.

Ethics Approval and Consent to Participate

Ethical committee approval was received and the patients and control subjects gave informed consent before the beginning of the study. The experimental procedures were based on the Declaration of Helsinki and relevant institutional regulations. An informed written consent was obtained from all patients.

CONFLICT OF INTEREST

None to declare.

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