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Short- and Long-term weight changes among United States veterans with diffuse large B-cell lymphoma treated with CHOP chemotherapy

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Abstract

Identifying weight changes associated with treatment of diffuse large B-cell lymphoma (DLBCL) has the potential to improve the long-term health of survivors. A retrospective cohort of United States veterans with a new diagnosis of DLBCL between October 1, 1998 and September 30, 2008, with follow-up until April 23, 2013, was assembled. Weight changes were evaluated before, during, and after treatment in 1,935 DLBCL patients who received cyclophosphamide, doxorubicin, vincristine, and prednisone, with or without rituximab (CHOP+/- R). Seventy-nine percent of patients were obese or overweight 1 year prior to treatment. During the 12 months leading up to treatment, 57% of the cohort lost weight. Among patients surviving 24 months after treatment initiation, weight increased an average of 2.9kg above weight at treatment completion. The weight change trends observed in these DLBCL patients suggest that weight management strategies may be an important part of long-term survivorship planning after conclusion of treatment.

Keywords

WEIGHT CHANGES; VETERANS; LYMPHOMA; CHOP CHEMOTHERAPY

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INTRODUCTION

Numerous studies examining the association between body mass index (BMI) and the incidence of DLBCL have been performed, however, little is known about weight changes experienced before, during, and after treatment of this disease.[1,2] The existing literature is limited by small sample sizes, short-term follow-up, inclusion of patients with a variety of non-Hodgkin lymphoma (NHL) subtypes and use of treatments other than cyclophosphamide, doxorubicin, vincristine, and prednisone, with or without rituximab (CHOP +/- R).[3-6] Since CHOP- R is the current standard of care front-line treatment for most patients with DLBCL, understanding long-term weight change patterns after CHOP-based therapy in patients with DLBCL has clear, clinical relevance.[7]

One goal of the Healthy People 2020 initiative is to “increase the mental and physical health of cancer survivors,” making it important to understand the patterns of weight change during and after treatment in patients with potentially curable malignancies, such as DLBCL. [8] Obesity is associated with both lower quality of life and poorer overall survival, making weight management an important component of survivorship care for DLBCL patients achieving complete remission, as many of these patients will be cured of their disease.[9,10] Clinically significant weight gain has been observed in patients with a variety of malignancies, both during treatment and after treatment completion.[11-13] Weight gain during treatment is thought to be in-part due to increased appetite from the corticosteroids used for chemotherapy-induced nausea and vomiting prophylaxis, while long-term weight increases in some instances may be due to chemotherapy-related hormonal changes.[14,15]

Weight management strategies used in cancer patients can involve dietary changes, increased physical activity, or a combination of both.[16] Previous research has demonstrated that a physical activity intervention is feasible in patients with NHL during treatment, and is associated with improved short-term outcomes.[17] However, the timing of weight management interventions in DLBCL patients should be tailored to the time of greatest need. To improve the overall understanding of the consequences of CHOP +/- R treatment on short- and long-term weight change, we evaluated a cohort of veterans with DLBCL diagnosed and treated within the United States Veterans Health Administration (VHA) system. The objective of this study is to describe when weight changes occur in patients with newly diagnosed and treated DLBCL in an effort to facilitate improved weight management among long-term survivors.

MATERIALS AND METHODS

Study Cohort

A retrospective cohort of patients with a new diagnosis of DLBCL between October 1, 1998 and September 30, 2008 (with follow-up ending April 23, 2013) was assembled from the Veteran's Health Administration Central Cancer Registry (VACCR) based on the InterLymph classification system (International Classification of Diseases (ICD) -O3 codes 9680/3 and 9684/3 for DLBCL).[18] Patients were excluded for the following reasons: missing vital status, primary central nervous system involvement, primary cutaneous

DLBCL, inadequate histologic confirmation, treatment with regimens other than CHOP +/- R, no treatment, or treatment outside of the VHA.

Data on histologic diagnosis, date of birth, date of diagnosis, race, sex, disease stage, and the presence of systemic B-symptoms (fever 100.4°F, weight loss >10% of body weight in 6 months, and night sweats) was provided by VACCR. Patient records were also linked to additional VHA administrative datasets to obtain vital sign data including height and weight, ICD-9 codes for co-morbid conditions, and date of death. Focused data abstraction was performed using the VHA Compensation and Pension Records Interchange software system to collect data on lactate dehydrogenase (LDH), and chemotherapy doses and dates of administration.

Data were obtained from all 21 VHA regions throughout the United States. The study was approved by the Veterans Affairs St. Louis Health Care System and Washington University institutional review boards prior to cohort assembly.

Measurements and Definitions

Weight at 1 year prior to treatment was defined as weight measured closest to but within ± 3 months of one year prior to date of first treatment. Weight at treatment initiation was defined as weight measured closest to but within 2 weeks of first treatment date. Weight at 3 months after treatment initiation was measured at the date closest to 3 months after first treatment date ± 1 month. Weight at 24 months after treatment initiation was measured at the date closest to 24 months after first treatment date ± 3 months.

Height consistently recorded at any time in the clinical history was considered accurate. BMI was calculated as weight measured in kilograms divided by the square of height measured in meters (kg/m^2) and were categorized in accordance with World Health Organization guidelines: underweight (BMI, $<18.5 \text{ kg}/\text{m}^2$), normal-weight (BMI, 18.5 to $24.9 \text{ kg}/\text{m}^2$), overweight (BMI, 25.0 to $29.9 \text{ kg}/\text{m}^2$), and obese categories (BMI, $\geq 30.0 \text{ kg}/\text{m}^2$). [19] Both height and weight information were captured by clinical staff at the time of vital sign assessment with either inpatient and outpatient clinical encounters.

The Romano adaptation of the Charlson co-morbidity index was calculated for patients included in the study cohort using ICD-9 codes for co-morbid conditions present at the time of diagnosis. [20] Age at diagnosis was used as a continuous variable in all analyses. To eliminate variance in laboratory reference ranges, LDH was dichotomized as elevated or not elevated at time of diagnosis based on local reference ranges.

Statistical Analyses

One-way ANOVA was used to evaluate the associations between mean weight changes during and after chemotherapy among DLBCL patients who survived 24 months after treatment initiation among those who: lost >5%, lost 5%, gained 5%, and gained >5% at 3 months after treatment initiation. Logistic regression explored the variables associated with weight gain >10% at 24 months. A two-tailed α significance level of 0.05 was considered statistically significant. A penalized B-spline curve of average weight change was used to assess the absolute weight change from 1 year prior to treatment until 36 months after start

of treatment, across the study cohort. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Demographics

Of the 3,227 DLBCL patients initially identified, 1,935 (60%) patients met inclusion criteria and were evaluable for weight change during treatment (Figure 1). The mean patient age was 64 years and most of the patients were men (97%) and Caucasian (87%). A mean comorbidity score at diagnosis of 2.4 was observed. Systemic B-symptoms were noted at diagnosis in 50% of patients and 57% had Stage III/IV disease. Lactate dehydrogenase was elevated in 54% of patients, and 74% received rituximab. Mean BMI at diagnosis was 27 kg/m² (overweight). (Table I)

Weight Change Trends

Seventy-seven percent of patients lost weight in the year prior to treatment (mean and median weight change -5.3 kg (-5.7% , SD 8.4) and -4.6 kg (-5.1%), respectively), with 52% losing $>5\%$ of initial weight by the time of initiation of treatment. A majority of patients (58%) also lost weight during treatment, with 31% losing $>5\%$ between the start of chemotherapy and 3 months after treatment initiation. The mean and median weight change during treatment (between treatment initiation and 3 months later) were -2.0 kg (-2.3% , SD 7.1) and -1.1 kg (-1.3%), respectively. Considerable weight gain occurred in most patients by 24 months after treatment initiation, compared to their weight at time of treatment initiation, with 25% of patients increasing their weight 10% or more. The mean and median long-term weight change from start of treatment until 24 months later was $+2.9$ kg ($+3.3\%$) and $+2.3$ kg ($+2.6\%$), respectively. Overall mean weight change between 12 months prior to and 24 months after treatment initiation was -1.7 kg (median -1.2 kg) among patients surviving to 24 months.

B-spline analyses of the average absolute weight change in the entire cohort of DLBCL patients from 12 months before until 24 months after treatment initiation demonstrated considerable weight loss between 12 months prior to treatment and approximately 4 months after first treatment. Weight gain was then noted; starting 4 months after treatment and ultimately reaching a plateau at approximately 24 months after treatment initiation. (Figure 2)

Additional B-Spline curves were generated, removing patients who died within one and two years of treatment initiation, to better understand how disease severity and competing risk factors for death influenced weight change trends during treatment. While the magnitude of weight loss during treatment in these sub-cohorts was reduced -1.4 kg and -1.0 kg at 3 months after treatment initiation, respectively, a majority of patients still lost weight leading up to and during treatment, with a weight loss nadir at approximately 4 months after treatment initiation. Weight gain in the 1 and 2 year survival sub-cohorts similarly increased after the conclusion of treatment until reaching a plateau and leveling off at 2.9 kg above

weight at treatment initiation by 24 months; a trend similar to the B-Spline in Figure 2. (Figures 3 and 4)

Distribution of BMI Groups

A sub-set of patients (n=496) with weight information at three time points (1 year prior to treatment, treatment initiation, and 24 months after treatment initiation) was analyzed to understand the distribution of BMI Groups over time. Twelve months prior to treatment, 40% of patients were obese and 39% were overweight. At the start of treatment, 29% were obese and 40% were overweight. By 24 months after treatment initiation, 36% were obese and 41% were overweight. The data demonstrate that the proportion of patients who were obese and overweight declined in the year leading up to diagnosis, but largely returned to levels observed one year prior to diagnosis during the 24 months following treatment initiation.

To explore trends within BMI groups over time, we looked at patients with weight information at 1 year prior to treatment initiation and at 24 months after treatment initiation. In those patients, 77% who were in the obese BMI group 1 year prior to treatment had maintained or returned to an obese BMI at 24 months after treatment initiation.

Weight Change Trend Associations and Factors

Across all groups, there was a highly significant association between weight change at 3 months and weight change at 24 months after treatment initiation ($p < 0.001$). Patients with weight increase of $>5\%$ at 3 months continued to remain above their starting weight at time of treatment at 24 months after treatment initiation, with mean overall weight gain of $+10.7$ kg (SD 11.51). While those with weight loss $>5\%$ in the first 3 months continued to remain below their initial weight at treatment initiation by 24 months after treatment initiation with mean weight loss of -2.7 kg (SD 8.65). Modest weight changes at 3 months were also associated with modest weight increases maintained at 24 months after treatment initiation (loss 5% at 3 months, mean $+0.9$ kg at 24 months, SD 8; and gain 5% at 3 months, mean $+5.22$ kg at 24 months, SD 8.56).

To better understand how clinical variables assessable by the end of treatment were associated with weight change at 24 months after treatment initiation, a logistic regression analysis was performed on those patients with weight information one year prior to treatment, at treatment, at 3 months, and at 24 months after treatment initiation. Weight gain $>10\%$ at 24 months after treatment initiation was associated with weight loss $>5\%$ and 10% in the year prior to treatment (OR 3.11, 95% CI 1.43–6.32), weight loss $>10\%$ in the year prior to treatment (OR 17.27, 95% CI 8.68–34.37), age 64 years and younger (OR 2.39, 95% CI 1.48–3.86), 4 or more cycles of chemotherapy (OR 2.76, 95% CI 1.07–7.15), and weight gain during treatment (OR 3.89, 95% CI 2.04–7.39). Stage, BMI at initiation of treatment, and elevated LDH were tested in the model but not found to be significant, and therefore were removed from the final model.

DISCUSSION

To our knowledge, this is the first large study evaluating weight change trends in a cohort of patients with DLBCL treated with CHOP +/- R chemotherapy, starting 12 months before and ending 36 months after treatment initiation. During the 12 months leading up to treatment, 57% of the cohort lost weight. While weight loss >10% in the six months leading up to diagnosis would be recorded as a systemic B-symptom, only 17% of the cohort met this specific B-symptom criterion. Thus, modest (but potentially clinically significant) weight loss was common in the 12 months leading up to a new diagnosis of DLBCL, even among those who did not have the B-symptom of weight loss. After treatment was initiated, a majority of patients continued to experience weight loss, reaching a nadir weight at approximately 4 months after chemotherapy initiation. The weight nadir roughly corresponds to when 6 cycles of CHOP +/- R chemotherapy would be completed. This was surprising, and contrary to our *a priori* assumptions, given the amount of prednisone typically administered with each cycle of CHOP, and the known effect of corticosteroids on appetite.[21]

After completion of treatment, most patients demonstrated clinically significant weight gain (mean + 2.9 kg at 24 months after treatment initiation) that markedly surpasses weight gains expected in a similarly aged population (mean +0.4 kg at 24 months).[22] A related observation unique to this study is that after treatment many patients may have simply been returning to overweight or obese BMI that was present prior to diagnosis. This was supported with further investigation of the within-BMI group distribution trend over time that found among patients who were obese in the year prior to treatment initiation, by 24 months after treatment initiation 77% had maintained or returned to an obese BMI. It can be postulated that as the side effects of chemotherapy subsided, patients returned to their previous dietary patterns and therefore returned to their previous weight. [14,15] Alternatively, it is possible that some of the weight gain observed following treatment may be explained by social or psychological factors, since many patients were returning to a weight that they or their families may have considered 'normal.' Previous studies have shown considerable spousal concordance in obesity, suggesting shared environmental exposure to high-energy food intake.[23] Furthermore, in a study of weight perceptions, one-third of overweight men considered their weight to be "about right." [24] Thus, it is possible that some of the men in this cohort may have perceived themselves to be relatively underweight following treatment.

In an effort to better stratify those at greatest risk for weight gain, we evaluated the association between weight change before and during treatment, and weight gain at 24 months after treatment initiation. The subgroup of patients who gained more than > 5% during treatment added nearly 11 kg by 24 months after treatment initiation. Furthermore, those who lost 5% or more in the year leading up to treatment were significantly more likely to gain >10% by 24 months after treatment initiation. Thus, between the clinical history obtained at the time of diagnosis and observations made during disease treatment, the patients at highest risk for weight gain can be identified.

This study was unable to determine how the rapid weight changes observed in this population correlated with skeletal muscle mass depletion (sarcopenia), which is a risk factor for loss of function, metabolic syndromes, and cardiovascular disease. [25] As observed in Figures 3 and 4, after removing patients who died within the first and second years following treatment initiation, DLBCL patients on average lost a total of -7.0 kg and -6.6 kg, respectively, in the year prior to diagnosis and during treatment. After treatment completion, patients gained weight but did not return to the level observed 1 year prior to treatment. This may be due in-part to loss of muscle mass prior to and during treatment, which was not adequately restored in the 2 years after treatment. Since muscle tissue has a higher density than adipose tissue, it is possible that patients gained weight until they subjectively felt they had returned to a normal size, but with higher adiposity, their weight was actually slightly lower than before. Future studies should explore the degree to which weight loss during treatment is the result of muscle loss and weight gain after treatment is due to fat deposition, resulting in so-called sarcopenic obesity. If DLBCL and its treatments are contributing to the development of sarcopenic obesity in this population, weight management interventions initiated after treatment should include strength training, designed to increase lean muscle mass, and improve functional status.

Overall, the pattern of marked weight gain following completion of treatment suggests that weight management interventions could be suggested at the time of diagnosis or shortly after the end of treatment in patients with DLBCL who achieve a complete remission. However, any intervention should recognize that different goals may exist depending upon the temporal relationship of an intervention to the diagnosis. For example, immediately following diagnosis (during treatment), preservation of muscle mass is an important goal, while weight control is the primary objective after conclusion of therapy. Such an approach would be consistent with survivorship guidelines from the American Society of Clinical Oncology, which recommend physical activity and nutritional counseling for cancer survivors.[26] Furthermore, previous studies have shown that patients with a recent diagnosis of cancer are particularly motivated to implement lifestyle changes, which would increase the likelihood healthy lifestyle changes would be adopted long-term.[27] A recent study demonstrating durable weight loss associated with a telephone-based lifestyle intervention in breast cancer patients on hormonal therapy supports that a similar approach may be feasible in DLBCL survivors.[28]

There are multiple strengths of this study. First, the VHA provided a large study cohort with comprehensive clinical data drawn from patients diagnosed and treated throughout the United States. Second, weight measurements were objectively measured and recorded for clinical care purposes, reducing potential reporting biases. Third, this study accumulated data on the population of DLBCL patients treated with CHOP +/- R across the VHA system, reducing the selection bias that may be observed in post-hoc studies of patients enrolled in clinical trials.

There are also limitations that should be noted. First, the study cohort was comprised almost entirely of men, which may limit our ability to extrapolate these findings to women. Second, we were unable to systematically assess how the observed weight changes were related to changes in body composition, which would influence the long-term health effects. Future

studies are warranted to assess how CHOP +/- R influences both short-term and long-term body composition. Third, the VHA patient population has a lower median income than that of the general population, which could result in more extreme average weight gain after treatment completion given the inverse relationship between income and obesity previously noted in the United States.[29] Finally, the VHA largely serves individuals who served in the United States military, who at the time of their service met the physical requirements for military enlistment. As a result, it is possible that the veteran population may be more physically fit than average, and have a lower proportion of body fat at each BMI level, potentially influencing the generalizability of our findings to the general population.

CONCLUSION

Overall, this study of the trends in weight change before, during, and after CHOP +/- R therapy in patients with DLBCL demonstrates that weight loss before and during treatment is common, followed by marked weight gain after treatment completion. Patients who were obese and overweight at the start of the study period were more likely to return to an obese or overweight BMI by 24 months. Among DLBCL patients who survived to 24 months after therapy, long-term weight gain was most pronounced in those who lost a significant amount of weight prior to treatment, as well as those who gained weight during treatment. Lifestyle interventions designed to manage obesity might best be timed to the completion of therapy based on observed weight trends before and during treatment. An intervention that includes strength training may be advised if future studies demonstrate that DLBCL survivors are developing sarcopenic obesity.

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Figure 1.

STROBE diagram

Abbreviations used: DLBCL = diffuse large b-cell lymphoma, CNS = Central Nervous System, OSH = outside hospital

Figure 2. Distribution of average weight change 1 year prior to first treatment through 36 months after start of treatment of US veterans diagnosed with DLBCL from 1998 to 2008.
Abbreviations used: DLBCL=Diffuse Large B-Cell Lymphoma; US=United States

Figure 3. Distribution of Average Weight Change Removing Death within 1 year after treatment of US veterans diagnosed with DLBCL from 1998 to 2008.

Abbreviations used: DLBCL=Diffuse Large B-Cell Lymphoma; US=United States

Figure 4. Distribution of Average Weight Change Removing Death within 2 years after treatment of US veterans diagnosed with DLBCL from 1998 to 2008.
Abbreviations used: DLBCL=Diffuse Large B-Cell Lymphoma; US=United States

Table I

Demographic and Clinical Characteristics of US veterans diagnosed with DLBCL from 1998 to 2008.

Demographic and Clinical Characteristics	DLBCL N=1935	
	n	%
Age (mean years, Std, IQR)	64.1 (12.1, 18)	-
Male Sex	1879	97.1
Race		
White	1685	87.1
Black	225	11.6
Other	25	1.3
Comorbidities (mean Charlson score, Std, IQR)	2.4 (2.3, 4)	-
Stage		
Stage I/II	807	41.7
Stage III/IV	1107	57.2
Unknown	21	1.1
LDH		
Elevated	1050	54.3
Not Elevated	672	34.7
Unknown	213	11
B-symptom		
Yes	960	49.6
No	881	45.5
Unknown	94	4.9
Rituximab use	1431	74
Year of diagnosis (median)	2004	-
Height at diagnosis (mean centimeters, Std, IQR)	177.1 (7.4, 10.2)	-
BMI groups at 1 year prior treatment initiation (kg/m ²)		
<18.5	10	0.5
18.5 - <25	251	13
25 - <30	465	24
>=30	414	21.4
Unknown	795	41.1
BMI groups at treatment initiation (kg/m ²)		
<18.5	45	2.3
18.5 - <25	593	30.7
25 - <30	615	31.8
>=30	410	21.2
Unknown	272	14.1
BMI groups at 24 months after treatment initiation (kg/m ²)		
<18.5	13	0.7

Demographic and Clinical Characteristics	DLBCL N=1935	
	n	%
18.5 - <25	226	11.7
25 - <30	351	18.1
>=30	303	15.7
Unknown	1042	53.9

[†]T-test,

* Chi-square test,

[‡] Cochran-Mantel-Haenszel (Nonzero Correlation) test,

[§] Wilcoxon test

Abbreviations used: DLBCL=Diffuse Large B-Cell Lymphoma; US=United States; Std= Standard Deviation; IQR= Inter Quartile Range; LDH= Lactate dehydrogenase; BMI= Body Mass Index.