Increased body mass index is associated with improved overall survival in diffuse large B-cell lymphoma

L. Weiss1,†, T. Melchardt1,†, S. Habringer1, A. Boekstegers1, C. Hufnagl1, D. Neureiter2, G. Hopfinger1, R. Greil† & A. Egle1*

1Department of Internal Medicine III, Paracelsus Medical University, Salzburg; 2Institute of Pathology, Paracelsus Medical University, Salzburg, Austria

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Background: Obesity is a well-known risk factor for the development of several types of cancer including lymphomas, but its influence on the course of disease is fairly unknown. Recently, a retrospective cancer registry analysis demonstrated significantly prolonged survival for overweight and obese patients with diffuse large B-cell lymphoma (DLBCL). The study population almost exclusively consisted of male US American patients of lower socioeconomic status and one-fifth of patients received cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy without rituximab. Therefore, it remains unclear if these results can be extrapolated to the general DLBCL population.

Patients and methods: This retrospective single-center analysis included 183 unselected DLBCL patients who were treated with rituximab and standard-dosed anthracycline-based chemoimmunotherapy as first-line therapy between January 2004 and December 2012. Patients were stratified by body mass index (BMI) into ‘low BMI’ (<25.0 kg/m²) and ‘high BMI’ (≥25.0 kg/m²).

Results: The two groups were well balanced regarding age, performance score, international prognostic index, B-symptoms and extranodal involvement. However, there was a trend for male sex (P = 0.053) and higher-stage disease (P = 0.066) in the high-BMI group. Patients with higher BMI had significantly longer overall survival (OS; hazard ratio [HR])...
introduction

Obesity is not only a well-known risk factor for the development of cardiovascular disease and diabetes [1], but also for the development of several types of cancer [2], including lymphomas [3].

Considering the present prevalence of excess body weight in the western hemisphere and its continuing global increase [4], medical oncologists are frequently confronted with overweight and obese patients, including their specific set of comorbidities [1] and differential pharmacokinetics [5]. So far, only little is known about the effects of obesity once a cancer diagnosis has been established, but a multitude of factors might influence the outcome of cancer therapy in patients with excess body weight. Drug distribution and elimination are reported to be influenced by obesity, an effect especially relevant for lipophilic drugs [6]. Drug metabolism may be altered by obesity-induced liver steatosis and changed hepatic blood flow, as well as the partially increased enzymatic activity of the cytochrome P450 superfamily in obese individuals [6]. Underdosing of chemotherapy is frequently seen in patients with a calculated body surface area of >2 m² [7] and a higher body mass index (BMI) might, in part, counterbalance tumor cachexia in advanced disease. The seemingly most logical pathophysiologic association between obesity and poor survival has been described for women with hormone receptor-positive breast cancer receiving aromatase inhibitors: overweight patients had a 60% increase in the risk of disease recurrence and more than a doubling in the risk of death compared with normal weight patients [8]. This effect is thought to be mediated by the increased presence of aromatase due to the increase in adipose tissue.

For hematological malignancies, several studies could not demonstrate a negative impact of overweight and obesity on survival: a retrospective analysis of 712 patients with B-cell non-Hodgkin’s lymphoma treated with chemotherapy showed no negative impact of higher BMI on overall survival (OS) or progression-free survival (PFS) [9]. Similar results were observed in two large series with patients undergoing autologous stem cell transplantation for Hodgkin’s or non-Hodgkin’s lymphoma (n = 4681) [10] or multiple myeloma (n = 1087) [11], as well as in patients undergoing allogeneic stem cell transplantation for various hematological malignancies [12, 13]. This is of special interest, since the hematopoietic cell transplantation-specific comorbidity index defines a BMI over 35 kg/m² as an adverse prognostic factor [14]. Recently, a cancer registry analysis reported significantly prolonged OS for overweight (BMI 25 to <30 kg/m²) and obese (BMI ≥30 kg/m²) patients with diffuse large B-cell lymphoma (DLBCL) [15] when compared with normal weight patients. However, this retrospective study was exclusively carried out in US veterans, and hence in predominantly male patients (97.4%) of lower socioeconomic status when compared with the general US American population. Furthermore, bias might be caused by the fact that rituximab treatment was only inferred from therapy in the rituximab era (February 2002 onward), but was not confirmed by individual patient chart data. In this study, one-fifth of patients did not receive chemoimmunotherapy with rituximab, the current standard first-line DLBCL therapy [16, 17]. Given these limitations, it is unknown whether these findings can be extrapolated to the general DLBCL population treated with chemoimmunotherapy with rituximab as first-line therapy.

We investigated the influence of BMI on survival in an unselected patient cohort with de novo DLBCL treated with rituximab and standard-dosed anthracycline-based chemoimmunotherapy in a single-center experience.

methods

This retrospective study was approved by the Ethics Committee of the provincial government of Salzburg, Austria (415-EP/73/127-2012). Retrospective chart analysis was performed in patients who were diagnosed with de novo DLBCL at the Department of Internal Medicine III of the Paracelsus Medical University Salzburg between January 2004 and December 2012. The pathologic diagnosis of DLBCL was established at the University Institute of Pathology Salzburg in 79.2% of cases (145 of 183) using a standard immunohistochemical panel of CD3, CD5, CD10, CD20, CD23, CD79a, bcl-2, bcl-6, MUM-1, and partially c-Myc and Ki-67. Patients must have received rituximab and standard-dosed anthracycline-based chemoimmunotherapy as the first-line treatment of inclusion in this analysis. Patients treated with more intensive, etoposide-containing regimens as well as those with a prior diagnosis of indolent lymphoma were excluded from analysis. BMI was calculated as weight (kg) divided by the square of height (m). Patients were stratified into BMI groups according to the WHO guidelines: underweight (BMI <18.5 kg/m²), normal weight (BMI 18.5 to <25 kg/m²), overweight (BMI 25 to <30 kg/m²), obesity class I (BMI 30 to <35 kg/m²), obesity class II (BMI 35 to <40 kg/m²) and obesity class III (≥40 kg/m²) [18]. Height and weight were consistently recorded at the first day of therapy. Clinical data including the Eastern Cooperative Oncology Group (ECOG) performance score, β2-microglobulin and albumin levels before treatment, B-symptoms, international prognostic index (IPI), stage according to Ann Arbor, OS, PFS and administered therapy were retrospectively analyzed by a chart-based review. Statistical analyses were carried out using the IBM® SPSS® statistics software, version 20. Mann–Whitney U test and Pearson’s χ² test were used for univariate analyses, where appropriate. Survival was estimated using Kaplan–Meier curve analysis, with statistical comparison using the log-rank statistic. A two-tailed significance level of 0.05 was considered statistically significant. Only statistically significant factors were included into multivariate Cox regression analysis.

results

patients characteristics

We analyzed 183 patients who were consecutively diagnosed with de novo DLBCL between January 2004 and December 2012.
and were treated with rituximab and standard-dosed anthracycline-based chemoimmunotherapy (see Table 1).

In detail, 66.7% (n = 122) of patients were treated with R-cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) using conventional doxorubicin (Ebewe Pharma, Austria), 30.1% (n = 55) were treated with rituximab, cyclophosphamide, vincristine, liposomal doxorubicin, prednisone (R-COMP) using liposomal non-pegylated doxorubicin (Teva, Israel) instead of conventional doxorubicin and 3.3% (n = 6) were treated with rituximab, cyclophosphamide, epirubicin, vincristine, prednisone (R-CEOP) using epirubicin (Ebewe Pharma, Austria) instead of conventional doxorubicin.

The type of therapy was decided by physician’s choice, with older age and pre-existing comorbidities being the primary reasons for choosing R-COMP or R-CEOP over R-CHOP [19]. The treatment groups showed no significant differences in the mean BMI (P = 0.255; Mann–Whitney U test), but as expected patients treated with R-COMP or R-CEOP showed significant differences in age distribution and ECOG performance status. Patients treated with R-COMP or R-CEOP (mean age 77.0 years) were significantly older than those treated with R-CHOP (mean age 62.1 years) (P < 0.001; Mann–Whitney U test). Good performance status (ECOG 0 and 1) were found in 89.3% of patients treated with R-CHOP, but only in 77.0% of patients treated with R-COMP or R-CEOP (P = 0.027; Pearson’s χ² test). To evaluate the influence of BMI on OS, we used the cut-off of 25.0 which separates normal weight and overweight patients according to the current WHO guidelines [18]. The adequacy of this cut-off in our cohort was confirmed by receiver operating characteristic calculation and Youden Index analysis for OS, which resulted in the nearly imperposable BMI cut-off value of 25.35 (data not shown). The low-BMI group (<25 kg/m²) was composed of only 3 underweight and 93 normal weight patients, whereas the high-BMI group (≥25 kg/m²) consisted of 55 overweight patients, 26 with obesity class I, 5 with obesity class II and only 1 with obesity class III.

The mean BMI for the whole cohort was 25.7 ± 4.4 kg/m² SD, with a range from 17.9 to 41.5 kg/m². These values are comparable with the general Austrian population with a mean BMI of 25.84 ± 4.32 kg/m² SD [20], but considerably differ from the reported mean BMI of 28.4 kg/m² for the general population in the USA [4].

BMI on OS, we used the cut-off of 25.0 which separates normal weight and overweight patients according to the current WHO guidelines [18]. The adequacy of this cut-off in our cohort was confirmed by receiver operating characteristic calculation and Youden Index analysis for OS, which resulted in the nearly imperposable BMI cut-off value of 25.35 (data not shown). The low-BMI group (<25 kg/m²) was composed of only 3 underweight and 93 normal weight patients, whereas the high-BMI group (≥25 kg/m²) consisted of 55 overweight patients, 26 with obesity class I, 5 with obesity class II and only 1 with obesity class III.

Mean age at diagnosis was 66.5 years with a range from 22 to 91 years, and 73.8% of patients were older than 60 years. Half of patients (53.6%) had higher stage (III/IV) disease, and the gross majority of patients (85.2%) was in good physical condition (ECOG performance score 0 or 1). Age and performance status were well balanced between the two BMI groups, but there was a trend toward a higher stage in overweight/obese patients (P = 0.066). Although not reaching statistical significance (P = 0.053), a slight predominance of male patients in the high-BMI group was apparent. According to the recent data, male sex might be associated with worse prognosis [21]. However, in our cohort, we could not detect an influence of sex on OS (P = 0.709, log-rank) or PFS (P = 0.550, log-rank).

Information on Central Nervous System or extranodal involvement, IPI and B-symptoms were also consistently available for all patients. There were no significant differences between patients with lower BMI when compared with those with higher BMI. Furthermore, no significant difference in BMI was observed in patients with B-symptoms when compared with those without B-symptoms (P = 0.418).

Despite a lack of information in a substantial portion of patients, in the subgroup of patients with existent data (n = 129 for albumin; n = 127 for β2-microglobulin), no significant difference was seen in the prevalence of decreased albumin levels (<3.5 g/dl) or elevated β2-microglobulin levels (>3.0 mg/l). Patients received a mean cumulative dose of 271.5 mg/m² doxorubicin (SD ±97.9 mg/m²), without significant differences

| Table 1. Clinical characteristics stratified by BMI (body mass index) |
|---------------------------------|---------------------------------|-------------------|
| Overall | Low BMI (<25.0) | High BMI (≥25.0) | P-value |
| N = 183 | N = 96 | N = 87 |

**BMI**
- Mean ± SD: 25.7 ± 4.4 vs. 22.5 ± 1.8 vs. 29.2 ± 3.7
- Range: 17.9–41.5 vs. 17.9–24.9 vs. 25.0–41.5

**Age (years)**
- Mean ± SD: 66.5 ± 14.3 vs. 66.0 ± 15.3 vs. 67.1 ± 13.1
- Range: 22–91 vs. 22–91 vs. 27–88
- >60 years (%): 73.8 vs. 71.9 vs. 75.9

**Sex (%)**
- Male: 55.7 vs. 49.0 vs. 63.2
- Female: 44.3 vs. 51.0 vs. 36.8

**Stage (%)**
- Low (1–2): 53.6 vs. 57.3 vs. 49.4
- High (3–4): 46.4 vs. 42.7 vs. 50.6

**ECOG (%)**
- 0: 49.7 vs. 51.0 vs. 48.3
- 1: 35.5 vs. 32.3 vs. 39.1
- 2: 8.7 vs. 11.5 vs. 5.7
- 3: 6.0 vs. 5.2 vs. 6.9

**IPI (%)**
- Low (0–1): 29.5 vs. 27.1 vs. 32.2
- Intermediate (2–3): 54.1 vs. 58.3 vs. 49.4
- High (4–5): 16.4 vs. 14.6 vs. 18.4

**B-symptoms (%)**
- Yes: 26.2 vs. 30.2 vs. 21.8
- No: 73.8 vs. 69.8 vs. 78.2

**CNS involvement (%)**
- Yes: 6.6 vs. 7.3 vs. 5.7
- No: 93.4 vs. 92.7 vs. 94.3

**Extranodal involvement (%)**
- Yes: 47.5 vs. 44.8 vs. 50.6
- No: 52.5 vs. 55.2 vs. 49.4

**Albumin (%)**
- <3.5 g/dl: 26.4 vs. 25.9 vs. 90.9
- ≥3.5 g/dl: 73.6 vs. 75.1 vs. 9.1

**β2-microglobulin (%)**
- <3.0 mg/l: 46.5 vs. 49.2 vs. 43.5
- ≥3.0 mg/l: 53.5 vs. 50.8 vs. 56.5

**Cumulative doxorubicin dose (mg/m²)**
- Mean ± SD: 271.5 ± 97.9 vs. 266.2 ± 113.7 vs. 277.4 ± 76.3
- Range: 29.3–449.3 vs. 29.4–449.3 vs. 38.0–391.8

**Extranodal involvement (%)**
- Yes: 26.2 vs. 30.2 vs. 21.8
- No: 73.8 vs. 92.7 vs. 78.2

**OS**
- Mean ± SD: 271.5 ± 97.9 vs. 266.2 ± 113.7 vs. 277.4 ± 76.3
- Range: 29.3–449.3 vs. 29.4–449.3 vs. 38.0–391.8

*P-values for albumin; **P-values for all patients. There were no significant differences between patients with lower BMI when compared with those with higher BMI. Furthermore, no significant difference in BMI was observed in patients with B-symptoms when compared with those without B-symptoms (P = 0.418).
in the mean cumulative dose between the two BMI groups ($P = 0.848$). This is important, since obese patients are frequently dose-capped when exceeding a body surface area of 2 m$^2$ [7]. Current guidelines, however, explicitly discourage this clinical practice and recommend full weight-based chemotherapy dosing [22] with a few exceptions. The median cycle number was 6 (range 1–9) in both groups.

**higher BMI is associated with longer progression-free and overall survival**

Patients with higher BMI had significantly longer PFS ($P = 0.01$, log-rank) with 74.1% of patients without progression at 3 years versus 57.5% in the low-BMI group (Figure 1). Median PFS was not reached at 104 months in the high-BMI group, but was only 55 months in the low-BMI group. Higher BMI also conferred significantly longer OS ($P = 0.032$, log-rank) with 80.9% of patients alive at 3 years versus 64.2% in the low-BMI group (Figure 2). Median OS was not reached at 104 months in the high-BMI group, but was 69 months for patients with lower BMI. The median follow-up for OS was 44 months.

**BMI is an independent predictor of overall survival**

To evaluate the importance of BMI compared with previously established prognostic markers in DLBCL, we carried out a Cox regression analysis. BMI as well as age, performance status, IPI and B-symptoms had significant prognostic power for OS in univariate analysis (Table 2). All significant parameters were further included into multivariate analysis. Age, BMI and B-symptoms remained significant, independent prognostic factors in multivariate testing, whereas performance status and IPI did not. Albumin and $\beta_2$-microglobulin were originally not included, since they were only available in a subgroup of 104 patients.

**discussion**

In the present study, we could show a significantly longer PFS and OS for overweight and obese patients treated with rituximab and standard-dosed anthracycline-based chemoimmunotherapy as the standard first-line treatment when compared with normal weight or underweight patients. Our analysis was carried out in an unselected cohort of patients diagnosed with de novo DLBCL at a single cancer center. Due to the characteristics of the Austrian health care system, this cohort comprises almost all DLBCL patients of the province of Salzburg with >500 000 inhabitants. Therefore, our analysis includes patients irrespective of sex, profession, insurance status or other socioeconomic factors. In addition, all patients in our cohort received rituximab-based chemoimmunotherapy without exception. Our study corroborates the results of the previously reported analysis by Carson et al. [15], which was limited to male US veterans and also included 19.2% of patients who did not receive rituximab.

Unfortunately, longitudinal data on weight over time were not available for our cohort. Considering the short time from lymphomagenesis to first diagnosis and treatment in aggressive lymphoma, it is rather unlikely that B-symptoms might effectively influence weight and thereby BMI. In our analysis, BMI did not significantly differ between patients with or without B-symptoms. Nevertheless, a possible bias cannot be excluded.

So besides its descriptive nature, what lesson can be learnt from the presented data? On the one hand, it will be worthwhile to investigate the underlying mechanisms resulting in the significantly different outcome between normal weight and overweight/obese DLBCL patients. We hypothesize that this phenomenon could be explained by pharmacokinetic differences caused by excess body weight. It may not be surprising that such an effect can be seen in DLBCL, where anthracyclines are part of the standard first-line

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[Figure 1. Progression Free Survival divided by BMI: patients with higher BMI ($\geq 25$ mg/m$^2$; $n = 96$) had significantly longer PFS than patients with lower BMI (<25 mg/m$^2$; $n = 87$).]

[Figure 2. Overall Survival divided by BMI: patients with higher BMI ($\geq 25$ mg/m$^2$; $n = 96$) had significantly longer OS than patients with lower BMI (<25 mg/m$^2$; $n = 87$).]
treatment. A high relative dose intensity and cumulative dosage of anthracyclines have been associated with a better outcome in DLBCL [23]. Anthracyclines are lipophilic drugs with a high volume of distribution, and doxorubicin dose levels (area under the curve) have been reported to be considerably higher in obese than in normal weight patients, an effect caused by reduced doxorubicin clearance [24]. We hypothesized that overweight/obese patients are exposed to higher cumulative anthracycline doses or rather have longer times of doxorubicin exposure, resulting in better outcomes.

Although an increased rituximab clearance and thereby lower rituximab serum levels have been observed in male patients [25, 26], we could not detect a negative predictive effect for male sex on OS (hazard ratio [HR] 1.106; P = 0.710).

On the other hand, these results may have far-reaching consequences for the interpretation and design of clinical trials. The reported 17% difference in survival between normal weight and overweight/obese DLBCL patients is comparable with that achieved by the addition of rituximab to CHOP chemotherapy [16, 17]. Depending on their pharmacokinetics, two different drugs of actual equipotence tested in a clinical trial might result in a significantly different outcome if groups are unbalanced regarding BMI. Although thereby adding another level of complexity, we therefore advocate the inclusion of BMI into standard stratification parameters.

In conclusion, body fat does make a difference in survival and we should draw more attention to its effects on our patients, even more so in light of the global increase in obesity.

disclosure

LW and TM received travel support from Roche. GH received speaking fees from Roche. RG and AE received speaking fees, research support and travel support from Roche. All remaining authors have declared no conflicts of interest.

Table 2. Cox regression analysis for overall survival

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references

The clinical features, management and prognostic effects of pathological fractures in a multicenter series of 373 patients with diffuse large B-cell lymphoma of the bone


¹Unit of Lymphoid Malignancies, Department of Onco-Hematology, San Raffaele Scientific Institute, Milan, Italy; ²Department of Oncology Inland Dr., Premion and Bond University, Tugun, Australia; ³Department of Medical Oncology, National Institute of Oncology and Radiobiology, La Habana, Cuba; ⁴Department of Oncology Auckland, Auckland Hospital, New Zealand; ⁵Department of Oncology, Christie Hospital, Manchester, UK; ⁶Department of Oncology, Seoul National University Hospital, Seoul; ⁷Department of Oncology, Korea Cancer Center Hospital, Seoul, Korea; ⁸Division of Hematology, European Institute of Oncology, Milan, Italy; ⁹Department of Oncology, Wesley Research Institute, Brisbane, Australia; ¹⁰Department of Oncology, Northern Centre for Cancer, New Castle, UK; ¹¹Department of Oncology, National Cancer Institute, Bratislava, Slovakia; ¹²Department of Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; ¹³Department of Radiation Oncology, Princess Margaret Hospital, Ontario Cancer Institute, Toronto, Canada

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Background: Pathological fractures (PFs) occur in 10%–20% of patients with diffuse large B-cell lymphoma (DLBCL) of the bone. The clinical features and the effects of this severe complication on management and prognosis have not been previously analyzed in a large series.

Patients and methods: The effects of PF on management and prognosis were reviewed in an international retrospective series of 373 patients with newly diagnosed bone DLBCL, comparing 78 patients with PF at presentation (group ‘PF-BL’) and 295 patients without PF (‘controls’).

*Correspondence to: Dr Andrés J. M. Ferreri, Unit of Lymphoid Malignancies, Division of OncoHematological Medicine, Department of OncoHematology, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy. Tel: +39-02-26437649; Fax: +39-02-26437625; E-mail: andres.ferreri@hsr.it

†These authors contributed equally.