

[ORIGINAL ARTICLE]

Prognostic Impact of a Body Mass Index Decrease during First Chemotherapy in Patients with Advanced Follicular Lymphoma

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Abstract:

Objective Follicular lymphoma (FL) is an indolent B-cell malignancy, usually treated by immunochemotherapy in advanced-stage and high-tumor-burden cases. Although some reports have shown no significant relationship between the pre-treatment body mass index (BMI) and the overall survival (OS) in FL, little is known regarding BMI changes during chemotherapy. We analyzed the impact of a BMI decrease during chemotherapy on the OS in FL patients.

Methods We retrospectively analyzed 56 patients with untreated advanced FL who underwent chemotherapy at our institute between July 2009 and December 2020. The BMI change was defined based on the BMI before and at three months after the first chemotherapy session. The cut-off for a BMI decrease was set at 1.42 kg/m² according to the receiver operating characteristics curve for the OS. We compared the survival outcome between two BMI groups based on this cut-off.

Results A BMI decrease was significantly associated with a worse OS (5-year OS: 86.7% vs. 60.5%, $p=0.019$), although the pre-treatment BMI showed no significant relationship with the survival. The adverse impact of a BMI decrease remained in a multivariate analysis for the OS (hazard ratio, 3.972; $p=0.045$). The decreased-BMI group tended to show a higher cumulative incidence of early-onset histological transformation (HT) than the non-decreased-BMI group (20% vs. 0.0%). A BMI decrease during chemotherapy in previously untreated FL patients might reflect the hyperactivation of tumor-induced metabolism related to HT.

Conclusion A BMI decrease during chemotherapy might be an independent adverse prognostic factor in FL patients. BMI changes in addition to the condition of FL patients should be monitored during chemotherapy.

Key words: body mass index (BMI), follicular lymphoma (FL), chemotherapy

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Introduction

Follicular lymphoma (FL) is one of the most common subtypes of indolent lymphoma and accounts for approximately 20% of malignant lymphomas (MLs). Despite being slow-growing with a favorable response to initial treatment, FL remains incurable because of its high relapse rate (1). In addition, FL may transform into aggressive lymphoma through histological transformation (HT) at a rate of 1-2% per year, and such transformation is associated with a poor prognosis (2).

Body weight loss is a general symptom of cancer, observed in 30-80% of patients (3). Cancer induces the abnormal metabolism of glucose, proteins and lipids, leading to a loss of body weight and excess catabolism of skeletal muscle and adipose tissues (4, 5). Recent studies of various solid tumors have revealed that malnutrition before and during chemotherapy affect the response to treatment, incidence of adverse events (AEs) and overall survival (OS). Indeed, an overweight or obese state at the initiation of treatment has been reported as a predictor of a better OS among patients with kidney, lung or metastatic cancer (6-8). However, the role of body weight loss during chemotherapy remains

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controversial in ML.

The body mass index (BMI), calculated as the individual's weight in kilograms divided by the square of their height in meters, is often used in biomedical research. Several retrospective studies into ML have reported a high BMI was associated with adverse outcomes for non-Hodgkin's lymphoma (NHL) (9), more favorable outcomes for Hodgkin's lymphoma (HL) (10), or no significant difference among HL, FL, and diffuse large B-cell lymphoma (DLBCL) (11). Thus, no consensus has yet been obtained regarding the influence of the BMI on ML patients.

To address this problem, we consider it necessary to monitor BMI changes over time, as FL progresses very slowly. However, no studies appear to have discussed BMI changes during chemotherapy for FL. We therefore retrospectively analyzed the impact of BMI decreases following the first chemotherapy session on the OS in patients with previously untreated advanced FL at our center.

Materials and Methods

We reviewed 68 consecutive patients with FL who underwent their first chemotherapy session at our institute between July 2009 and December 2020. The following patient characteristics were collected at the start of treatment (baseline): age, sex, BMI (baseline BMI), Eastern Cooperative Oncology Group performance status (ECOG-PS), B symptoms (features including a fever above 38°C, night sweats, and weight loss of more than 10% in the previous 6 months), clinical stage, Follicular Lymphoma International Prognostic Index (FLIPI), comorbidity of other second primary malignancy (SPM) and chemotherapy regimen.

We set three months after the start of treatment as the landmark point for collection of BMI data (landmark BMI). The BMI change was thus defined as the difference between the landmark BMI and baseline BMI values. A receiver operating characteristic (ROC) curve for the OS was plotted to define the cut-off value for the BMI decrease. The observation period was calculated from the landmark point. We defined obesity (BMI ≥ 30 kg/m²) and overweight (BMI ≥ 25 kg/m²) based on the World Health Organization criteria.

Exclusion criteria were as follows: treatment with rituximab alone due to low tumor burden; Eastern Cooperative Oncology Group Performance Status (ECOG-PS) >2 at baseline; death before the landmark point; or not having completed at least 2 cycles of chemotherapy by the landmark point. Data on adverse events (AEs) associated with treatment, histological transformation (HT) and SPMs were collected. The AE severity was determined from the post-baseline results using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (12).

Data for patient characteristics are expressed as the number and percentage for categorical variables and the mean and range for continuous variables. The significance of differences between two groups (decreased-BMI group vs. non-decreased-BMI groups) was assessed using Fisher's exact

test for categorical variables and the Mann-Whitney U test for non-parametric continuous variables. Kaplan-Meier curves were plotted for the OS and compared between two groups using log-rank testing (decreased-BMI vs. non-decreased-BMI groups and overweight vs. non-overweight groups). The cumulative incidence of HT and SPMs was compared between two groups using Gray's test, setting death without HT or SPM as competing risks, respectively. Cox's proportional hazard modeling was used for the multivariate analysis to identify independent predictors of the OS. Hazard ratios (HRs) and 95% confidence intervals (CIs) are shown as results. Statistical significance was assumed for confidence levels of 0.05 or less. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria) (13).

Results

A total of 56 patients were included in the final analysis. The ROC curve for the OS was plotted (area under the ROC curve=0.624). The cut-off for the BMI decrease was set at 1.42 kg/m², offering 55.6% sensitivity and 78.7% specificity. Patients with a BMI decrease ≥ 1.42 kg/m² were considered the decreased-BMI group (n=15), while those with BMI decrease <1.42 kg/m² were considered the non-decreased-BMI group (n=41). No significant differences in background factors were evident between groups (Table 1).

Other malignancies at baseline comprised breast cancer (n=1), bladder cancer (n=1), colon cancer (n=2), prostate cancer (n=1), lung cancer (n=1), tongue cancer (n=1), renal cancer (n=1) and endometrial cancer (n=1), none of which were seen to affect the survival outcomes during the observation period. The 5-year OS was significantly worse in the decreased-BMI group than in the non-decreased-BMI group [0.867 (95% CI 0.683-0.948) vs. 0.605 (0.284-0.819); $p=0.0191$], and the median OS was not reached in either group (Fig. 1a). The 5-year OS did not differ significantly between the BMI groups [overweight (n=11) vs. non-overweight (n=45)] based on the baseline BMI [overweight vs. non-overweight: 0.909 (0.508-0.987) vs. 0.767 (0.585-0.878); $p=0.446$] (Fig. 1b). Hematologic AEs, particularly anemia, were more frequent in the decreased-BMI group than in the non-decreased-BMI group ($p<0.05$), but no significant difference in non-hematologic AEs was evident between groups. The main causes of the 9 total deaths were HT (n=5), SPM (n=3) and unknown (n=1).

A subgroup analysis indicated that a BMI decrease in the Bendamustine-based regimen group correlated with a worse 2-year OS than no decrease [decreased-BMI vs. non-decreased-BMI: 0.444 (0.066-0.785) vs. 0.909 (0.508-0.987); $p=0.0256$]. A similar tendency was noted in the rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) group, but no significant difference was found in the 2-year OS regimen group due to a decreased

Table 1. Patient Characteristics between Non-decreased-BMI and Decreased-BMI Groups.

		Non-decreased BMI (n=41)	Decreased BMI (n=15)	P
Age, median (range)		65 (43-87)	63 (38-83)	0.704
Gender (%)	Male	24 (58.5)	5 (33.3)	0.133
	Female	17 (41.5)	10 (66.7)	
Baseline-BMI	Median (range)	21.46 (16.27-34.43)	21.83 (17.60-28.90)	0.482
	Overweight (%)	6 (14.6)	5 (33.3)	0.142
	Obese (%)	1 (2.4)	0 (0)	1.000
Landmark-BMI	Median (range)	21.12 (15.54-33.38)	19.76 (15.19-27.32)	0.186
	Overweight (%)	7 (17.0)	2 (13.3)	1.000
	Obese (%)	1 (2.4)	0 (0)	1.000
B symptom at the baseline (%)		1 (2.4)	1 (6.7)	0.468
FLIPI (%)	Low	11 (27.5)	4 (26.7)	0.928
	Int	16 (40.0)	5 (33.3)	
	High	13 (32.5)	6 (40.0)	
ECOG-PS (%)	0-1	39 (95.1)	12 (80.0)	0.113
	2-4	2 (4.9)	3 (20.0)	
Clinical stage (%)	I-II	8 (19.5)	3 (20.0)	0.901
	III-IV	33 (80.5)	12 (80.0)	
Chemotherapy (%)	R-CHOP	27 (65.9)	9 (60.0)	0.802
	R-B	9 (22.0)	4 (26.7)	
	G-B	4 (9.8)	2 (13.3)	
	Other	1 (2.4)	0 (0.0)	
AE G3-4 at the landmark (%)	Hematol.	10 (24.4)	7 (46.7)	0.188
	Non-hematol.	1 (2.6)	2 (13.3)	
Other malignancy at the baseline (%)		6 (14.6)	3 (20.0)	0.688

BMI: body mass index, Baseline-BMI: BMI at the initiation of chemotherapy, Landmark-BMI: BMI 3 months after the initiation of chemotherapy, FLIPI: Follicular Lymphoma International Prognostic Index, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, AE G3-4: adverse event grade 3 to 4, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, R-B: rituximab, bendamustine, G-B: Obinutuzumab, bendamustine. Overweight: BMI greater than or equal to 25, Obese: BMI greater than or equal to 30.

BMI [decreased-BMI vs. non-decreased-BMI: 0.889 (0.433-0.984) vs. 1.00 (NA-NA), $p=0.631$]. No significant difference in cumulative incidence of HT was evident at 2 years [decreased-BMI vs. non-decreased-BMI: 0.267 (0.077-0.505) vs. 0.101 (0.032-0.220), $p=0.156$], but the cumulative incidence of HT at 8 months tended to be higher in the decreased-BMI group [0.200 (0.045-0.433)] than in the non-decreased-BMI group [0.000 (0.000-0.000); $p=0.156$] (Fig. 2a). In the decreased-BMI patients, the cumulative incidence of HT at 2 years tended to be higher in patients treated with a Bendamustine-based regimen than in those with the R-CHOP regimen [R-CHOP vs. Bendamustine-based regimen: 0.111 (0.005-0.406) vs. 0.500 (0.077-0.829), $p=0.099$]. Although the cumulative incidence of SPM at 8 months tended to be higher in the decreased-BMI group [0.067 (0.004-0.269)] than in the non-decreased-BMI group [0.000 (0.000-0.000); $p=0.39$], the cumulative incidence at 10 years in the non-decreased-BMI group reached over 20% [0.239 (0.078-0.447); $p=0.500$] (Fig. 2b). A univariate analysis showed that a BMI decrease, B symptoms, ECOG PS >1 and the bendamustine-based chemotherapy regimen were significantly associated with a poor OS. A multivariate analysis was performed with adjusting for these factors, revealing that only a BMI decrease remained an independent

prognostic factor for the OS [hazard ratio, 4.823 (95% CI 1.189-19.56); $p=0.0276$] (Table 2).

Discussion

This retrospective analysis revealed for the first time that a decrease in the BMI of more than 1.42 kg/m² during the first round of chemotherapy is an independent inferior prognostic factor of the OS in advanced FL patients. In general, the association between the pretreatment BMI and prognosis has remained unclear in the area of ML (9-11). Regarding aggressive NHL, Yang et al. recently reported a lower pretreatment BMI as an independent risk factor in DLBCL (14). Li et al. set the cut-off value for pre-treatment BMI as 20 kg/m², and patients with a BMI >20 kg/m² showed better survival outcomes than those with a lower BMI in their retrospective analysis of 742 patients with nasal-type NK/T-cell lymphoma (15). Although some studies have reported that a higher BMI before treatment was associated with a better prognosis for aggressive NHL, the role of the BMI in FL has yet to be clarified. Our finding of a poorer prognosis in patients with a decreased BMI may indicate that FL shows a similar tendency to other NHLs.

Two main mechanisms are considered to underpin body

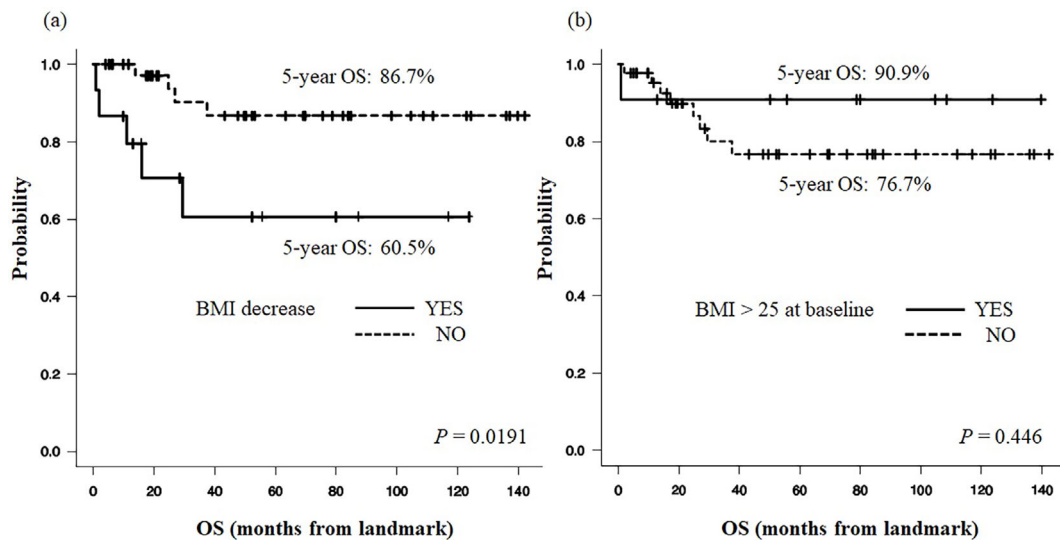


Figure 1. Kaplan-Meier curves for the OS according to the group comparison. (a) Body mass index (BMI) decrease during chemotherapy. (b) BMI status at baseline.

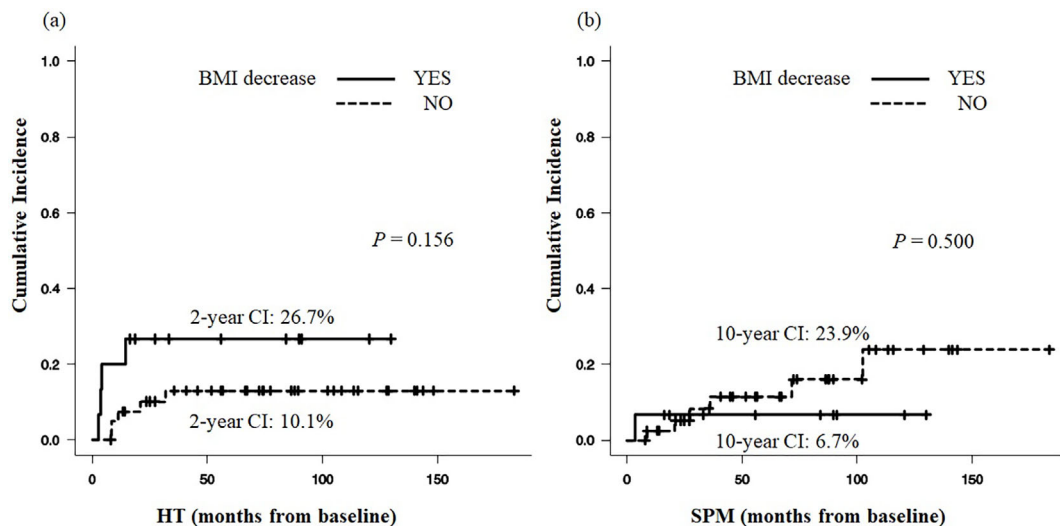


Figure 2. Cumulative incidence between the non-decreased-BMI and decreased-BMI groups. (a) Histologic transformation (HT). (b) Second primary malignancy (SPM).

weight loss in cancer patients: cancer-associated weight loss and cancer-induced weight loss. Cancer-associated weight loss is caused by stenosis or obstruction of the gastrointestinal tract or inappetence due to chemotherapy, while cancer-induced weight loss is triggered by metabolic abnormalities induced by cytokines produced by either the cancer cells themselves or the host immunocompetent cells (3).

Regarding cancer-associated weight loss, FL is rare in the gastrointestinal tract. When seen in this location, duodenal-type FL (D-FL) is the most common type and was first recognized as an independent entity in the 2017 World Health Organization classification update (1). D-FL is almost always diagnosed at a localized stage, unlike other types of FL, and its gene expressions and pathogenesis are considered closely related to extra-nodal marginal-zone lymphoma of mucosa-associated lymphoid tissue (16). D-FL therefore does not appear to be associated with physical obstruction

mechanisms of body weight loss in FL patients. In fact, all D-FL patients were excluded from the present analysis because of the exclusion criteria, as none had been treated with chemotherapy. Inappetence due to chemotherapy also appears unlikely to explain the relationship between a decreased BMI and poor OS, since the frequency of non-hematologic severe AEs did not differ markedly between the groups. A high rate of hematologic AEs in the decreased-BMI group would also not be the answer, as patients with ML often present with hematopoietic dysfunction at the end stage.

Regarding cancer-induced body weight loss, cancers are known to induce abnormal glucose, protein and lipid metabolism, leading to a loss of body weight and excess catabolism of skeletal muscle and adipose tissues (3, 4). Among MLs, sarcopenia due to skeletal muscle loss has been reported as a poor prognostic factor in DLBCL (17).

Table 2. Univariate and Multivariate Analysis for OS.

	Univariate		Multivariate	
	HR (95%CI)	p	HR (95%CI)	p
Age (>75 years old)	0.919 (0.114-7.433)	0.937	-	-
Gender (Male)	1.157 (0.310-4.315)	0.828	-	-
Baseline-overweight (BMI>25)	2.201 (0.275-17.62)	0.458	-	-
Landmark-overweight (BMI>25)	0.734 (0.152-3.534)	0.699	-	-
Decreased-BMI	4.252 (1.138-15.88)	0.0314	4.823 (1.189-19.56)	0.0276
B symptom at baseline	10.26 (1.135-92.84)	0.0382	3.862 (0.2934-50.84)	0.304
FLIPI (high)	4.358 (1.085-17.5)	0.0379	2.118 (0.367-12.21)	0.401
ECOG-PS (>1)	9.437 (2.282-39.02)	0.0019	2.602 (0.391-17.34)	0.323
Clinical stage (>II)	0.719 (0.149-3.485)	0.6824	-	-
Chemotherapy (other than R-CHOP)	5.361 (1.319-21.79)	0.0189	2.674 (0.495-14.45)	0.253
Non-hematological AE G3-4 (at the landmark)	3.579 (0.4415-29.02)	0.2324	-	-
Hematological AE G3-4 (at the landmark)	2.548 (0.6835-9.498)	0.1636	-	-
Other malignancy (at the baseline)	1.973 (0.4071-9.566)	0.3987		

BMI: body mass index, IPI: International Prognostic Index, FLIPI: Follicular Lymphoma International Prognostic Index, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, AE G3-4: adverse event grade 3 to 4, HR: hazard ratio

We consider cancer-induced body weight loss to be more important in FL than cancer-associated weight loss. Mozas et al. reported that patients with high serum levels of cytokines, such as interleukin (IL)-2, IL-6 and tumor necrosis factor (TNF)- α , showed an inferior prognosis to those without high levels in FL (18), while HT is known to activate the mitogen-activated protein kinase pathway in the process of developing aggressive lymphoma (19). Our study indicated an association between the survival outcomes and the BMI decrease over time, whereas no association was noted between the survival outcome and the pre-treatment BMI (baseline BMI) (Fig. 1). Since FL is an indolent lymphoma, FL itself may not affect changes in the BMI over time, but the state of high serum cytokines might be associated with BMI decreases, reflecting the onset of HT or SPM. In fact, the cumulative incidence of HT increased more markedly in the decreased-BMI group than in the non-decreased-BMI group during the early observation period (Fig. 2a). The BMI should thus be monitored continuously during chemotherapy and perhaps also after treatment. Taken together, these findings suggest that a BMI decrease during chemotherapy in FL may reflect the development of HT or SPM in the early period of treatment.

Several limitations associated with the present study warrant mention. First, the analysis was retrospective, not prospective, and was conducted at a single center. Second, the statistical power may have been insufficient for a prognostic factor analysis to detect significant differences due to the small sample size. Although the multivariate analysis showed that the BMI decrease was an independent prognostic factor with statistical significance, the number of samples

in this study was smaller than is usually expected in a survival analysis with time-to-event endpoints. Especially for B symptoms, the statistical power appeared insufficient because there were only two applicable cases. Therefore, the results of multivariate analysis should not be considered totally definitive even though our study showed the potential of statistical significance. An analysis of more samples from multiple centers is needed in the future. Third, the treatment regimen consisted of not only R-CHOP but also Bendamustine-based regimens. Although there was no significant difference in the two regimens as a background factor between the two BMI groups (Table 1), a subgroup analysis appeared to show less favorable impact of a BMI decrease on the OS in the Bendamustine-based regimen group than in the R-CHOP group. This may be due to the more frequent development of HT in the decreased-BMI group treated with Bendamustine, although no significance was noted ($p=0.099$). Since no previous studies regarding the BMI have included FL patients treated with Bendamustine (11), the BMI decrease in patients treated with only Bendamustine-based regimens should be evaluated in the future, with a larger sample size.

Nutritional intervention is considered important to prevent the BMI from decreasing during first-line chemotherapy. Several reports have noted that the administration of oral nutritional supplements to patients undergoing chemotherapy improved their condition (20, 21). The prognosis may be improved by active nutritional intervention during initial treatment, but we found no such reports in the literature on ML. The accumulation of more cases is important to determine whether or not nutritional interventions are beneficial.

Conclusion

Our findings suggest that the BMI decrease during chemotherapy may be an independent adverse prognostic factor in FL patients. The total condition of the patient, including the BMI, should be investigated when starting chemotherapy in FL patients.

This study was performed in conformity with the Declaration of Helsinki and was approved by our ethical committee.

The authors state that they have no Conflict of Interest (COI).

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