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ORIGINAL ARTICLE

Weight loss at the time of diagnosis is not associated with prognosis in patients with advanced-stage non-small cell lung cancer

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Summary

Purpose: *To investigate the prognostic value of weight loss before diagnosis in patients with advanced stage non-small cell lung cancer (NSCLC) treated with first-line chemotherapy.*

Methods: *A total of 81 NSCLC patients with stages IIIB/IV were included in this retrospective cross-sectional study. Study variables were weight loss in the last 3 months before diagnosis, patient demographic, clinical and laboratory characteristics and histological features of the tumor before administering first-line chemotherapy. Then, the patients were stratified into 4 groups based on their weight loss before being diagnosed with NSCLC.*

Results: *The patients were predominantly male (68%), with a smoking history (62%), 5 to 10 kg weight loss in the last 3 months (31%), and had metastatic disease (64%) and adenocarcinoma (40%) at the time of diagnosis. On the other hand, most of the patients with 5 to 10 kg weight loss in the last 3 months before diagnosis had squamous cell carcinoma (44%), stage IV disease (56%), and the first disease progression was in the brain (64%). Pre-diagnosis weight loss had a negative impact on progression-free survival (PFS), independent from weight loss during first-line chemotherapy, but no such effect was noticed on overall survival (OS).*

Conclusions: *Pre-diagnosis weight loss was found to have a negative impact on PFS in patients with NSCLC treated by first-line chemotherapy. Similar studies in larger patient series are warranted.*

Key words: *non-small cell lung cancer, prognosis, squamous carcinoma, weight loss*

Introduction

Lung cancer is one of the most common cancers affecting both men and women, and is the top cause of cancer-related death worldwide [1,2]. NSCLC accounts for about 85% of the lung cancers. Eighty percent of the patients with NSCLC have advanced disease at the time of diagnosis, and the 5-year [OVERALL?] survival rate ranges between 5 and 10% [1-3].

Given the heterogeneity of NSCLC patients, the effect of several clinical, histological, biological, chemical and genetic features on prognosis was investigated in previous years [3-5]. Some of the anatomical, clinical and socio-demographic factors are used as conventional prognostic factors in clinical practice. Disease stage, gender, age and histological type are among these prognostic factors for NSCLC. Nonetheless, some biological markers (lactate dehydrogenase/LDH and alkaline

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phosphatase/AP levels, presence of hypercalcemia and leukocytosis and neutrophil count), patient demographic and clinical characteristics (weight loss, smoking habits, comorbidities and ethnicity), and tumor-associated features (histological grade, number of metastases, lymphovascular invasion, nodal disease, malignant pleural effusion and primary tumor localization) have been considered as potential prognostic factors in several studies [4-6]. However, whether the factors specified in these studies are useful, practical and independent prognostic indicators remains to be clarified [4].

There are various reasons of weight loss in cancer patients, and many studies have shown that weight loss is associated with a poor prognosis [7-9]. This relationship has been suggested to be based on cancer cachexia itself and decreased compliance and tolerance to chemotherapy related to weight loss. Prognostic studies in lung cancer patients are limited and the results are conflicting, although it has been well-established that weight loss during chemotherapy or radiotherapy is associated with poor prognosis [10-12]. On the other hand, the information on the effect of the presence and the degree of weight loss at diagnosis on prognosis is limited.

In this study, we examined the effect of pre-diagnostics weight loss during the last 3 months before starting chemotherapy on the first-line chemotherapy-related events and the prognosis in patients with advanced stage NSCLC.

Methods

The medical records of 94 patients with NSCLC admitted to the Department of Medical Oncology between July 2011 and August 2014 were retrospectively reviewed. Of these, 81 patients were included in this study. All of the patients had histopathological diagnosis of NSCLC.

Demographic and clinical features, laboratory and histopathological findings, and properties of systemic chemotherapy were considered as study variables.

Demographic characteristics used as study variables included age, gender, smoking habit and alcohol consumption, comorbid systemic diseases and concomitant medications. Patient smoking status was expressed as the number of packs of cigarette per year, and patients were classified as never smoker, former smoker and current smoker.

Study variables regarding clinical features were body weigth, history of weight loss, ECOG performance status (PS), stage of disease (III and IV), presence of metastasis and metastatic sites.

Histological subtype and tumor stage were the histopathological factors recorded; and the laboratory variables were hemoglobin, leukocyte, neutrophil, and platelet counts, serum lactate dehydrogenase (LDH), calcium, albumin, and C-reactive protein (CRP) levels.

The treatment variables included first-line systemic chemotherapy regimen, number of cycles applied, and response to first-line systemic chemotherapy.

Patients with small cell lung cancer, those operated previously, and those with stage I-IIIA NSCLC who received neoadjuvant chemotherapy/chemo-radiotherapy or adjuvant chemotherapy/radiotherapy or chemo-radiotherapy were excluded from the study. All patients who did not meet any of these exclusion criteria, those who had histologically diagnosed NSCLC, and who had complete medical records were included in the study.

Laboratory analyses were performed on blood samples obtained after 8 to 12 hrs of fasting. Serum uric acid and LDH levels were analysed by using "Abbott/Aeroset system (™)". The determination of peripheral blood analysis parameters including Hb level, leucocyte (Leu) and platelet counts was performed with ABX-PENTRA 120 DX® Hematology Analyzer (ABX Diagnostics, France).

Survival analysis was performed for PFS, OS and time-to-brain metastasis separately using the Kaplan-Meier method.

Statistics

Statistical analyses were performed using SPSS 16.0 for Windows. Frequencies with percentages were generated for categorical variables and means and standard deviations were computed for continuous variables. Chi square test for categorical variables and Mann Whitney U test for non-parametric variables were used to assess the relationship between weight loss and other variables. Survival curves were constructed by using the Kaplan-Meier method and the curves were statistically compared using log-rank test. Univariate and multivariate analysis of predictive factors of survival were performed using Cox regression model calculating hazard ratios (HR). All analyses were performed with a 95% confidence interval (95% CI) and p values <0.05 were considered to be statistically significant.

Results

The mean patient age (N=81) was 64±8 years (range 43-79; median 64). Of these patients, 83% (N=67) were male and 17% (N=14) female. The mean age of male patients was 67±9 years (range 47-79; median 66) and of female patients it was 63±7 years (range 43-68; median 61) without any difference in age between genders (p=0.214).

Most of the patients with stage IIIB/IV NSCLC were male (71%), smoker (63%), experienced

≤10 kg weight loss in the past 3 months before diagnosis (59%), and had TNM stage IV (54%), poorly differentiated tumors (84%), and adenocarcinoma histology (58%). The main demographic, clinical and histopathological features, as well as laboratory characteristics are summarized in Table 1.

A total of 63 (78%) patients had died at the time of statistical analysis. Median follow-up time was 18 months (range 4-28).

Table 1. The baseline demographic, histological, clinical and laboratories characteristics of all patients in this study

Characteristics	*N (%) or mean±SD*
Patients	81 (100)
Age, years	
<65	36 (44)
>65	45 (56)
Gender	
Male	55 (68)
Female	26 (32)
Smoking	
Yes	50 (62)
No	31 (38)
Weight loss, kg (at the time of diagnosis, in last 3 months)	
No	22 (27)
< 5	18 (22)
5-10	25 (31)
> 10	16 (20)
ECOG performance status	
0	12 (15)
1	38 (47)
2	17 (21)
3-4	14 (17)
Clinical TNM stage	
IIIB	29 (36)
IV	52 (64)
Histological type	
Adeno	32 (40)
Squamous cell	24 (30)
Adeno-squamous cell	8 (9)
Non-small cell lung cancer (NOS)	17 (21)
Tumor grade	
1	16 (20)
2	34 (42)
3	27 (33)
Unknown	4 (5)
Metastatic sites for 52 stage IV patients	
Liver	14 (27)
Bone	4 (8)
Adrenals	3 (5)
Brain	9 (17)
Cervical or supraclavicular lymph node	4 (8)
Multiple sites	18 (35)
1st line chemotherapy	
Yes	67 (83)
No	14 (17)
First line chemotherapy regimen	
Cisplatin- docetaxel	16 (24)
Carboplatin- paclitaxel	24 (36)
Cisplatin- gemcitabine	17 (25)
Other*	10 (15)
Baseline leukocyte count ($x10^9$)	10.1±5.6
Baseline neutrophils count ($x10^9$)	5.3±3.4
Baseline platelet count ($x10^9$)	389 ± 107
Baseline hemoglobin level (g/dl)	10.2±2.9
Baseline serum calcium level (mg/dl)	8.6±1.9
Baseline serum albumin level (mg/dl)	3.1±0.8
Baseline serum LDH level (U/L)	218±61
Baseline C-reactive protein level	11 ± 7

±SD: mean±standard deviation, LDH: lactate dehydrogenase, NOS: not otherwise specified
*cisplatin-vinorelbine or single agent paclitaxel or single agent docetaxel or cisplatin-pemetrexed

The patients were classified in 4 groups according to weight loss in the last 3 months before diagnosis: Group 1, no weight loss; Group 2, <5 kg weight loss; Group 3, 5-10 kg weight loss; Group 4, >10 kg weight loss. Comparison of study variables between the groups is presented in Table 2.

Patients who had loss of appetite, nausea and vomiting during first-line systemic chemotherapy were fed with enteral nutrient solutions, and received megestrol acetate treatment. No significant difference was seen between groups with regard to weight loss during chemotherapy (Table 2).

The patients with >10 kg weight loss in the last 3 months of prediagnosis were found to be more likely to have squamous cell carcinoma (44%), brain metastases at the time of diagnosis (35%), and grade 3 tumor (56%) (Table 2). However, time-to-progression was not significantly shorter in these patients (Table 2). Additionally, in these patients, the most common site of cancer metastasis was the brain (35%) (Table 2). On the

Table 2. Comparison of demographic, histological and clinical characteristics and analysis of survival according to the level of weight loss

Characteristics	*Group 1 No weight loss N (%)*	*Group 2 <5 kg weight loss N (%)*	*Group 3 5-10 kg weight loss N (%)*	*Group 4 >10 kg weight loss N (%)*	*p value*
Patients	22	18	25	16	0.245
Age, years					0.283
≤65	10 (45)	8 (44)	11 (44)	7 (44)	
≥65	12 (55)	10 (56)	14 (56)	9 (56)	
Gender					0.121
Male	14 (64)	11 (61)	17 (68)	13 (81)	
Female	8 (36)	7 (39)	8 (32)	3 (19)	
ECOG performance status					0.108
0	2 (9)	2 (11)	5 (20)	3 (19)	
1	13 (59)	11 (61)	9 (36)	5 (31)	
2	4 (18)	3(17)	6 (24)	4 (25)	
3-4	3 (14)	2 (11)	5 (20)	4 (25)	
Clinical TNM stage					0.123
IIIB	8 (36)	5 (28)	11 (44)	5 (31)	
IV	14 (64)	13 (72)	14 (56)	11 (69)	
Histological type					0.106
Adeno	11 (50)	9 (50)	8 (32)	4 (25)	
Squamous cell	4 (18)	2 (11)	11 (44)	7 (44)	
Adeno-squamous cell	2 (9)	1 (6)	3 (12)	2 (12)	
Non-small cell lung cancer (NOS)	5 (23)	6 (33)	3 (12)	3 (19)	
Tumor grade					0.109
1	6 (27)	3 (17)	5 (20)	2 (12)	
2	9 (41)	4 (22)	16 (64)	5 (31)	
3	6 (27)	10 (56)	2 (8)	9 (56)	
Unknown	1 (5)	1 (5)	2 (8)	0	
Metastatic sites for 52 stage IV patients					0.044
Liver	4 (29)	3 (23)	6 (43)	1 (10)	
Bone	1 (7)	1 (8)	0	1 (10)	
Adrenals	1 (7)	1 (8)	1(7)	0	
Brain	2 (14)	2 (14)	1(7)	4 (35)	
Cervical or supraclavicular lymph node	1 (7)	1 (8)	1 (7)	1 (10)	
Multiple sites	5 (36)	5 (39)	4 (36)	4 (35)	
Baseline leukocyte count ($x10^9$)	9.2±3.4	9.3±4.1	9.3±3.8	10.3±3.8	0.042
Baseline neutrophils count ($x10^9$)	5.1±2.3	5.3±3.4	5.1±2.7	5.7±3.1	0.094

Baseline platelet count (x10^9)	341±84	324±87	344±94	371±87	0.198
Baseline hemoglobin level (g/dl)	9.2±3.3	10.2±2.7	10.1±1.4	9.9±1.3	0.217
Baseline serum LDH level (U/L)	194±37	211±28	204±39	217±48	0.037
Baseline serum albumin level (mg/dl)	2.9 ± 0.8	2.8 ± 1.4	3.1 ± 0.9	3.2 ± 1.1	0.197
Baseline serum calcium level (mg/dl)	9.1 ± 1.4	8.9 ± 2.6	9.4 ± 0.9	8.9 ± 1.3	0.218
Baseline C-reactive protein level (ng/L)	5.1 ± 1.8	6.4± 1.3	6.9 ± 3.7	7.1 ± 3.10	0.048
Chemotherapy-induced neutropenia					0.218
Grade 1	8 (36)	6 (33)	9 (36)	5 (31)	
Grade 2	3 (14)	2 (11)	4 (16)	3 (19)	
Grade 3	2 (9)	1 (6)	1 (4)	1 (7)	
Febrile	1 (5)	1 (6)	2 (8)	2 (12)	
No neutropenia	8 (36)	8 (44)	9 (36)	5 (31)	
Chemotherapy-induced thrombocytopenia					0.297
Grade 1	6 (27)	4 (21)	7 (28)	3 (9)	
Grade 2	2 (9)	1 (6)	2 (8)	1 (6)	
Grade 3	1 (5)	1 (6)	1 (4)	1 (6)	
No neutropenia	13 (59)	12 (67)	15 (60)	11 (69)	
Dose reduction (10%)					0.312
Yes	3 (14)	2 (11)	4 (6)	2 (12)	
No	19 (86)	16 (89)	21 (84)	14 (88)	
Weight loss during 1st line chemotherapy					0.249
No	10 (45)	8 (44)	11 (44)	7 (44)	
Yes	12 (55)	10 (56)	14 (56)	9 (56)	
Time to first recurrence with brain metastasis (months)	7±1	8±3	6±2	5±3	0.034
Progression-free survival (months)	8 ±5	9±3	9±4	9±2	0.214
Overall survival (months)	11±5	14±9	15±7	12±3	0.206

±SD: mean ±standard deviation, NOS: not otherwise specified

other hand, most of the patients presented with 5 to 10 kg weight loss in the last 3 months before diagnosis had squamous cell carcinoma (44%), stage IV (56%), and developed first disease progression in the brain (64%).

In addition, time-to-first recurrence with brain metastasis was significantly shorter in patients with >10kg weigh loss (group 4) than patients in other groups (Table 2) (p=0.034). However, OS and PFS were not significantly different among patients (Table 2).

When the patients were classified according to the presence or absence of weight loss, independently of the degree of weight loss, a positive significant correlation was found between the amount of weight loss and adenocarcinoma histology (r=0.541, p=0.021), poorly differentiated cancer (r=0.609, p=0.026), initial brain metastasis (r=0.623, p=0.023), smoking (r=0.671, p=0.021), stage IV (r=0.618, p=0.023), male gender (r=0.481, p=0.046), and serum LDH level (r=0.511, p=0.032), while a negative significant correlation was found between the amount of weight loss and Hb (r=-0.611, p=0.027) and serum albumin levels (r=-0.631, p=0.031).

In univariate analysis, the presence of weight

Table 3. Univariate analysis of the factors for poor survival in non-small cell lung cancer with stage IIIB/IV

Factors	*Hazard ratios (95% CI)*	*p value*
Age (<65 vs >65 years)	1.44 (0.45-3.14)	0.213
Gender (male vs female)	1.44 (0.81-3.27)	0.243
Smoking (presence vs absence)	1.38 (0.97-.11)	0.142
ECOG performance status (0 vs 1-2 vs 3-4)	1.71 (1.08-2.84)	0.035
Stage (III vs IV)	1.87 (0.41-2.32)	0.173
Histological type (adeno vs squamous vs other)	1.17 (0.22-1.78)	0.137
1st line chemotherapy (yes vs no)	1.78 (0.63-3.51)	0.136
Baseline serum LDH level (>200 U/L vs other)	1.18 (0.37-1.13)	0.145
Baseline serum calcium level (>7.49 vs other)	1.35 (0.48-2.02)	0.127
Baseline serum albumin level (<3.2 mg/dl vs other)	1.19 (0.87- 3.01)	0.245
Baseline leukocyte count (>9.5x10^9 vs other)	1.91 (1.25-3.98)	0.047
Baseline platelet count (>375x10^9 vs other)	1.48 (0.25-2.74)	0.118
Baseline hemoglobin level (9 g/dl vs other)	1.48 (0.53-1.99)	0.219
Metastatic site (brain vs other)	1.35 (1.28-2.09)	0.023
Weight loss before diagnosis (absent vs present)	1.48 (1.07-5.31)	0.034
Weight loss during 1st line chemotherapy (absent vs present)	1.36 (031-2.07)	0.208

loss at 3 months before diagnosis, initial brain metastasis, baseline leukocyte count, and ECOG PS were found to have prognostic significance (Table 3). No prominent independent prognostic factor was identified in multivariate analysis (Table 4).

Discussion

In this cross-sectional study, the relationship between pre-diagnosis weight loss and prognosis was investigated among 81 patients with stage IIIB/IV NSCLC. In our study, the OS of NSCLC patients with weight loss before diagnosis was similar to that of those without any weight loss, while the majority of patients with >10 kg weight loss in the last 3 months before the diagnosis had brain metastasis, and almost all of the patients with brain metastasis had squamous cell carcinoma.

Malnutrition is an important problem in cancer patients. The prevalence of weight loss in cancer patients ranges from 8 to 85%. The difference in the prevalence estimates may be associated with the location, type, and stage of cancer [13-15].

Weight loss is caused by negative protein and energy balance in cancer patients [15]. The reasons that underlie this negative balance include the cancer itself, surgery, side effects such as loss of appetite, early satiety, malabsorption, nausea, vomiting, diarrhea, mucositis, loss of taste caused by treatment modalities including radiotherapy and chemotherapy, and psychosocial factors such as depression, eating habits, smoking and alcohol intake [16-18]. Any one of these factors or multiple simultaneous factors may be responsible for the weight loss in cancer patients. Thus, malnutrition and its clinical outcome of weight loss in cancer patients have a multifactorial etiology. The catabolic process induced by immune response against tumor growth is associated with impaired energy balance. Impaired energy balance caused by immune mediated disorders and inflammatory response is referred to as cachexia [18].

The course of cancer has been reported to be more aggressive in patients with malnutrition, whatever the reason of malnutrition is. Weight loss is considered as an independent poor prognostic factor in some cancer types. Furthermore, it remained unclear whether the poor prognosis is related to aggressive biology of cancer or malnutrition exacerbated by toxic side effects of therapies. However, Andreyev et al. [19], in a study of 1555 patients with gastrointestinal tract cancer, reported that treatment-associated toxicity was more frequent in patients with weight loss, and these patients received lower total doses of medication and shorter duration of exposure.

In our study we found that weight loss before diagnosis was an independent risk factor for

Table 4. Multivariate analysis of factors for poor overall survival in stage IIIB/IV non-small cell lung cancer

Factors	*Hazard ratios (95% CI)*	*p value*
Age (<65 vs >65 years)	1.62 (0.75-2.07)	0.275
Gender (male vs female)	1.56 (0.98-2.46)	0.304
Smoking (presence vs absence)	1.71 (0.93-2.05)	0.197
ECOG performance status (0 vs 1-2 vs 3-4)	1.84 (0.37-2.36)	0.241
Stage (III vs IV)	1.43 (0.54-2.31)	0.264
Histological type (adeno vs squamous vs other)	1.29 (0.58-1.97)	0.148
1st line chemotherapy (yes vs no)	1.42 (0.34-2.63)	0.206
Baseline serum LDH level (>200 U/L vs other)	1.38 (0.89-3.41)	0.173
Baseline serum calcium level (>7.49 vs other)	1.09 (0.94-2.02)	0.241
Baseline serum albumin level (<3.2 mg/dl vs other)	1.19 (0.87-2.55)	0.342
Baseline leukocyte count (>9.5x10^9 vs other)	1.42 (0.91-2.34)	0.174
Baseline platelet count (>375x10^9 vs other)	1.08 (0.75-2.53)	0.211
Baseline hemoglobin level (<9 g/dl vs other)	1.24 (0.68-2.33)	0.204
Metastatic site (brain vs other)	1.42 (0.98-3.14)	0.176
Weight loss before diagnosis (absent vs present)	1.09 (0.84-2.24)	0.217
Weight loss during 1st line chemotherapy (absent vs present)	1.29 (0.37-1.98)	0.165

shorter PFS, but had no effect on OS. We also observed that weight loss during treatment had no contribution to this significant effect of pre-diagnosis weigth loss on PFS.

However, studies on prognostic characteristics of cancer patients have shown that weight loss during treatment had an impact on short-term PFS and OS. A prospective study has demonstrated that the difference between body weight and healthy life before cancer diagnosis is associated with significantly poor prognosis (log-rank: 29.95, p=0.0000) [10]. The authors of this study suggested that "while the loss of body weight is confirmed as a significant prognostic factor in NSCLC, the value of this factor is partially dependent on its definition" [10]. Another prospective study evaluated the relationship between weight loss in advanced NSCLC patients and systemic inflammation, and confirmed the negative effect of weight loss on quality of life [20].

Some studies reported in the literature have demonstrated that weight loss at the presentation of the patient was an independent prognostic factor for both NSCLC and small cell lung cancer [21-23]. However, previous studies have not established clearly whether the patients with weight loss may have a more aggressive disease than those without weight loss [4-6,10]. Thus, there is no obvious reason to explain the poor prognostic ability of weight loss at diagnosis. Nevertheless, there is a common belief that weight loss shortens survival by negatively affecting chemotherapy tolerance, continuation of chemotherapy, and diminishing the effective dose of chemotherapeutics. In our study, however, we observed that weight loss at diagnosis negatively affected PFS, independent from weight loss during chemotherapy. Also, we couldn't show any relationship between weight loss at diagnosis and disease aggressiveness. Hence, we determined that the degree of weight loss in patients with more advanced and aggressive disease was not greater than that of other patients. This can be explained under the assumption that there is not enough time to develop weight loss in patients suffering of advanced and aggressive disease. Also, some other studies [6,24,25] reported that weight loss is not related to the prognosis in patients with NSCLC.

The primary limitation of our study is the relatively low number of patients, inherent with single-center studies. Weight alterations occurring before the diagnosis of lung cancer cannot be measured objectively and they are stratified only according to the disease history from the retrospective data of the patients in their files and these are other important limitations of the study. The molecular and genetic indicators effective on disease prognosis were not part of this study and

may represent another study's negative aspect. However, we could not include these indicators due to the retrospective study design and included different histological types and the regimens used in the first-line treatment to be chosen independently from these indicators.

Our conclusion was that the degree of weight loss before the diagnosis in patients with NSCLC did not affect the general survival; however, it affected negatively the PFS. Consequently, we may suggest nutritional support during treatment in patients with weight loss in the period before diagnosis and a good management of treatment associated toxicity.

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