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Association between weight loss and death in patients with malignant melanoma: A retrospective study of 28 cases

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Abstract

Malignant melanoma (MM) is often associated with a poor prognosis due to metastasis and cancer death. The monitoring of prognostic factors is of vital importance, and among these factors, elevated lactate dehydrogenase (LDH) should be closely observed during the disease course. Important factors for predicting the survival of MM patients include tumor thickness, ulceration, the number of lymph node metastases, metastatic lesions, and the sites of metastasis. Weight loss is not generally included in the prognostic factors of MM; however, it is monitored in other cancers, such as lung cancer and gastrointestinal cancer. The objective of this study is to investigate the association between weight loss and MM prognosis. Using data from MM patients who have been treated at our institution, we assessed the prognoses of two groups: weight loss of at least 5% body weight or weight loss not exceeding 5% body weight within a 12-month period. As a result, a higher mortality rate was found for the former group. Further, the loss of at least 5% of body weight within a month was found to almost always adversely affect the patient's prognosis. The present study indicates that there may be an association between MM prognosis and weight loss of at least 5% within a year, and body weight could potentially serve as an informative factor for MM survival.

Introduction

Malignant melanoma (MM) is a skin cancer whose prevalence has been increasing worldwide.[1] Prognostic factors include histopathological factors such a, mitotic rate, ulceration, and clinical factors such as elevated LDH and metastasis.[1] Weight loss is associated with poor prognosis in certain cancers, including lung cancer and gastrointestinal cancer and it has been associated with cancer cachexia.[2,3] However, no studies have investigated the association between weight loss and MM prognosis. This study compares the difference in prognosis and examine the correlation between MM patients who had undergone a weight loss of at least 5% within 12 months and those who had undergone weight loss not exceeding 5% body weight within 12-month during the post-diagnosis course.

Methods

The Institutional Review Board of Hokkaido University Hospital approved the present retrospective study (approval numbers #022-0055, #021-0245). We monitored patients with cutaneous MM who had been treated at the Department of Dermatology, Hokkaido University Hospital. We collected clinical information using patient records from August 2005 to December 2021. In accordance with previous reports, we collected

data on age, sex, weight, primary origin, stage, metastasis, TT, *BRAF* mutation, LDH, WHO and Clark classifications, and treatments. The criterion for patient inclusion was detailed data on weight changes after MM diagnosis. Weight data was body weight measured at our institution. Patients who experienced at least a 5% decrease in weight within 12 months at any time after diagnosis were defined as the "weight-loss group". Patients with weight loss not exceeding 5% body weight within 12-month at any time after diagnosis were defined as the "non-weight-loss group". The 5% cutoff was based on the standardized definition of cachexia established in 2011.[4] Kaplan-Meier survival curves were calculated for the two groups, and log-rank tests were used to compare overall survival (OS) and disease-specific survival (DSS). We compared the parameters using the Mann–Whitney U test and Fisher's exact test.

Results

A total of 28 cases met the criteria. Nineteen cases lost at least 5% of their body weight within 1 year (the weight-loss group), whereas 9 cases not lost greater than 5% of their weight during the observation period (the non-weight-loss group). Fourteen of the 28 patients died, 13 of them from MM. Table 1 shows the characteristics of the 28 patients. There are significant differences between the two groups in terms of immune-

checkpoint inhibitor (ICI) administration and DTIC (dacarbazine) administration. However, no significant differences were observed in age, gender, weight at diagnosis, stage, lymph node metastasis, TT, or LDH. Supplemental table 1 shows the clinicopathological features of 28 patients based on WHO and Clark classification with no significant differences.

Figure 1 and Supplemental Figure 1 show Kaplan-Meier survival curves (OS and DSS respectively) for MM patients with/without at least 5% weight loss. There are significant differences between the two groups ($p<0.05$ log-rank test).

The duration of weight loss events was defined by a cutoff value of 1, 3, 6, or 12 months. When comparing the four groups in terms of survival versus mortality, each group was found to have significant differences in mortality regardless of the time taken to lose weight (Supplemental Table 2). All 6 patients with weight loss within 1 month passed away, whereas the 9 patients without weight loss survived the study period. The median survival period after at least 5% weight loss was 26.5 weeks.

Discussion

Prognostic clinical factors of MM have been reported to be age, sex, affected sites, lymphoma metastasis, and elevated LDH.[1] Weight loss has been recognized as a

marker of poor prognosis in certain advanced cancers, including lung cancer and gastrointestinal cancer.[2,3] Cachexia is a common symptom of late-stage cancer which includes anorexia, reduced food intake, hypercatabolic drive, decreased muscle mass and strength, and disruption of physical functions.[4] The cancer cells influence the host physiology and metabolism, usually resulting in the progressive loss of muscle mass and adipose tissue, probably due to inflammatory cytokines.[5] A previous study of patients with cancer showed low levels of albumin concentration resulting from the loss of body cell mass.[6] This could mean that hypoalbuminemia is a biological marker for cachexia, which is related to weight loss.

Several reports have addressed the relationship between cancer and weight loss. A retrospective study of patients with non-small-cell lung cancer found that body weight loss significantly correlates with a worse prognosis, unrelated to the combination of age, stage, gender, or performance status.[2] In advanced lung cancers (both small-cell and non-small-cell lung cancers), weight loss of at least 5% within 3 months correlates with a poor survival rate in a univariate analysis.[7] In breast cancer, cases with a body mass index (BMI) decrease of at least 0.5 kg/m^2/year, an adverse effect is observed in overall survival, breast cancer-specific survival, and disease-free survival, compared to cases with less than a 0.5 kg/m^2/year BMI decrease.[8] For patients whose BMI decreases, the

median time from recurrence to death is 24 months for Caucasians and 13 months for dark-skinned patients.[8] In colorectal cancer, within 3 months before death, there is an increase in resting energy consumption and a decrease in muscle and fat that results in significant weight loss.[9] Weight loss tends to be observed in advanced-stage cancer patients, and is associated with a poor prognosis in several malignancies. This could be similarly said in MM patients as well. Mortality may change depending on the time until at least 5% weight loss when MM patients are followed up. This results in the need to focus on the period until weight loss.

In stage IV MM, OS after progressive disease diagnosis has been reported to be 6–18 months.[10] The median survival is 7 months for patients with one metastatic site, but 2 months for patients with three or more metastatic sites.[10] Median survival time has been reported to be 3 months in patients with metastases of internal organs, and 8 months in patients with metastases in the skin or lymph nodes.[10] For the “at least 5% weight loss” group in our study, the survival period was approximately 3 months, similar to that reported for MM patients with metastases in three or more locations. Conversely, our patients with weight loss not exceeding 5% body weight all survived during the observation period. In the analysis with a 10% cutoff for weight loss, no significant difference was observed between OS and DSS (log-rank tests). There were significant

differences in mortality regardless of the time taken to lose weight (1, 3, 6, 12 months (Supplemental Table 2)), suggesting that weight loss of 5% at any time within 12 months could lead to a lower chance of survival. The median survival period after weight loss was 26.5 weeks, which is similar to that for metastasis. Reported prognostic factors during treatment are metastasis and elevated LDH. Weighing is less invasive and lower in cost than blood tests or computed tomography, and may be useful as an additional informative factor.

The present study has several limitations. The sample size is small; therefore, several factors in this study (TT, LDH, and treatment options) are imbalanced.

Moreover, the association between weight loss and underlying diseases for each patient was not considered. Factors such as heart failure and steroid use could contribute to weight loss. Our data included no patients with a past medical history of heart failure, steroid use, or liver failure. Further studies are needed to confirm the results.

In conclusion, there may be an association between MM prognosis and weight loss of at least 5% within a year, and body weight could potentially serve as an important informative factor for MM survival.

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Figure legends

Table 1. Clinical features of 28 patients in this study

Figure 1. Kaplan-Meier survival curves show MM patients in the weight-loss group and the non-weight-loss group (N = 28). The x-axis indicates the overall survival (months); the y-axis indicates the probability of survival.

Supplemental Figure 1. Kaplan-Meier survival curves show MM patients in the weight-loss group and the non-weight-loss group (N = 28). The x-axis indicates the disease-specific survival (months); the y-axis indicates the probability of survival.

Supplemental Table 1. Clinicopathological features of the 28 patients based on WHO and Clark classifications.

Supplemental Table 2. Association between time to at least 5% weight loss and patient survival.

Table 1. Clinical features of 28 melanoma patients (weight loss at least 5%)

Parameter	Weight loss	Non-weight loss	P-value
Number	19	9	
Mean Age (y, range)	67（34 - 82）	63（54 - 72）	0.2271
Sex (Female : Male)	8:11	3:6	0.7043
Weight (at time of diagnosis, average, kg)	64.1	64.4	> 0.9999
Origin (n)			
Head and neck	1	0	NA
Trunk	1	2	NA
Extremities	14	7	NA
Mucosa	2	0	NA
Unknown	1	0	NA
Stage at diagnosis			0.0744
I	1	1	
II	3	4	
III	13	4	
IV	2	0	
Metastasis in lymph node (n)	12	5	0.3942
TT (mm, median)	5.2	3.2	0.0571
BRAF gene mutation (n)			
positive/negative/not assessed	2/8/9	1/4/4	> 0.9999
LDH (at time of diagnosis, median)	191	189	0.0845
Treatments (n)			
Surgery	17	9	0.5476
ICI	17	2	0.0009
DTIC	5	0	0.0144
IFNβ	8	5	0.6891
DAV-feron	1	0	> 0.9999
Dab+Tra	0	1	> 0.9999

Weight loss: At least 5% weight loss within 12 months
Non-weight loss: Not exceeding 5% body weight within 12 months

Abbreviations: ICI, immune-checkpoint inhibitor; DTIC, dacarbazine; IFNβ, interferon beta; DAV-feron, dacarbazine, nimustine hydrochloride (ACNU), vincristine sulfate and interferon- 9; Dab+Tra, dabrafenib and trametinib

Figure 1. Kaplan-Meier overall survival curves for MM patients with or without body weight loss