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Cancer Cachexia Reduces the Efficacy of Nivolumab Treatment in Patients With Advanced Gastric Cancer

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Abstract. *Background/Aim: Nivolumab is effective against advanced gastric cancer (AGC) refractory to or in patients intolerant of standard chemotherapy. This study was designed to clarify the impact of cancer cachexia in patients with AGC who received nivolumab. Patients and Methods: We recruited AGC patients who were treated with nivolumab from October 2017 to December 2019. Clinical outcomes were compared between patients with and without cancer cachexia at the start of nivolumab. Cancer cachexia was defined as weight loss >5%; weight loss >2% and body mass index (BMI) <20; or sarcopenia and BMI <20. Primary endpoints were median overall survival (OS) and median time to treatment failure (TTF), while secondary endpoints were overall response rate (ORR) and incidence of adverse events. Results: The study enrolled 44 patients. Median OS and TTF were significantly shorter in patients with cancer cachexia than in those without cancer cachexia (OS: 6.6 vs. 2.3 months; HR=2.65; 95%CI=1.28-5.49; p=0.008, TTF: 2.6 vs. 1.9 months; HR=2.17; 95%CI=1.09-4.32, p=0.027). On Cox proportional hazards analysis, cancer cachexia was significantly associated with shorter OS. The incidence of adverse events did not differ between the two groups. Nivolumab was associated with better OS and TTF outcomes in AGC patients without cachexia than in those with cachexia, albeit there was no difference in the incidence of adverse events. Conclusion: Cancer cachexia may be associated with worse clinical outcomes in patients with AGC treated with nivolumab.*

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Gastric cancer is the third-leading cause of cancer-related mortality in the world (1). For patients with advanced gastric cancer (AGC), chemotherapy is the main treatment option. The most common first-line treatment for patients with AGC is combination chemotherapy with a fluoropyrimidine (*e.g.*, fluorouracil, S-1 [tegafur-gimeracil-oteracil potassium], capecitabine) plus a platinum agent (*e.g.*, cisplatin, oxaliplatin) (2-4). S-1 plus docetaxel therapy is also a choice for patients with compromised renal function and those who wish to avoid peripheral neuropathy associated with a platinum agent (5). As second-line treatment for AGC, ramucirumab, an anti-vascular endothelial growth factor receptor 2 (VEGFR-2) antibody, in combination with paclitaxel has been shown to prolong survival (6).

Nivolumab, an immune checkpoint inhibitor, is currently standard chemotherapy for AGC refractory to, or in patients intolerant of, two or more previous regimens of chemotherapy. In their Phase 3 study of nivolumab in 330 patients with AGC, Kang *et al.* reported that the nivolumab group exhibited clinical superiority over the placebo group with respect to overall survival (OS) and progression-free survival (PFS) [OS: 5.26 *vs.* 4.14 months; hazard ratio (HR)=0.63; 95% confidence interval (CI)=0.51-0.8; $p<0.0001$, PFS: 1.61 *vs.* 1.45 months; HR=0.60; 95% CI=0.49-0.75; $p<0.0001$] (7). However, they reported a response rate in patients treated with nivolumab of only about 11.2% and a disease control rate of 40%, with no treatment effect in more than half of these (7). We, therefore, considered that it was necessary to predict which patients would have a satisfactory therapeutic response to nivolumab.

Among recent findings, a poor Eastern Cooperative Oncology Group Performance status (ECOG PS) or steroid use was significantly associated with poor treatment outcomes for immune checkpoint inhibitor therapy in patients with advanced non-small-cell lung cancer (NSCLC) (8, 9), and loss of skeletal muscle mass (sarcopenia) was significantly associated with poor outcome for nivolumab in NSCLC patients (10, 11).

Cancer cachexia results in a poor ECOG PS and induces or exacerbates other risk factors associated with a poor treatment outcome (12). Cancer cachexia is a multifactorial syndrome defined by a continuous decrease in skeletal muscle mass that does not fully recover with conventional nutritional support, and leads to progressive dysfunction (13, 14).

Herein, to evaluate cancer cachexia as a predictor of treatment effect with nivolumab, we investigated the association between the presence of pre-treatment cancer cachexia and treatment efficacy in patients with AGC who received nivolumab.

Patients and Methods

Patients. In this retrospective observational study, the subjects were patients with AGC refractory to, or who were intolerant of, fluoropyrimidine, a platinum agent and paclitaxel who received nivolumab as third-line chemotherapy in our outpatient chemotherapy clinic between October 2017 and December 2019. Efficacy and safety were compared between patients with and without cancer cachexia. Patients were administrated with nivolumab at 240 mg/body or 3 mg/kg.

Data were obtained from electronic medical records in our hospital and analyzed retrospectively. The study was conducted in accordance with the guideline for human studies adopted by the Ethics Committee of Gifu University Graduate School of Medicine and the Japanese Government, and approved by the Medical Review Board of Gifu University Graduate School of Medicine (Institutional review board approval No. 2020-108). Due to the retrospective nature of the study, the need for informed consent from subjects was not mandated.

Assessment of cancer cachexia prior to initiation of nivolumab therapy. Fearon *et al*. defined cancer cachexia is as a multifactorial syndrome characterized by a continuous decrease in skeletal muscle mass (with or without fat loss) that does not fully recover with conventional nutritional support and which leads to progressive dysfunction (13). Based on this definition, we defined cancer cachexia as any of the following conditions based on a comparison with the status 6 months prior to the start of nivolumab: (1) weight loss of more than 5%; (2) BMI less than 20 kg/m2 and weight loss of more than 2%; or (3) sarcopenia and weight loss of more than 2%.

Nishioka *et al*. dichotomized patients with NSCLC who received nivolumab by a rate of change in psoas major muscle area (PMMA) of more than 10% (sarcopenia group) and less than 10% (non-sarcopenia group), and reported that sarcopenia had a significantly negative correlation with the therapeutic effect of nivolumab in patients with NSCLC (10). Accordingly, we defined sarcopenia as a change in PMMA of more than 10% from just prior to the start of nivolumab compared with 6 months before. PMMA was calculated as the sum of areas of the right and left psoas major muscles between the levels of the second and third lumber vertebra. These areas were measured in the region of interest by tracing an outline, using "IBM CIS image viewer".

We also investigated weight loss and the development of sarcopenia, which corresponds to cancer cachexia as previously defined (12), compared to 6 months before the start of nivolumab. Body weight measurements were performed at every administration after the start of nivolumab therapy. Sarcopenia was also measured at every computed tomography (CT) investigation.

Efficacy of chemotherapy. OS and time to treatment failure (TTF) were used as primary indicators of the efficacy of nivolumab, and tumor response rate was used as a secondary indicator. We defined OS as the time from the start of therapy to death. Tumor response was assessed as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) using the patient's computed tomography scan, in accordance with the Response Evaluation Criteria in Solid Tumors guideline version 1.1. (15). Overall response rate (ORR) was defined as CR plus PR, and disease control rate (DCR) as CR+ PR+SD. We defined TTF as the time from the start of therapy to the end of the therapy.

Assessment of adverse events. Adverse events included pneumonitis, colitis, hypothyroidism, adrenal insufficiency, renal dysfunction, pancreatitis, hepatitis, severe skin toxicity and infusion-related reaction. The severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events version 4.0 (16). Incidence rates of adverse events were compared between patients with and without cancer cachexia.

Statistical analyses. All analyses were conducted using IBM SPSS version 22 (IBM Japan Ltd., Tokyo, Japan) and R software version 3.5.1 (www.r-project.org), with *p*-values less than 0.05 considered significant. Patient characteristics were summarized as medians with 25th and 75th percentiles for continuous variables, and frequencies and percentages for categorical variables. For the primary analysis, a Kaplan-Meier estimate and log-rank test were used to assess OS and TTF by development of cancer cachexia. Cox proportional hazards regression was used to evaluate the association between OS and cancer cachexia with adjustment for covariates. These were restricted to three variables to avoid overfitting. Selection was based on clinical judgment and previous research, and included the number of metastatic organs/sites (≥2) (17), Neutrophil-to-lymphocyte ratio (NLR) (18) and the modified Glasgow Prognostic Score (mGPS) (18) owing to their expected strong associations with the outcome and cancer cachexia. To adjust for confounding of these factors and age with cancer cachexia on prolongation of survival, multivariable Cox proportional hazard analysis was performed, with NLR treated as a continuous variable. Categorical variables, such as incidence of adverse events, were compared between patients with and without cancer cachexia using the Chi-squared test.

Results

Patient demographics. A total of 44 AGC patients who received nivolumab were eligible. All enrolled patients had been treated with fluoropyrimidine, a platinum agent and paclitaxel. There were 25 and 19 patients with and without cancer cachexia, respectively (Table I), giving an overall incidence rate of cancer cachexia at the start of nivolumab of 56.8% (25/44). Among the 25 patients with cancer cachexia, (1) weight loss of more than 5%, (2) BMI less than 20 kg/m2 and weight loss of more than 2% and (3) sarcopenia and weight loss of more than 2% accounted for 72% (18/25), 12% (3/25) and 16% (4/25) of patients, respectively.

Table I. *Patient demographics and baseline characteristic of patients who received nivolumab with or without cachexia.*

	With cachexia (n=25)		Without cachexia (n=19)	
Gender (male/female)	13/12		10/9	
Age, median	69.0	44.0-82.0	69.0	42.0-84.0
Height (cm)	160.0	155.5-168.5	158.4	152.3-170.7
Body weight (kg)	49.4	45.4-56.5	46.4	43.4-58.3
Body mass index	19.5	18.1-21.0	18.8	18.5-19.8
Albumin (mg/dl)	3.6	3.2-3.9	3.5	3.3-4.0
Aspartate aminotransferase (IU/l)	27.0	22.0-46.0	32.0	27-47.5
Alanine aminotransferase (IU/l)	14.0	11.0-30.0	30.0	17-35.5
Serum creatinine (mg/dl)	0.71	0.57-0.95	0.72	0.59-0.87
Total bilirubin (mg/dl)	0.5	0.4-0.6	0.5	0.4-0.6
C-reactive protein (CRP, mg/dl)	0.65	0.35-2.38	0.22	0.06-0.96
Neutrophil (/l)	4,900.0	3,400-5,881	3,050.0	2,335-5,181
Lymphocyte (/l)	1,185.0	929-1,609	1,447.0	1,074-1,675.5
White blood cells (/l)	7,550.0	4,920-9,890	5,620.0	4,175-7,880
Hemoglobin (g/dl)	10.8	10-11.4	11.1	10.2-11.9
Platelet (104/l)	20.5	13.1-29.2	20.8	17.0-27.0
Modified Glasgow prognostic score (mGPS, 0/1/2)	15/5/5		14/2/3	
Neutrophil-lymphocyte ratio (NLR)	3.66	2.79-6.99	2.37	1.60-4.11
Carcinoembryonic antigen (CEA, U/ml)	6.1	3.9-69.7	4.4	2.95-7.5
Carbohydrate antigen 19-9 (CA19-9, U/ml)	60.2	12.4-379	42.4	13.1-367.3
Time from start of first-line chemotherapy(months)	18.7	10.8-25.2	15.7	10.7-27.2
Number of metastatic organs/sites (1/≥2)	12/13	8/11		
Metastatic organ				
Liver (%)	5 (20.0%)		5 (26.3%)	
Lung	3 (12%)		3 (15.8%)	
Lymph nodes	8 (32.0%)		7 (36.8%)	
Peritoneum	9 (36.0%)		10 (52.6%)	
Recurrent/Advanced	22/3		8/11	

Data indicate medians with 25th and 75th percentiles or number.

Efficacy of nivolumab between patients with and without cancer cachexia. The relative dose intensity (RDI) of nivolumab in patients with and without cancer cachexia was 0.86 and 1.00, respectively. Median follow-up was 3.51 months [interquartile range (IQR)=2.1-6.6]. Survival analysis for OS and TTF were done at the point at which 34 OS events (77.3%) and 42 TTF events (95.4%) had occurred. For all included patients who received nivolumab, OS and TTF were 3.8 months (95% CI=2.7-5.0) and 2.0 months (95%CI=1.6-2.4), respectively.

Following treatment with nivolumab, median OS and TTF were significantly shorter in patients with cancer cachexia than in those without [OS: 2.3 (95% CI=1.9-4.2) *vs*. 6.6 months (95% CI=3.6-12.6); HR=2.65; 95%CI=1.28-5.49; p=0.008, TTF: 1.8 (95% CI=1.4-2.4) *vs*. 2.6 months (95% CI=1.9-4.2); HR=2.17; 95%CI=1.09-4.32; p=0.027; Figure 1].

On Cox proportional hazards regression, the relationship between cancer cachexia and OS was significant after adjusting for number of metastatic organs/sites (>2), NLR and mGPS (HR=2.34; 95% CI=1.06-5.16; p=0.034, Table II).

One-year survival was slightly but not significantly lower in patients with cancer cachexia than in those without (0% *vs*. 15.7%; p=0.073). There was no significant difference in tumor response rate between the two groups (RR; 8% *vs*. 5.3%; p=1.000, DCR; 28% *vs*. 15.8%; p=0.474; Table III). Post-treatment with nivolumab was performed in 16.6% and 31.5% of patients with and without cachexia, respectively (Table IV).

Incidence of adverse events between patients with and without cancer cachexia. No significant differences in the incidence rates of adverse events, including pneumonitis, colitis, hypothyroidism, adrenal insufficiency, renal dysfunction, pancreatitis, hepatitis, severe skin toxicity and infusion-related reaction, were observed between patients with and without cancer cachexia (Table V).

Overall survival by change in cancer cachexia status during nivolumab treatment. Among the 25 AGC patients with cancer cachexia, 4 showed an improvement in cachexia

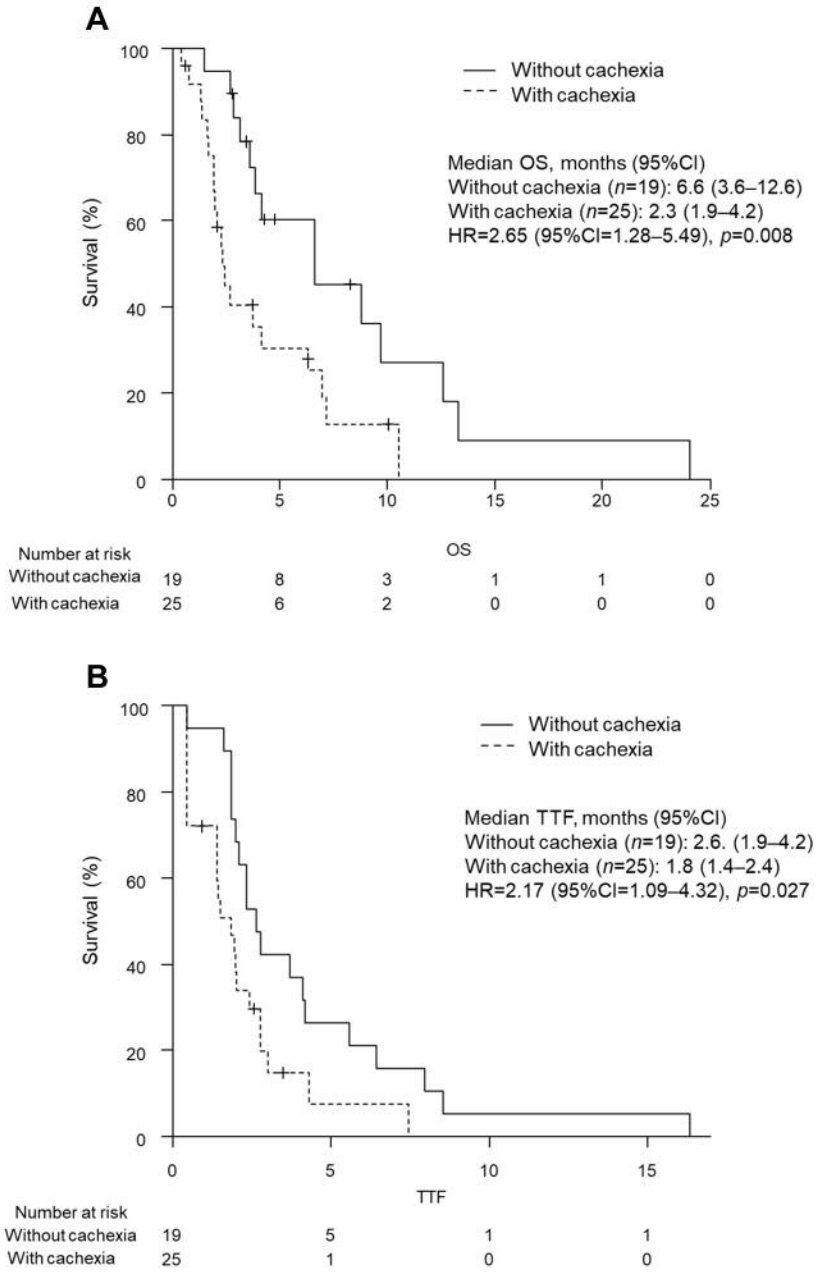

Figure 1. *Kaplan-Meier curves for comparison of overall survival (A) and time to treatment failure (B) in advanced gastric cancer patients who received nivolumab with or without cancer cachexia.*

during nivolumab treatment. In the 19 patients without cancer cachexia, in contrast, 10 developed cachexia during nivolumab treatment.

We compared survival between the following four groups and found the following results (Figure 2): patients without cancer cachexia for the overall period [Group A: 6.6 months; 95% CI=2.7-NA, (NA indicates calculation impossible)], patients who newly developed cancer cachexia during treatment (Group B: 6.6 months; 95% CI=1.5-9.7), patients who had an improvement in cancer cachexia after the start of treatment (Group C: 5.6 months; 95% CI=3.7-NA) and patients who had cancer cachexia throughout the overall period (Group D: 2.3 months; 95% CI=1.7-2.7). Compared to Group A, no significant differences were seen with Group

Table II. *Cox proportional hazard analysis of the risk of overall survival in advanced gastric cancer patients who received nivolumab.*

Factor	HR	95% CI	*p*-Value
With cancer cachexia	2.34	(1.06-5.16)	0.034
Number of metastatic organs/sites (≥2)	0.86	(0.53-1.40)	0.547
Neutrophil-lymphocyte ratio (IQR:2.21-4.85)	0.99	(0.92-1.05)	0.692
Modified Glasgow prognostic score	2.14	(1.21-3.77)	0.009

Hazard ratio (HR), 95% confidence intervals (CI) and interquartile range (IQR) are indicated.

Table III. *Comparison of median time to treatment failure and disease control rate in advanced gastric cancer patients with or without cachexia.*

Effect	With cachexia (n=25)	Without cachexia (n=19)	*p*-Value
Tumor response rate (%)			
Response rate (CR+PR)	8 (2/25)	5.3 (1/19)	1.000[a]
Disease control rate (CR+PR+SD)	28 (7/25)	15.8 (3/19)	0.474[a]
One-year survival (%)	0 (0/25)	15.7 (3/19)	0.073[a]

Data were statistically analyzed by [a]Fisher's exact probability test. CI: Confidence interval; NA: calculation impossible; CR: complete response; PR: partial response; SD: stable disease.

B (HR=1.14; 95% CI=0.38-3.62; p=0.811) and Group C (HR=1.38; 95% CI=0.29-6.53; p=0.682). In contrast, survival was significantly shorter in Group D (HR=3.50; 95% CI=1.45-8.52; p=0.005).

Discussion

In this study of the effect of cancer cachexia on the therapeutic effect of nivolumab in patients with AGC, we found that nivolumab resulted in better OS and TTF in patients without cachexia than in those with cachexia. Further, the incidence of AEs did not differ between the two groups. These findings suggest that avoidance of cachexia does not reduce the therapeutic effect of nivolumab in patients with AGC.

The present study showed that median OS and TTF were significantly shorter in AGC patients with cancer cachexia than in those without this condition (OS: 6.6 *vs*. 2.3 months; p=0.008, TTF: 2.6 *vs*. 1.9 months; p=0.027). In contrast, the incidence of nivolumab-related adverse events did not significantly differ between AGC patients with and without cancer cachexia.

In our study, OS in patients receiving nivolumab was 3.8 months. This finding is inconsistent with the ATRRACTION-02 trial of Kang *et al*. (7), who reported an OS of 5.26 months in 330 patients with unresectable advanced gastric or gastroesophageal cancer receiving nivolumab. However, our findings for TTF (2.0 months) and RR (8.0%) are reasonably consistent with their findings for PFS (1.61 months) and RR (11.2%). This difference in OS might be ascribable to recruitment: the ATRRACTION-02 trial was a Phase 3 clinical trial which limited recruitment to patients with a life expectancy of at least 3 months (7), whereas our present study recruited all patients who received nivolumab in real-world clinical practice, including those in poor general condition. In addition, we considered cachexia as a factor in some patients with poor condition, who are not typically included in clinical trials. Indeed, more than half of our patients had cachexia, while the OS of patients who did not have this condition (6.6 months) was generally similar to that of the nivolumab group (5.26 months) in the ATRRACTION-02 trial (7).

Table IV. *Post-treatment in patients who received nivolumab with or without cancer cachexia.*

	With cachexia (n=25)	Without cachexia (n=19)
Any treatment	16.0% (4/25)	31.5% (6/19)
Irinotecan	4.0% (1/25)	15.8% (3/19)
TAS-102	4.0% (1/25)	10.5% (2/19)
CapeOX or capecitabine	4.0% (1/25)	5.2% (1/19)
Ramucirumab	4.0% (1/25)	0% (0/19)

TAS-102: Trifluridine plus tipiracil hydrochloride, CapeOX: Capecitabine plus oxaliplatin.

Kato *et al*. reported that chemotherapy after progression on anti-PD-(L)1 antibody such as nivolumab could be expected as a favorable efficacy in intensively treated patients with metastatic gastric cancer (19). Although we were also concerned that post-treatment in patients who received nivolumab might affect OS, there was no significant difference in the proportion of patients who received post-treatment after progression on nivolumab between patients with and without cancer cachexia (p=0.286).

Among patients with AGC treated with nivolumab in this study, 56.8% (25/44) had weight loss or sarcopenia leading to a diagnosis of cancer cachexia (13). Pressoir *et al*. reported that 63.2% of patients with upper digestive cancer, including esophagus, stomach and pancreas cancers, and liver carcinoma, had a weight loss of 10% or more at 6 months (20). In addition, upper digestive cancer was independently associated with malnutrition in multivariate analysis (20). Although cancer cachexia is a prognostic factor in gastric cancer patients (21-23), it was associated with the shortening of not only OS, but also TTF in our

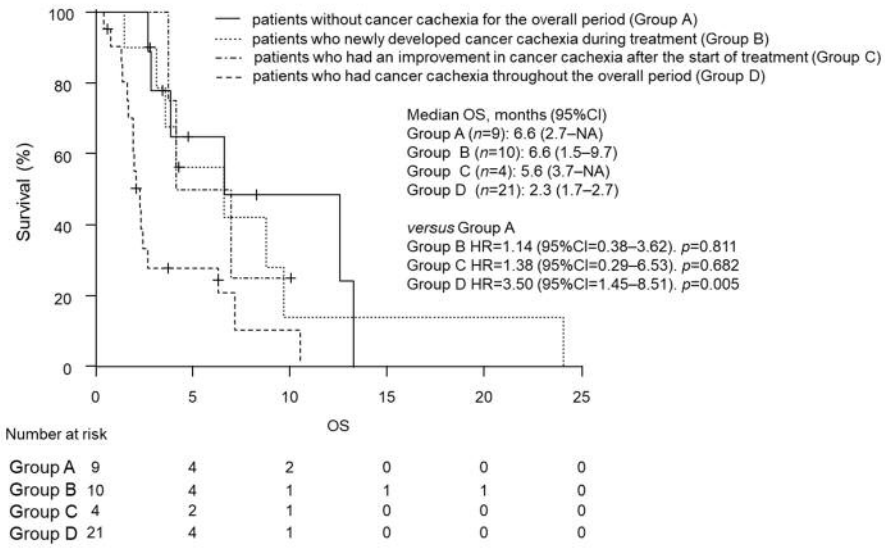

Figure 2. *Kaplan–Meier curves for comparison of overall survival in advanced gastric cancer patients who received nivolumab among four group: patients without cancer cachexia for the overall period (Group A), patients who newly developed cancer cachexia during treatment (Group B), patients who had an improvement in cancer cachexia after the start of treatment (Group C), and patients who had cancer cachexia throughout the overall period (Group D).*

Table V. *Comparison of the incidence of adverse events (≥Grade2) in advanced gastric cancer patients with or without cachexia.*

Adverse Effect	With cachexia (n=25)		Without cachexia (n=19)		*p*-Value
	%	(presence/absence)	%	(presence/absence)	
Pneumonitis	0	(0/25)	0	(0/19)	1
Colitis	0	(0/25)	0	(0/19)	1
Hypothyroidism	12	(3/25)	5.2	(1/19)	0.622
Adrenal insufficiency	0	(0/25)	0	(0/19)	1
Renal dysfunction	8	(2/25)	15.8	(3/19)	0.638
Pancreatitis	0	(0/25)	0	(0/19)	1
Hepatitis	4	(1/25)	10.5	(2/19)	0.57
Severe skin toxicity	4	(1/25)	5.2	(1/19)	1
Infusion-related reaction	0	(0/25)	0	(0/19)	1

Data were statistically analyzed by Fisher's exact probability test.

study. It is possible that the immunostimulatory effects of nivolumab were not sufficient in those of our AGC patients whose immunity was compromised by cancer cachexia.

The European Palliative Care Research Collaborative (EPCRC) classifies cancer cachexia stages as "pre-cancer cachexia", "cachexia", and "refractory cachexia" (13). The definition we used in our present study is "cachexia". Treatment of "refractory cachexia" in the advanced stage is difficult, and early diagnosis and intervention in the pre-challenged stage are important. It is considered that preventing the exacerbation of "pre-cancer cachexia" to "cachexia" may enhance the therapeutic effect of nivolumab.

The metabolic changes associated with cancer cachexia may down-regulate anti-tumor immunity. Cancer cells induce pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1, resulting in weight loss due to degradation of skeletal muscle and adipose tissue and anorexia (13, 24). IL-6 is an important mediator in the human defense mechanism which acts by regulating the immune response via signaling through a cell-surface type I cytokine receptor complex (25). For example, Flint *et al*. found that tumor-induced IL-6 inhibits hepatic ketone body formation, and that this inhibition causes marked glucocorticoid secretion during caloric deficiency (26). Furthermore, they reported that this stress-induced hormonal

response suppressed intra-tumoral immunity and caused the failure of anticancer immunotherapy (26).

For cancer cachexia, both pharmacological and non-pharmacological treatments are available. Among pharmacological treatment, corticosteroids, non-steroidal anti-inflammatory drugs and progesterone have been reported to be effective (27-29). However, these treatments are associated with adverse events such as infection and gastrointestinal bleeding (27-29). Anamorelin, an orally active, high-affinity, selective ghrelin receptor agonist, was shown to significantly increase lean body mass, but not handgrip strength, in patients with advanced non-small-cell lung cancer (30). Non-pharmacological treatments include dietary treatment (31) and physical exercise (32). However, physical exercise is problematic in that many patients with advanced cancer drop out (33). In addition, interventions limited to pharmacological treatment or dietary treatment only have been shown to be not fully effective (12, 34-35), and it is therefore necessary to combine pharmacological treatment with dietary treatment and physical exercise.

Cancer cachexia has been reported to increase the incidence of cytotoxic chemotherapy-related adverse events associated with chemotherapy (36). However, the decrease in immunity due to cancer cachexia may suppress not only the effect of nivolumab but also the occurrence of immune-related adverse events. This effect may explain the lack of difference in the incidence of immune-related adverse events between patients with and without cancer cachexia in our study.

Our study had several limitations. First, the survey was conducted under a retrospective design at a single Center. Second, the confounding factors may have been poorly considered given that the sample size was small and the number of factors included in the multivariable analysis was limited to avoid overfitting. Our results, therefore, require confirmation in a large prospective study. Third, we could not obtain PS data, and were thus unable to fully consider the confounding of cachexia and PS.

In conclusion, cancer cachexia is associated with a poor clinical outcome in gastric cancer patients using nivolumab and may be useful in determining treatment indications. Early intervention for improving cancer cachexia is suggested to be important for successful nivolumab treatment and should be considered in the future.

Conflicts of Interest

Kazuhiro Yoshida has received honoraria for lectures from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Eli Lilly and Company, Yakult Honsha Co., Ltd., Merck Sharp & Dohme Co., Ltd., Daiichi Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., Johnson & Johnson Co., Ltd., Covidien Co., Ltd., Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Sanofi K.K., Nippon Kayaku Co., Ltd., Asahi Kasei Co., Ltd., Tsumura Co., Ltd., EA Pharma Co., Ltd., Bayer Yakuhin Co., Ltd., Olympus Co., Ltd., Terumo Co., Ltd., Bristol-Myers Squibb Co., Ltd., Denka Co., Ltd., Teijin Co., Ltd., SBI Pharmaceuticals Co., Ltd., Intuitive Surgical Co., Ltd., Novartis Pharma K.K., and Pfizer Inc.; and research funding from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Eli Lilly and Company, Yakult Honsha Co., Ltd., Merck Sharp & Dohme Co., Ltd., Daiichi Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., Johnson & Johnson Co., Ltd., Covidien Co., Ltd., Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Sanofi K.K., Nippon Kayaku Co., Ltd., Asahi Kasei Co., Ltd., Tsumura Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Astellas Pharma Co., Ltd., Toyama Chemical Co., Ltd., Kinetic Concepts Co., Ltd., Abbott Japan Co., Ltd., and Toray Industries, Co., Ltd. outside the submitted work. Akitaka Makiyama has received honoraria for lectures from Eli Lilly and Company., Taiho Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Co., Ltd. The other authors have no conflicts of interest.

Authors' Contributions

Hironori Fujii and Hirotoshi Iihara conceptualized this study. Hironori Fujii, Senri Yamamoto and Takeharu Imai acquired the clinical data. Akitaka Makiyama, Hirotoshi Iihara, Naoki Okumura, Shinichiro Arakawa, Ryo Kobayashi, Yoshihiro Tanaka, Kazuhiro Yoshida and Akio Suzuki were responsible for the data interpretation. Hironori Fujii and Akitaka Makiyama drafted the manuscript. All Authors have read and approved the current version of the manuscript.

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