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ORIGINAL ARTICLE

Obesity is a predictive biomarker of poor benefit from single-agent bevacizumab therapy in recurrent ovarian cancer patients

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Summary

Purpose: *Bevacizumab, an anti-angiogenic agent targeting vascular endothelial growth factor (VEGF), is widely used for the treatment of ovarian cancer. However, no predictive biomarkers of clinical outcome for bevacizumab therapy have been identified. Adipose tissue secretes various growth factors, including VEGF, which may neutralize bevacizumab and attenuate its effects. Therefore, we evaluated whether obesity is a predictive biomarker of clinical outcome in ovarian cancer patients treated with single-agent bevacizumab.*

Methods: *Thirty patients with recurrent ovarian cancer treated with single-agent bevacizumab were studied. Body mass index (BMI) and visceral fat area (VFA) were measured to assess the presence of obesity. VFA was measured using computed tomography volume-analyzing software. The association of BMI and VFA with clinical outcomes were evaluated.*

Results: *High BMI and high VFA were significantly correlated with progressive disease (p=0.0195 and p=0.0352, respectively). A significant correlation was identified between high BMI and progressive disease in multivariate analysis (p=0.0459). Furthermore, there was a trend toward shorter progression-free survival and a significant shortening of overall survival in high-BMI patients compared with low-BMI patients (p=0.101 and p=0.0417, respectively).*

Conclusions: *This study demonstrated that obesity is a predictive biomarker of poor benefit from single-agent bevacizumab therapy in recurrent ovarian cancer patients. Obesity may be a useful benchmark for the administration of bevacizumab in daily clinical practice.*

Key words: *bevacizumab, obesity, ovarian cancer, predictive biomarker*

Introduction

Angiogenesis is known to play an important role in the growth and metastasis of ovarian cancer. Bevacizumab, an anti-angiogenic agent targeting vascular endothelial growth factor (VEGF), was shown to be effective in ovarian cancer in several randomized phase 3 trials [1-3] and is currently used for the initial and recurrent treatment of ovarian cancer. Nonetheless, only some patient populations respond and the overall clinical efficacy is limited. In addition, bevacizumab has been associated with a significant side effect profile, including hypertension, nephrotoxicity, bleeding, wound healing complications, gastrointestinal perforation, and thromboembolic events [4]. Therefore, it is necessary to select patients who are expected to benefit from bevacizumab. However, to date, no predictive biomarker has been identified that accurately estimates the efficacy of bevacizumab in ovarian cancer patients.

Adipose tissue has been reported to secrete a various of growth factors, including VEGF [5-7]. It is speculated that VEGF secreted by adipose tissue

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binds and neutralizes the VEGF inhibitor bevacizumab and attenuates its effects. Therefore, the presence or absence of obesity may be a potential predictive biomarker for bevacizumab efficacy. Obesity can be assessed in several ways, such as body mass index (BMI) or visceral fat area (VFA) [8,9]. Therefore, the association between BMI or VFA and bevacizumab efficacy has been investigated in a variety of cancer types [10,11]. Artac et al showed that patients with a higher BMI had significantly shorter progression-free survival (PFS) than those with a lower BMI in metastatic colorectal cancer treated with bevacizumab combination therapy [10]. In addition, Ladoire et al reported in a study of metastatic renal cancer treated with anti-angiogenic agents, including bevacizumab, that patients with a higher VFA had shorter time to progression and overall survival (OS) than those with a lower VFA [11]. These studies suggest that obesity may be a predictive biomarker for bevacizumab efficacy. However, few reports have examined the association between obesity and the efficacy of bevacizumab in ovarian cancer, and it is currently unclear whether obesity is a predictive biomarker for bevacizumab therapy in patients with ovarian cancer. Therefore, in this study, we examined whether BMI and VFA could be predictive biomarkers for single-agent bevacizumab therapy in ovarian cancer.

Methods

Patients

This retrospective study enrolled 30 patients with recurrent ovarian cancer who were treated between May 2014 and February 2019. This study was approved by the ethics committee of Saitama Medical University International Medical Center, and informed consent was obtained from all patients prior to the procedures. All procedures were in accordance with the ethical standards of the institutional research committee and with the 1975 Helsinki declaration and its later amendments. The International Federation of Gynecology and Obstetrics (FIGO) system was used for the staging of each patient [12]. The eligibilities of the patients were as follows: histologically confirmed ovarian cancer that relapsed after at least one previous line of platinum-based chemotherapy; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2; and adequate baseline hematological, liver, and renal functions. Patients were excluded from this study if they had a history of gastrointestinal perforation or fistula, or evidence of bowel obstruction. Patients were also excluded if the surgery was performed within 28 days of bevacizumab treatment.

Treatment and response evaluation

Bevacizumab (15 mg/kg) was administered intravenously to enrolled patients every 21 days. At the first cycle, bevacizumab was administered for 90 min, after which the duration of the infusion was shortened to 30–60 min if no significant adverse events were observed. Bevacizumab treatment was discontinued if there was progressive disease or toxicity that required interruption of the bevacizumab treatment. The tumor responses to bevacizumab treatment was assessed every two or three cycles by computed tomography (CT) according to the Response Evaluation Criteria in Solid Tumors (RECIST) [13]. The best response was considered for the response evaluation. Disease control was defined as the sum of complete response, partial response, and stable disease.

Evaluation of BMI and VFA

BMI values were calculated just before the initiation of bevacizumab treatment by dividing weight in kilograms by the square of the height in meters. High BMI (H-BMI) was defined as a value of ≥25 kg/m^2, and low BMI (L-BMI) was <25 kg/m^2, according to the criteria for obesity as established by the Japan Society for the Study of Obesity [14]. CT scans were undertaken just before the initiation of bevacizumab treatment and were analyzed by the Volume Analyzer SYNAPSE VINCENT 3D image analysis system (FUJIFILM Medical, Tokyo, Japan) for measuring the VFA. VFA was calculated using the axial cross-sectional area in cm^2 of the visceral compartments at the navel level with pixel attenuation restricted to −140 to −40 Hounsfield units [9].

Statistics

Chi-square test or Fisher's exact test were used to evaluate the categorical variables, as appropriate for the category size. We performed multivariate logistic regression analysis to estimate the odds ratio for the progressive disease adjusting for the potential baseline confounders of stage (I/II vs. III/IV), histology (serous vs. non-serous), and platinum sensitivity status (sensitive vs. resistant). PFS and OS were evaluated using Kaplan-Meier curves. PFS was defined as the time from the first day of bevacizumab treatment to the first recorded evidence of progression or death from any cause. For patients without progression, survivors were censored at the last follow-up and non-survivors without progression were censored at the date of death. OS was defined as the time from the date of the initial bevacizumab treatment to any cause of death. Survivors were censored at the last follow-up. Survival between the different groups was compared using a generalized Wilcoxon test. $P < 0.05$ was used to determine significant differences. All analyses were performed using JMP software package v13.0 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Table 1 shows the clinical profile of the patients. The mean age was 58.5 years and PS was 0 in 90% of cases. Eighty percent of the patients were at stage 3 or 4, and the histology was serous in 56.7% of the cases. In terms of platinum-sensitivity status, 13.3% of the patients were platinum-

sensitive (cancer that progressed ≥ 6 months after platinum-based chemotherapy) and 86.7% were platinum-resistant (those progressing < 6 months after platinum-based chemotherapy). Seventy percent of the patients had L-BMI and 30% had H-BMI. The mean VFA of the patients was 59.3 cm^2.

Table 1. Patient characteristics

	n (%)
Age (years, mean ± SD)	58.5 ± 8.76
ECOG PS	
0	27 (90)
1/2	3 (10)
Stage	
I/II	6 (20)
III/IV	24 (80)
Histology	
Serous	17 (56.7)
Other	13 (43.3)
Platinum-sensitivity status	
Sensitive	4 (13.3
Resistant	26 (86.7)
BMI (kg/m^2)	
L-BMI	21 (70)
H-BMI	9 (30)
VFA (cm^2, mean ± SD)	

SD: standard deviation; ECOG PS: Eastern Cooperative Oncology Group performance status; BMI: body mass index; L-BMI: low body mass index; H-BMI: high body mass index; VFA: visceral fat area

Tumor response and predictors of progressive disease

Table 2 shows the tumor response to single-agent bevacizumab therapy; there were no patients with complete or partial response, while 25 had stable disease, and 5 had progressive disease. Disease control was evident in 83.3% of patients. The correlations between various clinicopathological factors and progressive disease are shown in Table 3. There was no significant correlation between age, PS, stage, histology, or platinum-sensitivity status and progressive disease. With respect to BMI, 80% of H-BMI cases and 20% of L-BMI cases had progressive disease, and there was a significant correlation between BMI and progressive disease (p=0.0195). VFA was 85.8 cm^2 in patients with progressive disease and 54.0 cm2 in patients with disease control, showing a significant correlation between VFA and progressive disease (p=0.0352). Multivariate logistic regression analysis revealed a significant correlation between H-BMI and pro-

Table 2. Best overall response to bevacizumab

Response	*n=30* *n (%)*
Complete response	0 (0)
Partial response	0 (0)
Stable disease	25 (83.3)
Progressive disease	5 (16.7)

Table 3. Patient characteristics and progressive disease

	Disease control[a] *(n=25)* *n (%)*	*Progressive disease (n=5)* *n (%)*	*p value*
Age (years, mean ± SD)	58.9 ± 8.97	56.2 ± 8.14	0.536
ECOG PS			> 0.99
0	22 (88)	5 (100)	
1/2	3 (12)	0 (0)	
Stage			> 0.99
I/II	5 (20)	1 (20)	
III/IV	20 (80)	4 (80)	
Histology			> 0.99
Serous	14 (56)	3 (60)	
Others	11 (44)	2 (40)	
Platinum-sensitivity status			> 0.99
Sensitive	4 (16)	0 (0)	
Resistant	21 (84)	5 (100)	
BMI (kg/m^2)			0.0195
L-BMI	20 (80)	1 (20)	
H-BMI	5 (20)	4 (80)	
VFA (cm^2, mean ± SD)	54.0 ± 29.0	85.8 ± 30.9	0.0352

SD: standard deviation; ECOG PS: Eastern Cooperative Oncology Group performance status; BMI: body mass index; L-BMI: low body mass index; H-BMI: high body mass index; VFA: visceral fat area
[a]Evaluated by RECIST v 4.0. Complete response + partial response + stable disease

gressive disease (odds ratio=22.58; 95% confidence interval=1.059-481.6; p=0.0459) (Table 4).

BMI and survival

The relationship between BMI and survival is shown in Figure 1. There was a trend toward shorter PFS in H-BMI patients compared with L-BMI patients (median survival time (MST) 5 months vs. 8 months; p=0.101) (Figure 1A). There was a significant shortening of OS in the H-BMI cases compared with the L-BMI cases (MST 8 months vs. 18 months; p=0.0417) (Figure 1B).

Discussion

In this study, we showed that obese ovarian cancer patients treated with single-agent bevacizumab therapy had lower tumor response and poorer prognosis. These results suggest that obesity may be a potential predictive biomarker for bevacizumab therapy in ovarian cancer patients.

In the current study, significantly more obese patients showed progressive disease on single-agent bevacizumab therapy compared with non-obese patients. Because adipose tissue secretes VEGF, serum VEGF in obese patients is higher than in non-obese patients [5-7]. The result of our study may be due to the neutralization of bevacizumab by serum VEGF secreted from adipose tissue. In fact, Guiu et al reported similar results in a study in patients with colorectal cancer treated with bevacizumab. In this study, high BMI, high VFA and high subcutaneous fat area were significantly associated with reduced tumor response to bevacizumab [15]. However, only a few reports have examined the relationship between obesity and the tumor response to bevacizumab. To our knowledge, our study is the first report to show that the tumor response to bevacizumab therapy is lower in obese patients with ovarian cancer.

In our study, the survival prognosis of recurrent ovarian cancer after bevacizumab therapy was shown to be poor in obese patients. Previous studies in ovarian cancer patients have reported similar results [5,16]; Slaughter et al studied patients with ovarian cancer who received bevacizumab combination therapy as first-line treatment and found that patients with a higher BMI had a significantly shorter PFS compared with patients with a lower BMI [5]. In addition, a study analyzing patients who participated in the GOG218 study reported that patients with a lower BMI and VFA tended to have a better prognosis [1,16]. However, these previous reports in ovarian cancer have evaluated patients treated with bevacizumab in combination with other anticancer agents, such as carboplatin,

Table 4. Multivariate analyses of the association between patients' characteristics and progressive disease

Variables	*Odds ratio*	*95% CI*	*p value*
BMI (kg/m^2, H-BMI/L-BMI)	22.58	1.059-481.6	0.0459
VFA (cm^2, continuous)	1.024	0.974-1.075	0.353

CI: confidence interval; BMI: body mass index; L-BMI: low body mass index; H-BMI: high body mass index; VFA: visceral fat area
Multivariate analyses adjusted for stage, histology, and platinum sensitivity status

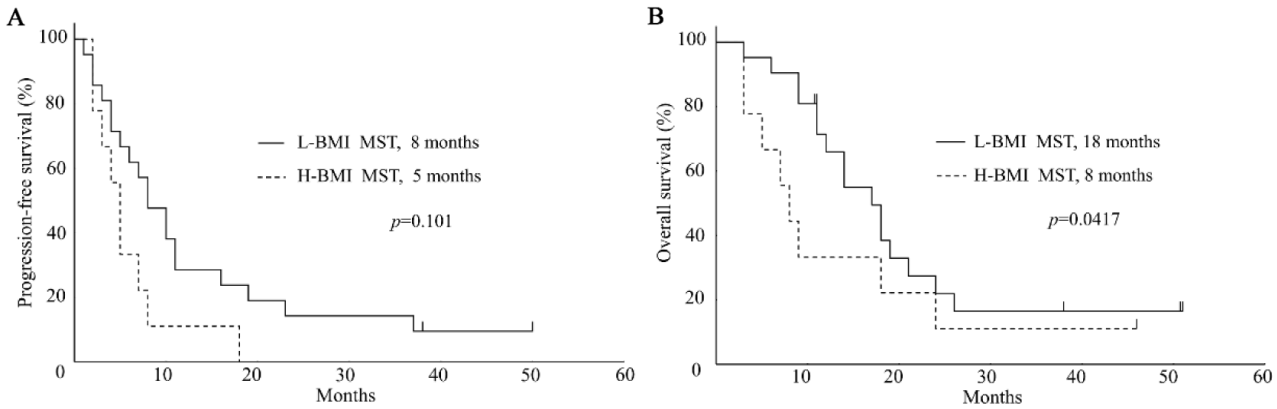

Figure 1. Kaplan–Meier curves of progression-free **(A)** and overall survival **(B)**. There was a trend toward shorter progression-free survival in H-BMI patients compared with L-BMI patients (MST 5 months vs. 8 months; p=0.101). There was a significant shortening of overall survival in H-BMI patients compared with L-BMI patients (MST 8 months vs. 18 months; p=0.0417). H-BMI: high BMI; L-BMI: low BMI; MST: median survival time.

rather than single-agent bevacizumab. Therefore, the results of previous reports do not exclude the effects of obesity on anticancer agents other than bevacizumab. In fact, Wright et al reported that among ovarian cancer patients who received carboplatin-containing chemotherapy, obese patients tended to show a higher occurrence of disease progression [17]. Furthermore, it has been reported that adipose tissue secretes angiopoietin-like 4, which causes carboplatin resistance in ovarian cancer [18]. Unlike previous studies, we evaluated the patients treated with bevacizumab which is not combined with other anticancer agents, such as carboplatin. Therefore, we believe that our study assesses more accurately the association between obesity and the effects of bevacizumab in ovarian cancer.

There are several limitations to this study. It was a retrospective study and the number of cases was relatively small. In addition, the activity of single-agent bevacizumab therapy in patients with recurrent ovarian cancer has not been fully confirmed. Although several reports have shown the efficacy of single-agent bevacizumab therapy in recurrent ovarian cancer [19-21], further studies are necessary to confirm this activity in this patient population. Therefore, in this study, single-agent bevacizumab was administered with a full explanation and consent to patients who refused or were unable to receive other anticancer agents due to potential adverse events.

In this study, we have shown that obesity may be a predictive biomarker for the tumor response and prognosis of bevacizumab therapy for ovarian cancer. In recent years, the efficacy of PARP inhibitors and immunotherapies for ovarian cancer has been demonstrated, and thus the number of treatment options for ovarian cancer is increasing [22], making it difficult for gynecologists to determine which treatment approach is most suitable for ovarian cancer patients in clinical practice. Therefore, being able to predict which ovarian cancer patients will respond to bevacizumab would be helpful in selecting the most appropriate treatment for patients. Our study suggests that obesity may become an important selection criterion in choosing bevacizumab therapy for patients with ovarian cancer. In addition, BMI and VFA may be useful as predictive biomarkers because they are non-invasive, easy to measure, and inexpensive. Future prospective studies with larger numbers of patients are required.

Conflict of interest

Keiichi Fujiwara has received research grants and a speaker honorarium from Chugai-Roche. All other authors declare that they have no conflict of interest.

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