Prevalence and profiles of ramucirumab-associated severe ascites in patients with hepatocellular carcinoma

NAOKI KAMACHI[1], SHIGEO SHIMOSE[1], KEISUKE HIROTA[2], SHUNJI KOYA[2], HIDEKI IWAMOTO[1], TAKASHI NIIZEKI[1], TOMOTAKE SHIRONO[1], MASAHITO NAKANO[1], RYUKI HASHIDA[2,3], TAKUMI KAWAGUCHI[1], HIROO MATUSE[2], KAZUNORI NOGUCHI[4], HIRONORI KOGA[1] and TAKUJI TORIMURA[1]

[1]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine; [2]Division of Rehabilitation, Kurume University Hospital; [3]Department of Orthopedics, Kurume University School of Medicine, Kurume, Fukuoka 830-0011; [4]Department of Gastroenterology and Hepatology, Omuta City Hospital, Omuta, Fukuoka 832-0077, Japan

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Abstract. Severe ascites is an adverse event of ramucirumab (RAM), a second-line treatment for hepatocellular carcinoma (HCC). Ascites can be associated with various factors, including nutritional status and muscle quality. The aim of the present study was to investigate the prevalence and profiles of RAM-associated severe ascites in patients with HCC. This retrospective study enrolled 14 consecutive patients with HCC treated with RAM (median age, 72 years; Barcelona Clinic Liver Cancer stage B/C, 6/8). Nutritional status and muscle quality were evaluated using the controlling nutritional status (CONUT) score and intramuscular adipose tissue (IMAT) content, respectively. Factors associated with severe ascites were evaluated using decision-tree analysis. The median progression-free survival (PFS) time was 2.1 months, and the overall objective response and disease control rates were 14 and 50%, respectively. Severe ascites developed in 57.1% of the patients, and the median onset was 37.5 days (range, 14-61 days) after initiation of RAM treatment. In the decision-tree analysis, the CONUT score and IMAT content were the first and second splitting variables for the development of severe ascites. In patients with a CONUT score ≥5 and IMAT <-0.54, the prevalence of severe ascites was 80 and 100%, respectively. A high incidence of severe ascites was observed in patients treated with RAM. A CONUT score ≥5 and an IMAT <-0.54 were associated with severe ascites. Thus, caution must be taken for severe ascites in patients with HCC treated with RAM, in particular patients with malnutrition and fat infiltration in muscle.

Correspondence to: Dr Shigeo Shimose, Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan
E-mail: shimose_shigeo@med.kurume-u.ac.jp

Abbreviations: HCC, hepatocellular carcinoma; MTA, molecular targeted agent; RAM, ramucirumab; AFP, α-fetoprotein; VEGF; vascular endothelial growth factor; PFS, progression-free survival; CONUT, Controlling Nutritional Status; IMAT, intramuscular adipose tissue; ALBI, albumin-bilirubin; CT, computed tomography; AE, adverse event; LEN, lenvatinib

Key words: AE, hepatoma, malnutrition, RAM, severe ascites

Introduction

Hepatocellular carcinoma (HCC) is a common malignancy and one of the major leading causes of cancer deaths worldwide (1) Patients with unresectable HCC show poor prognoses (2) Systemic chemotherapy is a treatment strategy for unresectable HCC. Molecular targeted agents (MTAs), such as sorafenib (SORA), regorafenib (REGO), and lenvatinib (LEN), are available for the treatment of unresectable HCC (3-5). Ramucirumab (RAM), an MTA, has recently been approved for second-line treatment of unresectable HCC patients with a baseline α-fetoprotein (AFP) concentration ≥400 ng/ml (6).

RAM is a human immunoglobulin G1 (IgG1) monoclonal antibody that inhibits ligand activation of vascular endothelial growth factor (VEGF) receptor 2. In a phase 3 trial (REACH-2 trial) involving unresectable HCC patients, RAM significantly improved progression-free survival (PFS) and overall survival relative to placebo (6) However, in the REACH-1 trial, more than 5% of the patients treated with RAM suffered grade ≥3 treatment-emergent adverse events (AEs), including ascites. Moreover, according to the REACH-2 trial, patients with Child-Pugh scores of 7 and 8 showed a higher incidence of RAM-related grade 3 ascites than those with Child-Pugh scores of 5 or 6 (7).

The development of ascites in patients with HCC is associated with various factors, including malnutrition (8) The controlling nutritional status (CONUT) score is a nutritional index consisting of three parameters: Serum albumin level, total cholesterol level, and lymphocyte count (9) CONUT is superior than other nutritional assessment tools such as the Nutrition Risk Screening-2002 and subjective global assessment to predict infectious complication in patients with

digestive diseases (10). In addition, the CONUT score was reported to predict the development of ascites in patients with HCC (11) While, intramuscular adipose tissue (IMAT) content is a method for the quantification of fatty infiltration in skeletal muscles (12) IMAT is reported to be an independent risk factor for mortality in patients with HCC (13) IMAT was also reported to be significantly associated with liver dysfunction and the prognosis of HCC patients who underwent hepatectomy (14).

The aim of this study was to investigate patient profiles, including the CONUT score and IMAT content, associated with the development of RAM-related ascites in patients with HCC.

Materials and methods

Study design. This retrospective study was conducted at the Kurume University Hospital and Omuta City Hospital. The protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committees of the Kurume University School of Medicine (approval no. 19203). An opt-out approach was employed to obtain informed consent from the patients, and personal information was protected during data collection.

Inclusion and exclusion criteria. The patient inclusion criteria for this study were as follows: i) diagnosis of unresectable HCC according to the Barcelona Clinic Liver Cancer (BCLC) staging system (15); ii) age ≥18 years; iii) Eastern Cooperative Oncology Group performance status 0; iv) history of pretreatment with MTAs; and v) completion of follow-up until death or study cessation (August 30, 2020). The patient exclusion criteria were as follows: i) history of a malignant tumor other than HCC in the 5 years preceding the study; ii) participation in any clinical trial; iii) Child-Pugh class C; iv) creatinine >1.5 mg/dl; v) chronic heart failure; vi) infiltrative HCC; vii) presence of ascites; viii) esophageal varices with a high risk of rupture; and ix) history of liver transplantation.

Patients. A total of 16 consecutive HCC patients who received RAM treatment between September 19, 2019 and July 31, 2020 were registered. The data cutoff date for this analysis was August 31, 2020. Patients meeting any of the exclusion criteria were excluded from the analysis (n=2). Thus, a total of 14 patients were enrolled in the study.

Assessment of nutritional status and liver function. CONUT score, used to assess nutritional status, was calculated from serum albumin level, total cholesterol level, and lymphocyte count, as previously described (9) Albumin concentrations of ≥3.5, 3.0-3.49, 2.5-2.99, and <2.5 g/dl were scored as 0, 2, 4 and 6 points, respectively. Total lymphocyte counts of ≥1,600, 1,200-1,599, 800-1,199, and <800/μl were scored as 0, 1, 2 and 3 points, respectively. Total cholesterol concentrations of ≥180, 140-179, 100-139 and <100 mg/dl were scored as 0, 1, 2 and 3 points, respectively. Liver function was evaluated using the albumin-bilirubin (ALBI) score, as previously described (16) It based on serum albumin and total bilirubin levels; ALBI-score = [log10 bilirubin (μmol /l) x 0.66] + [albumin (g/l) x -0.085], and was graded as following: ≤-2.60 = ALBI grade 1, >-2.60 to ≤-1.39 = ALBI grade 2, >-1.39 = ALBI grade 3).

Evaluation of skeletal muscle index. The skeletal muscle index (SMI) was evaluated at the third lumbar vertebra level on computed tomography (CT) scans, which were obtained as part of the HCC assessment (17) SMI were calculated by normalizing the L3 skeletal muscle areas by the square of the height (m^2) (18). The targets of measurement were psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis. The measurement was performed by two government-certified physical therapists (S.K. and K.H.) who were blinded to the patients' information. This analysis was performed using diagnostic software ImageJ Version 1.50 software (National Institutes of Health) (19).

Evaluation of visceral fat area (VFA). We measured VFA using diagnostic CT scans at the umbilical level, as previously described (20) CT scanning was performed for HCC evaluation. The measurement was performed by two government-certified physical therapists (S.K. and K.H.) who were blinded to the patients' information. The VFA was also measured by the diagnostic software ImageJ Version 1.50 software (National Institutes of Health) (19).

Evaluation of IMAT. Muscle quality was evaluated by measuring the IMAT content. The IMAT was calculated as the psoas muscle-to-subcutaneous fat attenuation ratio using diagnostic CT scans at the umbilical level as previously described (21) A higher IMAT indicates a greater amount of adipose tissue within the skeletal muscle (22) The SMI, VFA, and IMAT were measured by two government-certified physical therapists (S.K. and K.H.) who were blinded to patient information.

Diagnosis of HCC. HCC was diagnosed using a combination of tests for serum tumor markers, such as AFP and des-γ-carboxy prothrombin (DCP), and imaging procedures, such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). HCC was classified using the BCLC staging system (15).

Treatment with RAM and evaluation of therapeutic response. RAM was intravenously injected at a dose of 8 mg/kg once every 2 weeks. Therapeutic response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (23), using dynamic CT or magnetic resonance imaging. The evaluation was conducted 4-6 weeks after initiation of treatment with RAM, and thereafter, at intervals of 2-3 months until death or study cessation.

Assessment of AEs and ascites. AEs and ascites were assessed every month after the initiation of RAM treatment. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Definition of severe ascites. Ascites were assessed by ultrasonography and CT scan images. Severe ascites were defined as diuretic-resistant ascites.

Statistical analysis. All data are expressed as frequency or median (range). All statistical analyses were performed using

Table I. Clinicopathological characteristics of patients with hepatocellular carcinoma (n=14).

Characteristic	Value
Median age (range), years	72.5 (36-87)
Sex, female/male	4/10
Median body mass index (range)	20.7 (16.4-24.2)
Etiology, HBV/HCV/others	4/5/5
Child-Pugh class, A/B	11/3
Median total cholesterol (range), mg/dl	166 (135-254)
Median ALBI score (range)	-2.19 (-2.74 - -1.65)
Modified ALBI grade, 1/2a/2b/3	1/6/7/0
Controlling nutritional status score	
0-1 (normal)	3
2-4 (mild)	6
5-8 (moderate)	5
≥9 (severe)	0
Median tumor diameter (range), mm	47.8 (11.0-132.0)
Number of tumors, <5/≥5	1/13
Barcelona clinic liver cancer stage, B/C	6/8
Macroscopic portal vein invasion, yes/no	2/12
Extrahepatic metastasis, yes/no	8/6
Median α-fetoprotein (range), ng/ml	5,917 (906-612,770)
Median des-γ-carboxy prothrombin (range), mAU/ml	2,035 (22-292,689)
Intramuscular adipose tissue	-0.51 (-0.72 - -0.38)
Median visceral fat mass (range), cm^2	79.92 (24.5-162.3)
Muscle atrophy, yes/no	11/5
Prior treatment with molecular targeted agents, SORA/SORA+LEN/LEN	4/5/5
Diuretic, +/-	8/6
Median follow-up duration (range), months	4.5 (1.3-11.5)

HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI, albumin-bilirubin; SORA; sorafenib; LEN, lenvatinib.

JMP Pro, version 14 (SAS Institute Inc.). PFS was calculated using the Kaplan-Meier method and analyzed using the log-rank test. We also performed decision tree analysis to identify factors associated with severe ascites, as previously described (24).

Results

Patient characteristics. Patient profiles are summarized in Table I. The median patient age was 72.5 years, and 28.5% of the patients were female. The median body mass index (BMI) was 20.7 kg/m^2, and 78.6% of patients (11/14) showed Child-Pugh class A. ALBI grade 2 was observed in 92.3% of the patients, and ALBI 2a was observed in 42.9%. The frequencies of CONUT scores of 0-1 (normal nutrition), 2-4 (mild malnutrition), 5-8 (moderate malnutrition), and ≥9 (severe malnutrition) were 21.4, 42.9, 35.7 and 0.0%, respectively (Table I). BCLC stage B HCC was seen in 42.8% of the patients. The median IMAT and VFA were -0.51 and 79.92 cm^2, respectively. Prior treatment with sorafenib (SORA), SORA+LEN, and LEN was seen in 28.6 (4/14), 35.7 (5/14), and 35.7% (5/14) of the patients, respectively. The median observation period was 4.5 months (1.3-11.5 months) (Table I).

Table II. Treatment response rate to ramucirumab in patients with hepatocellular carcinoma (n=14).

Response	N (%)
Complete response	0 (0)
Partial response	2 (14)
Stable disease	5 (36)
Progressive disease	7 (50)
Objective response rate	2 (14)
Disease control rate	7 (50)

Evaluation of treatment response and PFS. The therapeutic responses to RAM are shown in Table II. Complete response, partial response, stable disease, and progressive disease were observed in 0, 14, 36 and 50% of the patients, respectively (Table II). The overall objective response rate and disease control rate were 14 and 50%, respectively (Table II). The median PFS time was 2.1 months (Fig. 1).

AEs of RAM. AEs determined by the attending physician are shown in Table III. Ascites was the most frequent AE and was

Table III. Adverse events associated with ramucirumab treatment in patients with hepatocellular carcinoma (n=14).

Adverse event	Any, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade ≥3, n (%)
Ascites	8 (57.1)	0 (0.0)	2 (14.2)	6 (42.9)
Appetite loss	7 (50.0)	3 (21.4)	3 (21.4)	1 (7.2)
Fatigue	7 (50.0)	4 (28.6)	3 (21.4)	0 (0.0)
Hypertension	5 (35.6)	3 (21.4)	2 (14.2)	0 (0.0)
Diarrhea	5 (35.6)	3 (21.4)	2 (14.2)	0 (0.0)
Proteinuria	4 (28.6)	1 (7.2)	3 (21.4)	0 (0.0)
Hand-foot-skin-reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infusion reaction	1 (7.2)	0 (0.0)	1 (7.2)	0 (0.0)

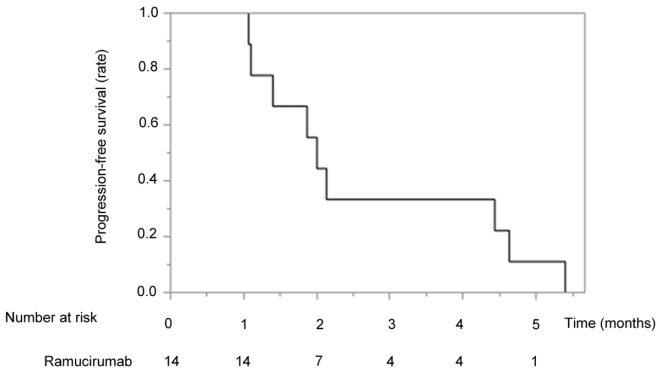

Figure 1. Kaplan-Meier curve for progression-free survival of patients with hepatocellular carcinoma treated with ramucirumab (n=14).

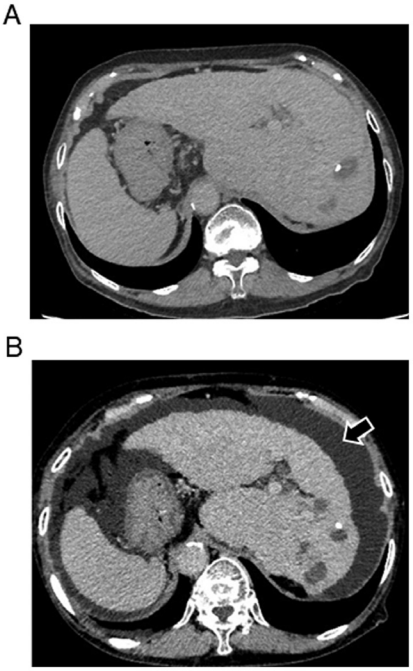

Figure 2. Representative CT images of a patient with visceral inversion administered with RAM. (A) CT image before administration of RAM. No ascites are seen. (B) CT image 27 days after administration of RAM. Severe ascites are seen (arrow). CT, computed tomography; RAM, ramucirumab.

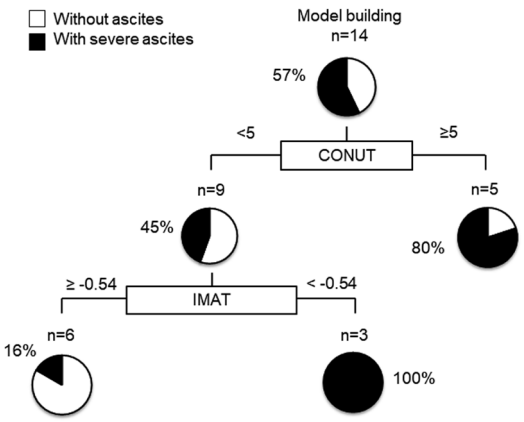

Figure 3. Profiles associated with the development of severe ascites in patients with hepatocellular carcinoma treated with RAM. Decision-tree algorithm for the development of RAM-associated severe ascites. The pie graphs indicate the percentage of patients without severe ascites (white) or with severe ascites (black) in each group. RAM, ramucirumab; CONUT, Controlling Nutritional Status; IMAT, intramuscular adipose tissue.

seen in 57.1% (8/14). Appetite loss and fatigue were seen in 50 (7/14) and 50% (7/14), respectively. The infusion reaction was seen in 7.2% (1/14).

Prevalence of RAM-related severe ascites. RAM-related severe ascites developed in 57.1% (8/14) of the patients, and the median onset was 37.5 days (14-61 days) after RAM treatment initiation. Although ascites was treated with diuretics, RAM was discontinued in 87.5% (7/8) of patients who developed severe ascites. A representative case of the development of severe ascites treated with RAM is shown in Fig. 2A and B. Visceral inversion was seen in this case. No ascites was seen when multiple recurrent hepatic nodules developed after LEN treatment (Fig. 2A). Severe ascites developed 27 days after the initiation of treatment with RAM (Fig. 2B).

Decision-tree analysis for RAM-related severe ascites. In this study, severe ascites developed in 57% of all the subjects by the time of study cessation. To determine the profiles associated with RAM-related severe ascites, decision tree analysis was performed. We revealed that the CONUT score was the first splitting variable for the development of RMA-related severe ascites. In patients with a CONUT score <5, the second splitting variable was the IMAT (Fig. 2). Although severe ascites developed in all patients with an IMAT <-0.54 and a CONUT score <5, severe ascites developed in only 16% of patients with an IMAT ≥-0.54 and a CONUT score <5 (Fig. 3).

Discussion

In this study, we found a high incidence of severe ascites in patients with HCC treated with RAM. Moreover, we revealed that the development of RAM-related severe ascites was associated with a profile characterized by a CONUT score ≥5 and an IMAT <-0.54.

Our results showed a high incidence of severe ascites after treatment with RAM, even in patients with preserved liver function. RAM inhibits ligand activation of VEGF receptor 2, which promotes blood vessel permeability (25) Thus, RAM is theoretically supposed to inhibit the development of severe ascites. In fact, severe ascites has not been reported in patients with advanced gastric cancer or colon cancer treated with RAM (26,27) Moreover, RAM had acceptable tolerability and safety in patients with preserved liver function in phase 3 clinical trial. Thus, our findings were different from those of previous studies. The mechanism underlying the development of severe ascites in HCC patients treated with RAM remains unclear.

In this study, the CONUT score was identified as the initial spread variable for the development of RAM-related severe ascites. A CONUT score ≥5 was associated with the development of RAM-related severe ascites. A CONUT score ≥5 is classified as moderate to severe malnutrition (28) Malnutrition has been associated with the development of severe ascites (29) The CONUT score is based on the total lymphocyte count, total cholesterol level, and serum albumin level. All three parameters have been reported to be associated with ascites (30,31) Therefore, the CONUT score may be associated with the development of severe ascites by reflecting malnutritional status.

In patients with a CONUT score <5, IMAT content was selected as the variable for the second split associated with the development of RAM-related severe ascites. The prevalence of severe ascites was higher in patients with lower IMAT content. The findings suggest that the development of severe ascites was associated with low-fat infiltration of muscles. Our findings were different from a previous report that suggested that low-fat infiltration of muscles was an independent negative predictor of postoperative complications in patients with HCC (32) The reason for the association of low-fat muscle infiltration with RAM-related severe ascites in this study remains unclear. However, Addison *et al* reported that lower IMAT content was related to a decrease in muscle capillarization in older adults (33) Additionally, Solomon *et al* reported that impairment of muscle capillarization was associated with high plasma nitric oxide levels in older adults (34) Higher plasma nitric oxide levels are known to be important for the development of ascites (35,36) Therefore, a lower IMAT content may be associated with the development of severe ascites through the impairment of muscle capillarization and the subsequent increase in nitric oxide production.

This study has several limitations. First, this was a retrospective study with small sample size. Second, the observational period was short. Third, no information was available on factors associated with nutritional status and IMAT content, including energy intake and physical activity. Thus, further multicenter prospective studies with large sample sizes, longer observational periods, and including lifestyle information are warranted.

In conclusion, a high incidence of severe ascites was seen in patients treated with RAM. Moreover, the development of severe ascites was associated with a CONUT score ≥5 and IMAT <-0.54. Accordingly, we must be cautious of severe ascites in patients with HCC treated with RAM, in particular patients with malnutrition and muscle fatty infiltration.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

NK and SS participated in the conception and design of the study, acquisition and interpretation of data, and drafting of the manuscript. KH, SK, HI, TN, TS, MN and RH participated in the acquisition of data. TK participated in the analysis and interpretation of data, and drafting of the manuscript. HM, KN, HK and TT participated in the conception, design and critical revision of the study. NK and SS confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethical Committee of Kurume University School of Medicine (approval no. 19203; Kurume, Japan), and an opt-out approach was used to obtain informed consent from the patients.

Patient consent for publication

An opt-out approach was used to obtain patient informed consent for publication.

Competing interests

TK received an honorarium (lecture fee) from Mitsubishi Tanabe Pharma Corporation and Otsuka Pharmaceutical Co., Ltd. All other authors declare that they have no competing interests.

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