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CASE REPORT

Effective Treatment of Cytotoxic Agent Refractory Alpha-Fetoprotein-Producing Gastric Cancer with Ramucirumab: a Case Report and Review of the Literature

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Introduction

Alpha-fetoprotein (AFP), an oncofetal glycoprotein that is mainly produced by the liver, yolk sac, and gastrointestinal tract during fetal development [1], is significantly expressed in several pathological conditions, especially hepatocellular carcinoma [2]. Elevated AFP levels are also observed in other malignant tumors, including gastric cancer [3]. In 1970, Bourreille et al. [4] initially reported cases of patients with AFP-producing gastric cancer (AFP-GC) and simultaneous liver metastases. AFP-GC is a relatively rare, aggressive malignancy that accounts for 1.3–15.0% of all GC cases [5, 6]. However, AFP-GC is associated with an extremely poor prognosis, because it can easily metastasize to the liver and lymph nodes [7, 8]. Currently, there is no standard therapy for patients with AFP-GC. Hence, there is an urgent need to develop an effective chemotherapeutic regimen for AFP-GC.

Angiogenesis is a fundamental factor in tumor growth [9]. Vascular endothelial growth factor receptor-2 (VEGFR-2), which is the most important signal transducer in angiogenesis, plays a pivotal role in the proliferation, migration, permeability, invasion, and tube formation of endothelial cells. Therefore, VEGFR-2 activation and subsequent angiogenesis are critical for the proliferation of cancer cells, by supplying oxygen and nutrients [9, 10]. Ramucirumab is a humanized immunoglobulin G1 monoclonal antibody that selectively inhibits VEGFR-2 and blocks the signaling pathways that mediate angiogenesis in endothelial cells. In the phase III REGARD trial [11], which compared ramucirumab monotherapy with best supportive care as second-line treatment for patients with advanced GC, a survival benefit was observed in those treated with ramucirumab monotherapy. Ramucirumab was subsequently approved as a single agent for the treatment of patients with advanced GC who had progressed on previous treatment regimens.

Herein, we describe a rare case of an elderly patient who was diagnosed with GC and had extremely high levels of serum AFP (> 80,000.0 ng/mL). To our knowledge, this is the second case of a patient with cytotoxic agent refractory AFP-GC that responded to ramucirumab monotherapy [12].

Case Presentation

A 69-year-old female Japanese patient was referred to our department with a gastric tumor. Esophagogastroduodenoscopy revealed a Borrmann type V tumor located in the anterior side of the lower part of the stomach (Fig. 1a). The pathological diagnosis of the biopsy specimen obtained by endoscopy was poorly differentiated gastric adenocarcinoma (Fig. 1b). Immunohistochemical staining for AFP was positive (Fig. 1c). Abdominal computed tomography revealed the presence of multiple liver metastases (Fig. 2a), with portal venous tumor thrombosis (Fig. 2b), perigastric lymph node metastasis, and peritoneal dissemination (Fig. 2a–c). Serum AFP levels were extremely high at initial diagnosis (6585.0 ng/mL).

Based on the examination findings, the patient was diagnosed as having AFP-GC with distant metastases and peritoneal dissemination and systemic chemotherapy was performed. Tegafur/gimeracil/oteracil (80.0–120.0 mg/day for 2 weeks) plus oxaliplatin (100.0 mg/m^2 on day 1 every 3 weeks) was administered as the first-line treatment. After 4 cycles, the portal venous tumor thrombus had disappeared. However, the liver and lymph node metastases had become

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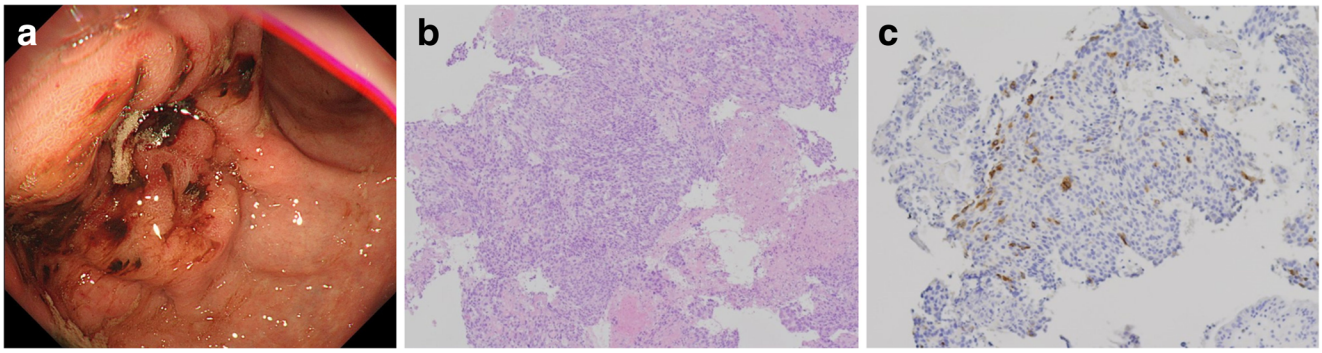

Fig. 1 Endoscopic and pathological features of the tumor. An advanced Borrmann type V tumor was located in the anterior side of the lower part of the stomach (**a**), hematoxylin and eosin staining revealed that the tumor was a poorly differentiated adenocarcinoma (**b**), and immunohistochemical analysis revealed that the tumor cells were stained positively for alpha-fetoprotein (**c**) (original magnification × 40)

visibly larger (Fig. 3a). Therefore, 3 cycles of weekly paclitaxel (80.0 mg/m^2 on days 1, 8, and 15 every 4 weeks), 3 cycles of docetaxel (60.0 mg/m^2 on day 1 every 3 weeks), and 3 cycles of irinotecan (150.0 mg/m^2 on days 1 and 15 every 4 weeks) were administered as second-, third-, and fourth-line treatments, respectively. However, the patient was refractory to all treatments, and the liver and lymph node metastases and peritoneal dissemination progressed rapidly (Fig. 3b). Upper abdominal pain and serum C-reactive protein levels increased, and the patient's Eastern Cooperative Oncology Group (ECOG) performance status score turned worse to 2 from 0. Serum AFP levels reached a maximum of 87,413.0 ng/mL. At this point, ramucirumab monotherapy (8.0 mg/kg once every 2 weeks) was commenced as fifth-line treatment.

After commencing ramucirumab monotherapy, the abdominal pain disappeared, according to a reduction in serum C-reactive protein levels. Serum AFP levels were also immediately reduced, and the patient's ECOG performance status score improved from 2 to 1. After 6 cycles of this regimen, computed tomography demonstrated suppression of the progression of the disease (Fig. 3c). Serum AFP levels were reduced to 19,291.0 ng/mL and remained suppressed to approximately 20,000.0 ng/mL during ramucirumab treatment (Fig. 4). The patient was in a temporary lull. However, ascites began to develop after approximately 9 cycles. After 12 cycles, computed tomography showed disease progression and the treatment was terminated. The patient died from cancer 7 months after commencing treatment with ramucirumab monotherapy (i.e., 18 months after the diagnosis of AFP-GC).

Discussion

AFP-GC is frequently detected at an advanced stage, which contributes to its poor prognosis [13, 14]. The incidence of synchronous and metachronous liver metastases, which are important independent prognostic factors, is high in patients with AFP-GC [13, 15]. Due to the rarity of this cancer, no standard therapy is currently available and the prognosis remains extremely poor. Recent molecular biological studies of AFP-GC have suggested that its malignant potential is related to high vessel density and high VEGF and VEGF-C expression [16, 17]. Because VEGF and VEGF-C are associated with tumor progression via angiogenic- and lymphangiogenic-mediated functions [18], several drugs that target VEGFs and their receptor VEGFR-2 have been developed as new antitumor agents [19].

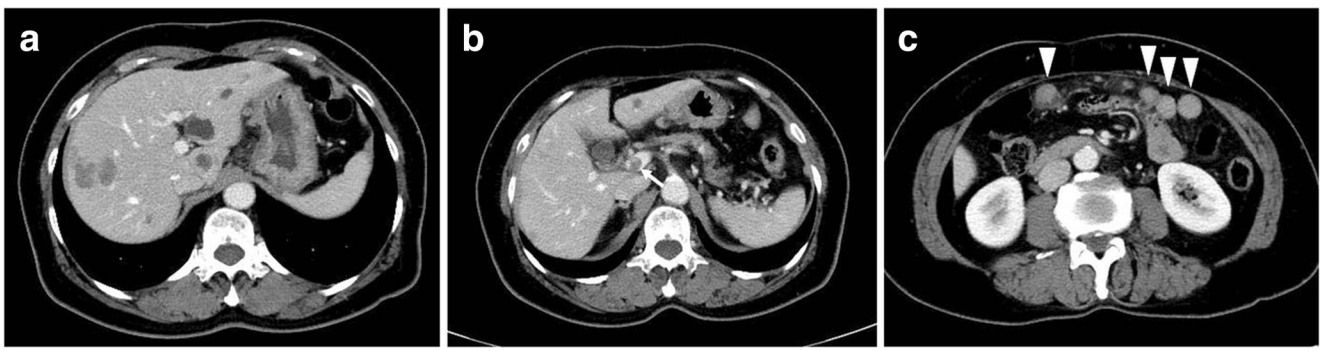

Fig. 2 Abdominal computed tomography findings at the first medical examination. Multiple liver metastases (**a**), portal venous tumor thrombosis (**b**) (arrow), and peritoneal dissemination (**c**) (arrowheads) were observed

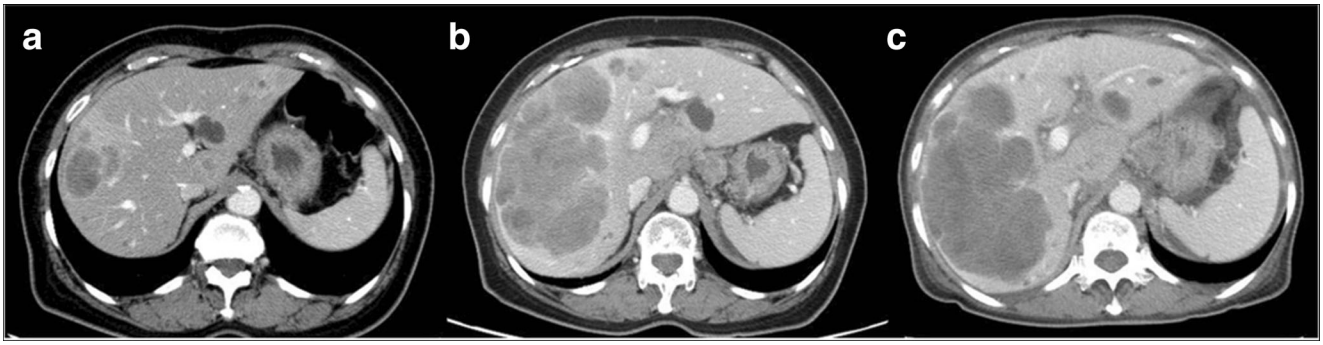

Fig. 3 Abdominal computed tomography findings after chemotherapy. Four cycles of tegafur/gimeracil/oteracil plus oxaliplatin as first-line treatment (**a**), 3 cycles of irinotecan as fourth-line treatment (**b**), and 6 cycles of ramucirumab monotherapy as fifth-line treatment (**c**)

Ramucirumab was approved by the United States Food and Drug Administration in 2014 as a single agent for the treatment of patients with advanced GC, during or following first-line treatment with fluoropyrimidine or platinum-containing chemotherapy. The approval was based on the results of the phase III REGARD trial [11], which showed improvements in the median progression-free survival (2.1 vs. 1.3 months; $P < 0.001$) and overall survival (5.2 vs. 3.8 months; $P = 0.047$) of patients treated with ramucirumab versus best supportive care. Ramucirumab prevents the binding of VEGFR-2 to its ligand VEGFs, which inhibits receptor activation and VEGF signaling pathways, resulting in reduced tumor neovascularization and growth [20]. Because patients with AFP-GC tend to have high levels of VEGF-C expression [17], we speculated that ramucirumab may be effective for the treatment of patients who are resistant to conventional cytotoxic chemotherapy. High levels of AFP expression may also be associated with a good response to ramucirumab in these cases because ramucirumab has been shown to exert a significant survival benefit in patients with hepatocellular carcinoma who express high levels of AFP [21].

One reason why the efficacy of ramucirumab was limited in our case, despite repeated rounds of chemotherapy, is that the tumor volume was already very large at the start of the treatment. However, it should be emphasized that ≥ 3 months of progression-free survival and 7 months of overall survival were achieved without any additional toxicity, both of which were longer than those of patients in the REGARD trial [11].

In conclusion, the clinical course of our patient suggests that ramucirumab may be an effective agent for the treatment of AFP-GC. Ramucirumab should be administered to patients with AFP-GC at an appropriate time, preferably after measurements of the levels of VEGFs have been taken, especially VEGF-C.

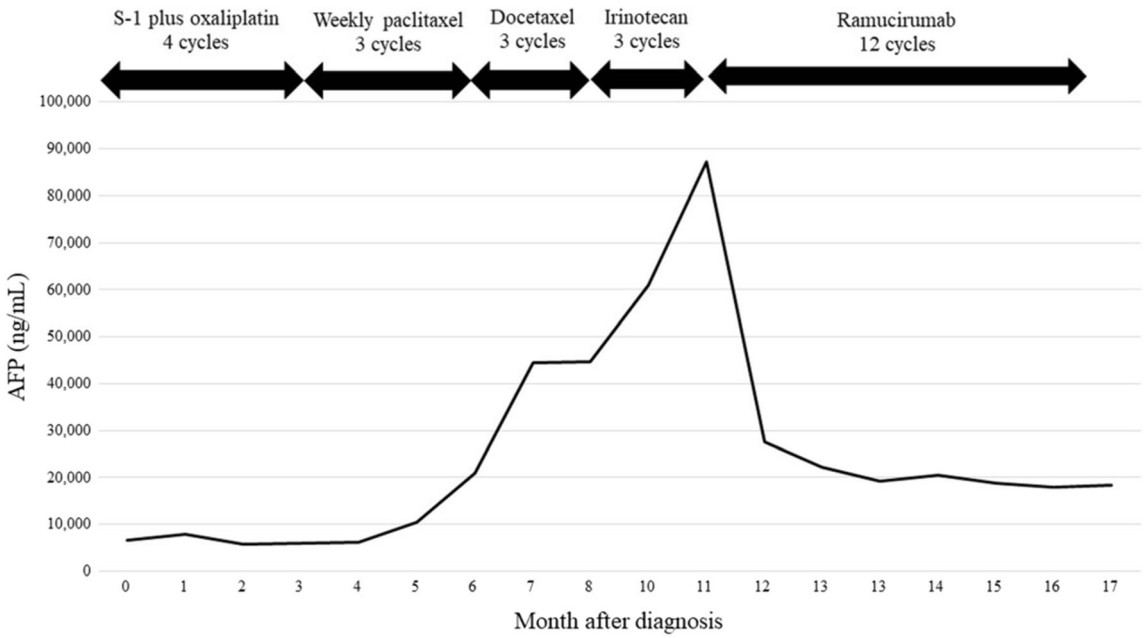

Fig. 4 Effect of ramucirumab monotherapy on serum levels of alpha-fetoprotein. Time course changes in serum alpha-fetoprotein (AFP) levels during chemotherapy. S-1, tegafur/gimeracil/oteracil

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human Rights Statement and Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent to be included in the study, or the equivalent, was obtained from the patient. Additional informed consent was obtained from the patient for which identifying information is included in this article.

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