

[CASE REPORT]

Neuroendocrine Carcinoma of the Stomach: A Response to Combination Chemotherapy Consisting of Ramucirumab Plus Paclitaxel

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Abstract:

Extrapulmonary neuroendocrine carcinoma (NEC) is a rare disease, and there is no standard chemotherapy. A 73-year-old man was diagnosed with advanced gastric NEC. He received chemotherapy of irinotecan plus cisplatin, and amrubicin monotherapy. After failure of second-line chemotherapy, he received ramucirumab plus paclitaxel; this treatment was chosen because vascular endothelial growth factor 2 was strongly expressed in the tumor endothelial cells. After two cycles, his NEC had markedly reduced in size, and he continued with this treatment for over eight months. In this case, the combination of an anti-angiogenic inhibitor and a cytotoxic agent was highly effective for gastric NEC.

Key words: paclitaxel, ramucirumab, neuroendocrine carcinoma, chemotherapy, VEGFR2

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Introduction

Neuroendocrine carcinoma (NEC) is a subgroup of neuroendocrine neoplasms (NENs) in the stomach. It exhibits high proliferative activity and vascularity as well as aggressive clinical behavior and has a poor prognosis. Platinum-based combination chemotherapy has been commonly used as a first-line treatment for NEC, and the efficacy of etoposide plus cisplatin versus irinotecan plus cisplatin has been compared in a phase III study for advanced gastrointestinal, hepatobiliary, or pancreatic NEC (1). However, no standard chemotherapy has been established for implementation following first-line treatment. Combination therapy of temozolomide plus capecitabine, amrubicin monotherapy, S-1, and retreatment with cisplatin plus etoposide have been reported, although the efficacy of these regimens is poor (2, 3).

We herein report a case of gastric NEC for which ramucirumab plus paclitaxel, an anti-angiogenic inhibitor, was

highly effective in the third-line setting. In addition, we analyzed the human epidermal growth factor 2 (HER2) and vascular endothelial growth factor 2 (VEGFR2) protein expression in the patient's tumor to determine the optimum salvage chemotherapy strategy.

Case Report

A 73-year-old man was referred to our institution in June 2015 with complaints of anorexia and abdominal pain. A physical examination revealed a mass in the right upper quadrant. Blood tests failed to show leukocytosis or anemia, and the results of liver and renal function tests were within normal limits. The serum levels of neuro-specific enolase (NSE) and pro-gastrin-releasing peptide (proGRP), which are tumor markers for small cell lung cancer (SCLC), were 19.1 ng/mL (normal <16.3 ng/mL) and 39.4 pg/mL (normal <81.0 pg/mL), respectively. Upper gastrointestinal endoscopy revealed an irregularly and deeply ulcerated tumor in the posterior wall of the antral region of the stomach

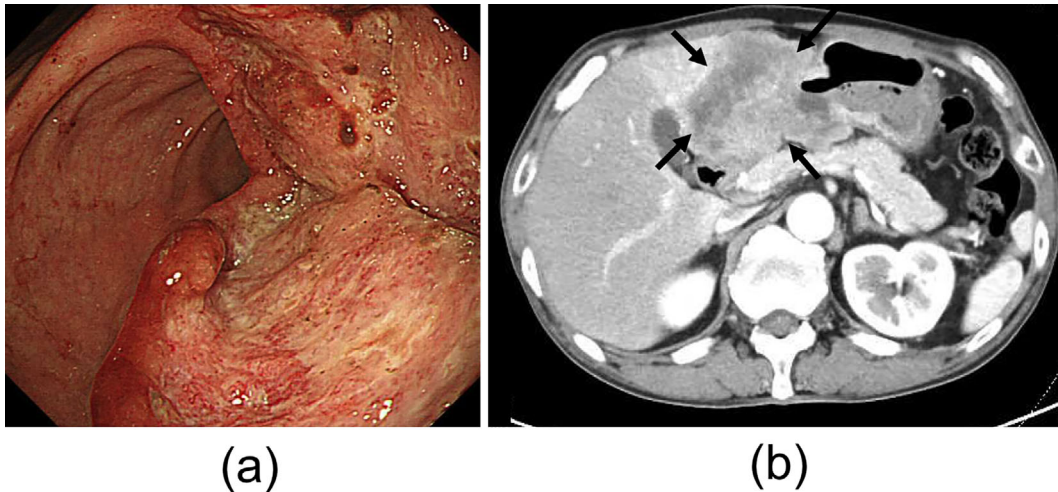


Figure 1. Endoscopic and abdominal computed tomography (CT) findings. (a) Esophagogastroduodenoscopy revealed an irregularly and deeply ulcerated tumor in the posterior wall of the antral region of the stomach. (b) CT scan showing the gastric tumor with bulky lymph nodes and liver metastases.

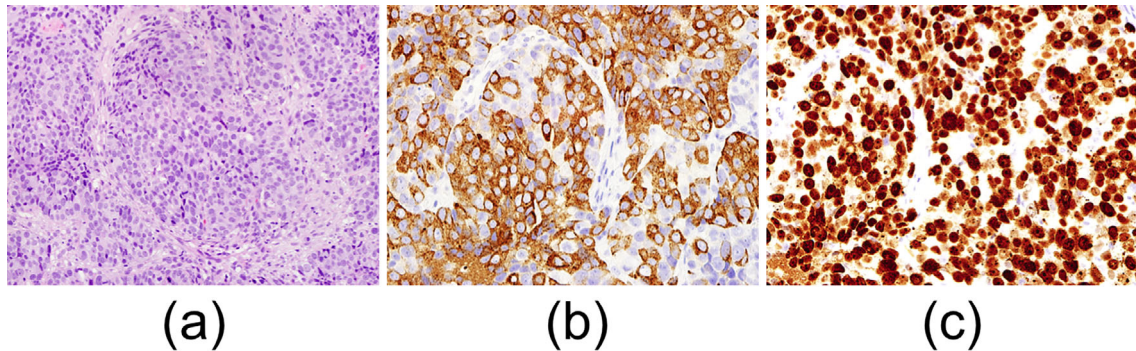


Figure 2. Histopathological findings of tumor biopsy specimens. (a) Hematoxylin and Eosin staining showing hyperchromatic and well-visible nucleoli. (b) and (c) immunohistochemistry. Cancer cells demonstrated positive staining for synaptophysin (b) with a high Ki-67 labeling index (c).

(Fig. 1a). Whole-body computed tomography (CT) revealed a gastric tumor and bulky lymph nodes with liver metastases (Fig. 1b). A histopathological examination of biopsy specimens showed cells with well-visible nucleoli arranged in sheets. Immunohistochemically, the cancer cells demonstrated positive staining for synaptophysin, a diagnostic marker of NENs. Based on these findings as well as the high Ki-67 labeling index (>90%), a pathological diagnosis of gastric NEC was made (Fig. 2). The clinical disease stage was T4bN2M1, stage IV according to the tumor-node-metastasis staging system of the International Union Against Cancer.

Chemotherapy was considered as a treatment strategy, and its response was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1, while its toxicity was evaluated according to the National Cancer Institute-Common Toxicity Criteria, version 4.0. The patient received irinotecan plus cisplatin treatment from August 2015 in accordance with the standard treatment for SCLC (4). He re-

ceived 60 mg/m² of irinotecan on day 1 and 60 mg/m² of cisplatin on days 1, 8, and 15 every 4 weeks. Two weeks later, his abdominal pain had almost disappeared, and the best response was stable disease during four cycles of chemotherapy. However, CT showed enlarged lymph node metastasis, and disease progression was evident four months after the induction of first-line chemotherapy. We then started amrubicin monotherapy as a second-line treatment from January 2016. The patient received 40 mg/m² of amrubicin for 3 days every 3 weeks. The best response was stable disease during eight cycles of amrubicin monotherapy. However, a new metastatic lesion was identified in the liver 6 months after commencing second-line chemotherapy, and the serum levels of NSE had increased to 56.9 ng/mL.

At this point, no further optimal chemotherapy options were available for this patient. In July 2016, following amrubicin monotherapy, the patient's performance status was 0, and his complete blood count (CBC) was not abnormal. A biochemical examination revealed high levels of lactate de-

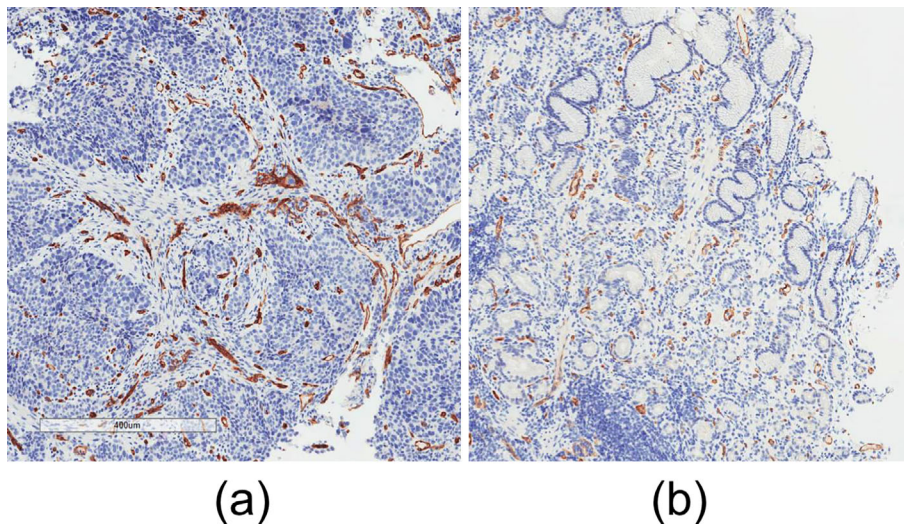


Figure 3. Protein expression of vascular endothelial growth factor 2 (VEGFR2). (a) and (b) Immunohistochemical staining showed strong expression of VEGFR2 in tumor endothelial cells (a) compared with non-cancerous gastric mucosa (b).

hydrogenase (LDH) (372 U/L), alkaline phosphatase (ALP) (621 U/L), and γ GTP (259 U/L). A discussion was held with the patient about empirical treatment according to gastric adenocarcinoma (3), although a histological evaluation by a repeated endoscopic biopsy did not concur with adenocarcinoma. We also analyzed the HER2 and VEGFR2 protein expression using biopsy specimens of gastric NEC for further treatment. The HER2 expression was negative in cancer cells, while VEGFR2 was strongly expressed in tumor endothelial cells compared with non-cancerous gastric mucosa (Fig. 3) and negative in cancer cells.

We ultimately decided to initiate combination chemotherapy of ramucirumab plus paclitaxel as a third-line treatment, which is a standard treatment in the salvage setting for gastric adenocarcinoma (5). The patient was enthusiastic to receive this treatment, and its use was approved by our institution. Ramucirumab (8 mg/kg) and paclitaxel (80 mg/m²) were administered by intravenous infusion on days 1 and 15, and paclitaxel (80 mg/m²) alone was administered by intravenous infusion on day 8 of a 28-day cycle. After two cycles of combination chemotherapy, the liver and lymph node metastases had reduced markedly in CT scans and become partially hypoattenuated (Fig. 4). The patient's response to this treatment was evaluated as a partial response, and the serum levels of NSE had decreased. Endoscopically, we also found that the cancerous ulcer had reduced in size. The patient received this treatment for nine cycles, and the progression-free survival was 248 days after the induction of third-line treatment. In terms of adverse events, the patient experienced grade 1 hand-foot syndrome and malaise.

Discussion

Combination chemotherapy of irinotecan plus cisplatin or etoposide plus cisplatin is most commonly selected for ad-

vanced NEC, based on the clinical and pathological similarities between extrapulmonary NEC and SCLC (6). However, the molecular features of extrapulmonary NEC are largely unknown. In cases of gastric NEC, an adenocarcinoma component is frequently seen in the superficial region, and this suggests that the cell clone of NEC originates from the stem cells of adenocarcinoma (7). Therefore, it may be necessary to select chemotherapy regimens based on the biological characteristics of the tumor. We experienced a patient with gastric NEC who responded to chemotherapy involving ramucirumab and paclitaxel as a third-line regimen; tests also showed that the endothelial VEGFR2 expression in this patient's tumor was high. To our knowledge, this is the first report to show that the combination treatment of an anti-angiogenic inhibitor and a cytotoxic agent is highly effective for NEC.

Angiogenesis, defined as the formation of new blood vessels, plays an important role in physiological and pathological processes and is regulated by a number of molecules, including VEGF, fibroblastic growth factor, and hypoxia-inducible factor 1. Ramucirumab is a human IgG1 monoclonal antibody that binds to VEGFR2 on blood vessel endothelial cells, thereby inhibiting VEGF ligand binding and receptor signaling. The efficacy of ramucirumab monotherapy has been confirmed in patients with advanced gastric or gastroesophageal junctional adenocarcinoma who experienced disease progression following first-line fluoropyrimidine or platinum-containing chemotherapy [median survival: 5.2 vs. 3.8 months for ramucirumab and placebo, respectively; hazard ratio (HR), 0.776; 95% confidential interval (CI), 0.603-0.998, $p=0.0047$] (8). In the present study, biomarker analyses revealed that high endothelial VEGFR2 expression was associated with a non-significant prognostic trend toward a shorter progression-free survival, and the benefit of ramucirumab has been shown to be more pronounced in patients

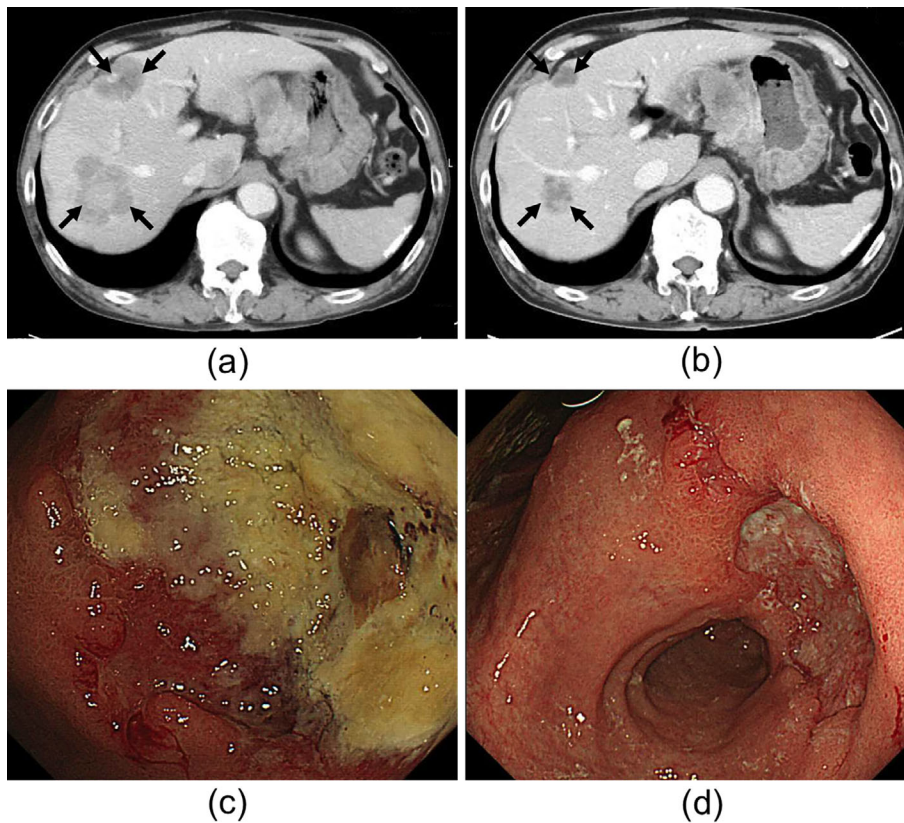


Figure 4. Computed tomography (CT) and endoscopic findings before and after treatment with ramucirumab and paclitaxel. (a) and (c) Before third-line treatment. (b) and (d) After two cycles, CT showed that the size of the liver metastases had markedly decreased, with partial hypo-attenuation (a, b). Endoscopic findings also showed that the gastric NEC had responded to this treatment. NEC: neuroendocrine carcinoma

with a high VEGFR2 expression (9). Recently, the combination of ramucirumab plus paclitaxel was shown to significantly increase the OS compared with placebo plus paclitaxel (median survival: 9.6 vs. 7.4 months; hazard HR, 0.807; 95% CI, 0.678-0.962, $p=0.017$) (5). NENs are well known to be highly vascular neoplasms, and the immunohistochemical analyses of vasohibin-1, CD31, and endogolin have shown that pancreatic NECs exhibit higher angiogenic activity in endothelial cells than grade 1 or 2 pancreatic NETs (10). In our case, the protein expression of VEGFR2 in the patient's vascular tumor was high, which might be one of the reasons for the high activity of ramucirumab and paclitaxel against gastric NEC.

A tumor's response to chemotherapy with anti-angiogenic inhibitor is characteristic (11). The optimum morphological response to bevacizumab, a monoclonal antibody against VEGF, has been shown to result in homogeneous morphology and hypo-attenuation with a sharply defined tumor-normal liver interface (12). It has been reported that the optimum morphological response was observed in 47% of patients treated with bevacizumab and 12% treated without bevacizumab and was associated with a pathological response and the OS in patients with colorectal liver metastases (12). In patients with hepatocellular carcinoma treated with sorafenib, evidence of greater benefit has been shown

via the assessment of treatment efficacy using the modified RECIST criteria, which take tumor vascularity into account, than using the original RECIST criteria (13). In our case, the morphological response was only partially detected in the metastatic lesion, so we cannot report that the response was typical of ramucirumab. The likely explanation is that paclitaxel was also effective for this tumor, as it has been proven to be an active agent in clinical trials for SCLC as well as gastric adenocarcinoma (14).

In conclusion, we experienced a case wherein gastric NEC responded to the combination chemotherapy of ramucirumab plus paclitaxel in a salvage setting. Anti-angiogenic inhibitors might be effective for NEC, which has high angiogenic activity.

The authors state that they have no Conflict of Interest (COI).

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