Case report

Recurrent hepatogastric fistula during lenvatinib therapy for advanced hepatocellular carcinoma managed by over-the-scope clip closure: a case report

Takao Miwa¹, Takahiro Kochi¹, Keitaro Watanabe¹, Tatsunori Hanai², ³, Kenji Imai², Atsushi Suetsugu², Koji Takai², ³, Makoto Shiraki², Naoki Katsumura¹, and Masahito Shimizu²

¹Department of Gastroenterology, Chuno Kosei Hospital, Japan
²Department of Gastroenterology/Internal Medicine, Gifu University Graduate School of Medicine, Japan
³Division for Regional Cancer Control, Gifu University Graduate School of Medicine, Japan

Abstract

Objective: Lenvatinib is an oral multitarget tyrosine kinase inhibitor (mTKI) and is recommended for patients with advanced hepatocellular carcinoma (HCC) with Child-Pugh A liver function, who are not amenable to surgical resection, locoregional treatment, or transcatheter arterial chemoembolization. Hepatogastric fistula is a rare complication with a poor prognosis in patients with HCC. Previous reports on fistula formation during mTKI therapy for HCC were all associated with sorafenib. Here, we report the first case of recurrent hepatogastric fistula during lenvatinib therapy for advanced HCC managed using an over-the-scope clip (OTSC).

Patient: We present the case of a 73-year-old man with alcoholic liver cirrhosis who was treated for multiple HCC for 7 years. HCC was treated using repetitive transcatheter arterial chemoembolization, radiofrequency ablation, and sorafenib. Owing to disease progression, lenvatinib treatment was started. During lenvatinib treatment, recurrent hepatogastric fistulas developed. An OTSC was useful for fistula closure and prevention of recurrence.

Results: The major cause of fistula formation is considered to be the direct invasion of HCC; however, HCC treatment might also be a contributing factor in our case. In addition, OTSC was useful for fistula closure.

Conclusion: Clinicians should be aware of the fatal complications during HCC treatment.

Key words: fistula, hepatocellular carcinoma, lenvatinib, over-the-scope clip, tyrosine kinase inhibitor

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, which is the fifth most common cancer and the second leading cause of cancer-related death worldwide⁹. In early stage HCC, liver transplantation, liver resection, radiofrequency ablation, and transcatheter arterial chemoembolization are effective treatments. However, in advanced HCC, extrahepatic metastasis is detected in up to 15% of patients with HCC at the time of diagnosis⁷. In addition, the cumulative incidence rate of extrahepatic metastasis after the HCC treatment was reported to be approximately 13% at 5 years⁹. The prognosis of metastatic HCC is extremely poor, and the survival rates at 1, 3, and 5 years after the diagnosis were reported as 39.3%, 7.4%, and 4%, respectively⁴. The most common metastatic sites include the lungs (53.8%), bones (38.5%), lymph nodes (33.8%), and adrenal glands (16.9%)⁵. Gastrointestinal tract involvement was reported in 0.4–12% of the patients with HCC⁶–⁷. In particular, HCC patients with gastric metastasis showed poor survival outcomes owing to bleeding problems⁵–⁸. Previous reports have shown that direct invasion and HCC treatment might be the reasons for fistula formation related to HCC⁶–⁷, ⁹.

Effective treatments for unresectable HCC emerged only
with the recent advent of novel multitarget tyrosine kinase inhibitors (mTKIs) (e.g., sorafenib, regorafenib, and lenvatinib). In 2009, sorafenib became available for unresectable HCC in Japan, and it was administered as the first-line treatment as it could increase the survival time and the time to radiologic progression10. Further, in 2017, regorafenib became available for patients with HCC who had progressive disease and showed good tolerability to sorafenib11. Lenvatinib is an oral mTKI that targets the vascular endothelial growth factor (VEGF) receptors 1-3, fibroblast growth factor (FGF) receptors 1-4, platelet-derived growth factor receptor α, rearranged during transfection receptor, and kinase receptors12. The phase 3 trial revealed that lenvatinib was non-inferior to sorafenib in terms of overall survival as the first-line treatment for unresectable HCC12, and it was available since 2018 in Japan. The current clinical practice guidelines for HCC in Japan recommend sorafenib or lenvatinib as the first-line mTKI therapy for patients with advanced HCC having Child-Pugh A liver function who are not amenable to surgical resection, locoregional treatment, or transcatheter arterial chemoembolization13. After the approval of lenvatinib, several studies have shown the efficacy of lenvatinib for advanced HCC in the clinical setting14, 15. However, several fatal adverse events, including fistula formation, have been reported during the administration of mTKIs (e.g., sorafenib16, regorafenib17, and lenvatinib18–20) in other cancers. In HCC treatment, there are only a few reports on fistula formation with the use of sorafenib18, 19, and there are no reports on fistula formation during lenvatinib administration in patients with HCC.

We report the first case of advanced HCC with recurrent hepatogastric fistulas during lenvatinib treatment successfully managed by an over-the-scope clip (OTSC) closure.

Case presentation

The patient was a 73-year-old man with hypertension, diabetes, and alcohol liver cirrhosis. The patient consumed >60 g of alcohol per day until the initial diagnosis of HCC approximately 7 years ago. HCC was treated using repetitive transcatheter arterial chemoembolization and radiofrequency ablation. However, the patient had progressive disease and presented with lung metastases, and the administration of oral sorafenib was initiated a year ago. After a year of sorafenib treatment, the disease worsened, which resulted in the appearance of newly developed intrahepatic HCC in S6, bone metastasis, and enlargement of lung metastasis. Therefore, we decided to change the administration of sorafenib to lenvatinib after obtaining informed consent.

At the start of lenvatinib treatment, the patient had a body height and weight of 165 cm and 55 kg, respectively. The Eastern Cooperative Oncology Group performance status was 0. Liver function was Child-Pugh grade A (5 points). Computed tomography (CT) with contrast in the arterial phase showed treated HCC in the left lobe with lipiodol accumulation without an enhanced area, which was considered as complete remission at that time (Figure 1A and B). Oral lenvatinib 8 mg/day was started in accordance with the phase 3 study protocol; however, lenvatinib was decreased to 4 mg/day because of grade 2 anorexia. Enhanced 58 mm × 52 mm, exophytic HCC with lipiodol accumulation was observed on a CT scan with contrast after 4 months of lenvatinib treatment (Figure 1C and D). The S6 HCC showed a decreased enhancement at the same time. In addition, there were no obvious gastric metastatic lesions. Therefore, lenvatinib was increased to 8 mg/day after the recovery of appetite. After 7 months of lenvatinib treatment, the patient presented to our emergency unit with fever and epigastric pain. The laboratory tests showed elevated levels of C-reactive protein and liver enzymes (Table 1). The clinical course of the patient is shown in Figure 2. CT with contrast revealed an initial fistula with air detected inside the left lobular HCC (Figure 1E and F). Dynamic CT with contrast revealed reduced enhancement of the left lobular HCC in the arterial phase, although air was detected inside (Figure 3A and B). In the portal phase, the target lesion was observed to be a defect lesion (Figure 3C and D). Esophagogastroduodenoscopy revealed the presence of a pinhole at the posterior wall of the upper gastric body (Figure 3E), and using the transendoscopic diatrizoate megilumine and diatrizoate sodium injection, a hepatogastric fistula was detected (Figure 3F). Esophagogastroduodenoscopy performed 4 years prior showed no obvious abnormality. The hepatogastric fistula was treated by 2 weeks of abstention from food and the administration of intravenous antibiotics. We confirmed closure of the hepatogastric fistula and the patient resumed lenvatinib treatment, with careful informed consent from the patient. Tumor markers (α-fetoprotein and des-γ-carboxy prothrombin) were observed to be increased, although the enlargement of HCC was not detected on the CT scan. Therefore, we decided to continue lenvatinib until obvious progression was observed on the CT scan. However, the patient experienced recurrence of the hepatogastric fistula 9 months after the initial fistula. The CT scan showed air in the left lobular HCC (Figure 1G and H). Esophagogastroduodenoscopy revealed recurrence of the fistula at the posterior wall of the upper gastric body (Figure 4A). No malignant cells were found on the biopsy of the fistula. The patient was treated with intravenous antibiotics for a week as well as abstention from food. However, the recurrent fistula did not close this time; therefore, we decided to perform endoscopic treatment.

A type 12/6 type t OTSC applicator cap (Ovesco Endoscopy AG, Germany) was mounted on the tip of the endoscope (Figure 4B). The endoscope was advanced to the hepatogastric fistula site. We used the tissue anchor introduced into the
fistula to pull the fistula opening inside the cap; however, the fistula tissue was weak and could not be pulled using the tissue anchor. Therefore, the twin grasper, with two branches that could be opened independently and closed, was used to hold the fistula; subsequently, the clip closure was performed (Figure 4C and D). After the fistula closure, the patient was able to resume oral ingestion. The closure of the fistula was confirmed using endoscopy and CT. The patient died as the HCC progressed 2 months after the OTSC closure without recurrence of the hepatogastric fistula.

**Figure 1** Images of computed tomography (CT) with contrast in the arterial phase. (A and B) At the initiation of lenvatinib administration, the hepatocellular carcinoma (HCC) in the left lobe showed lipiodol accumulation without an enhanced area (arrow). (C and D) CT 4 months from the start of lenvatinib administration showed enhanced 58 mm × 52 mm, exophytic HCC with lipiodol accumulation in the left lobe (arrow). (E and F) After 7 months of lenvatinib treatment, the CT revealed reduced enhancement of the left lobular HCC compared to the CT performed 4 months from the start of the lenvatinib treatment, although air was detected inside (arrow). (G and H) After 9 months from the initial fistula, CT revealed recurrence of air in the left lobular lesion (arrow).
Table 1  Laboratory data of the initial hepatogastric fistula

| <Peripheral blood> | <Coagulation> | UA | 6.3 mg/dL |
|-------------------|---------------|----|-----------|
| WBC 10,700 μL     | PT 73 %       | BUN 29.9 mg/dL |
| Neutro 80 %       | PT-INR 1.18   | Cr 0.85 mg/dL |
| Eosi 0.2 %        | APTT 38.6 sec | Na 129 mEq/L |
| Baso 12 %         |              | K 4.5 mEq/L |
| Lym 12.6 %        | TP 6.2 g/dL   | Cl 97 mEq/L |
| Mono 7.1 %        | Alb 2.7 g/dL  | CRP 27.37 μg/dL |
| RBC 415 × 10⁴ μL | T-Bil 0.8 mg/dL | PCT 5.2 ng/mL |
| Hb 13 g/dL        | AST 52 U/L    | <Tumor markers> |
| Ht 36.5 %         | ALT 35 U/L    | AFP 220.6 ng/mL |
| MCV 88.2 fl       | LDH 149 U/L   | DCP 3,506 mAU/mL |
| MCH 31.3 pg       | ALP 402 U/L   | <Viral markers> |
| MCHC 35.6 %       | γ-GTP 226 U/L | HBs-Ag (–) |
| Plt 10.3 × 10⁴ μL | Che 89 U/L    | HCV-Ab (–) |

AFP: α-fetoprotein; Alb: albumin; ALP: alkaline phosphatase; ALT: alanine aminotransferase; APTT: active partial thromboplastin time; AST: aspartate aminotransferase; Baso: basophil; BUN: blood urea nitrogen; ChE: cholinesterase; Cl: chloride; Cr: creatinine; CRP: C-reactive protein; DCP: des-γ-carboxy prothrombin; Eosi: eosinophil; GTP: glutamyl transferase; Hb: hemoglobin; HBs-Ag: hepatitis B surface antigen; HCV-Ab: hepatitis C virus antibody; Ht: hematocrit; INR: international normalized ratio; K: kalium; LDH: lactate dehydrogenase; Lym: lymphocyte; MCH: mean corpuscular hemoglobin; mean MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; Mono: monocyte; Na: natrium; Neutro: neutrophil; PCT: procalcitonin; Plt: platelet; PT: prothrombin time; RBC: red blood cell; T-Bil: total bilirubin; TP: total protein; UA: uric acid; WBC: white blood cell.

Figure 2  Clinical course of the patient. (A) Treatment schedule of the patient. Administered dose of lenvatinib, adverse events, the timing of fistula formation, timing of endoscopic treatment, and timing of death are shown. (B) Clinical course of α-fetoprotein and des-γ-carboxy prothrombin, which are tumor markers of hepatocellular carcinoma. (C) Clinical course of C-reactive protein. Abbreviations: AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; CRP, C-reactive protein; HFS, hand foot syndrome; OTSC, over-the-scope clip.
Informed consent and ethics of experimentation

Chuno Kosei Hospital, Ethical Committee, declares that a single case report does not require an ethical review by the committee. The patient signed an informed consent form for permission to use clinical data and images.

Discussion

There are two findings in this case. First, our patient with advanced HCC sustained hepatogastric fistula formation during lenvatinib treatment. Second, the OTSC performed was useful for the treatment of recurrent hepatogastric fistula.

Figure 3  Findings at the time of initial hepatogastric fistula. (A and B) In the arterial phase of the dynamic computed tomography (CT) with contrast, the left lobular target lesion showed decreased enhancement compared to the CT scan at 4 months from the start of lenvatinib administration, although air was detected inside (arrow). (C and D) In the portal phase of the dynamic CT with contrast, the target lesion was shown as a defect lesion (arrow). (E) Esophagastroduodenoscopy showed the presence of a pinhole at the posterior wall of the upper gastric body. (F) Transendoscopic diatrizoate meglumine and diatrizoate sodium injection demonstrated a hepatogastric fistula.
The first finding is that our patient with advanced HCC sustained hepatogastric fistula formation during lenvatinib treatment. Gastrointestinal tract involvement was reported in 0.4–12% of patients with HCC5–7). The sites of gastrointestinal tract involvement include the stomach, duodenum, jejunum, and colon5–7). Hepatogastric fistula is a rare complication related to HCC, and is usually observed as a complication of pyogenic and amebic liver abscess22). Direct invasion and HCC treatment might be the reasons for fistula formation. Large, subcapsular, massive type HCC could be a high-risk feature of the gastrointestinal tract invasion of HCC5). In the present case, previously treated left lobular HCC showed no enhancement at the time of the initiation of lenvatinib treatment. However, enhanced exophytic HCC was observed in the left lobe 4 months after lenvatinib treatment. In addition, contrast-enhanced CT of the target lesion revealed slight enhancement in the arterial phase and defect in the portal phase, indicating the presence of HCC in the left lobular lesion. Therefore, we concluded that the direct gastric invasion of HCC might be the first reason for the formation of hepatogastric fistula in this case.

While we consider the direct invasion of HCC to be the major cause of fistula formation, HCC treatment might also be another reason for fistula formation. HCC treatments, such as transcatheter arterial chemoembolization, radio frequency ablation, radiation, and mTKIs, are also related to gastrointestinal involvement in patients with HCC5–7, 9). In this case, exophytic HCC was close to the stomach, and the left lobular HCC showed increased enhancement after 4 months of lenvatinib treatment. We believe that this was due to a reduction in the dosage of lenvatinib owing to anorexia. In addition, the S6 HCC showed a favorable efficacy with a decreased enhancement at the same time. Therefore, we decided to increase the dose and continue with the administration of lenvatinib after recovery of appetite. At the time of initial fistula, contrast-enhanced CT showed decreased enhancement of exophytic HCC compared to the previous CT scans, and the tumor markers were decreased at the time of initial fistula formation. Therefore, not only direct invasion of HCC, but also lenvatinib treatment might have

Figure 4  Endoscopic treatment of the recurrent hepatogastric fistula. (A) Esophagogastroduodenoscopy revealed recurrence of the hepatogastric fistula 9 months from the initial fistula. (B) A type 12/6 type 1 over-the-scope-clip applicator cap was mounted on the tip of the endoscope. (C, D) The twin grasper instrument, which has two branches that can be opened independently and closed, was used to hold the fistula; subsequently, the clip closure was performed.
contributed to the formation of hepatogastric fistula in the present case.

The relationship between mTKIs and fatal adverse events, such as fistula formation, gastrointestinal perforation, and gastrointestinal bleeding is elusive. Common adverse events that were reported based on the phase 3 trial of lenvatinib were hypertension, diarrhea, anorexia, decreased weight, and fatigue\(^1\)\(^2\). Fatal adverse events such as hepatic failure, cerebral hemorrhage, and respiratory failure occurred in very few patients (2\%)\(^1\)\(^2\). Fistula formation was not reported in the phase 3 trial. However, it is well known that bevacizumab, a VEGF neutralizing monoclonal antibody, is associated with the disruption of the gastrointestinal wall\(^2\)\(^3\). Several lines of preclinical data suggest that impairment of tissue healing at the site of gastrointestinal injury is the most common dominator in bevacizumab treatment\(^4\)\(^5\). The same mechanism may be associated with the usage of mTKI therapy.

There are only three reports on fistula formation related to the use of mTKIs in the treatment of HCC, including the present case (Table 2)\(^7\)\(^-\)\(^2\)\(^1\). Previous cases were all related to the use of sorafenib\(^7\)\(^-\)\(^2\)\(^1\), for which more reports and data are available with regard to the use of sorafenib for the treatment of HCC compared to lenvatinib. It is known that 0.7–7.7\% of the patients treated with sorafenib experienced gastrointestinal perforation\(^2\)\(^6\)\(^-\)\(^2\)\(^7\). Lenvatinib can inhibit VEGF- and FGF-driven angiogenesis and result in hemostasis between the vascular endothelium and platelets, which could lead to ischemic damage and delayed healing\(^2\)\(^8\). In the phase 3 trial, lenvatinib showed a better objective response than sorafenib\(^2\)\(^2\)\(^-\)\(^2\)\(^9\). A high response rate and rapid tumor shrinkage could be expected as a result of lenvatinib treatment, and the rapid shrinkage of the tumor, severe inflammation, and delayed tissue healing might result in fistula formation\(^2\)\(^1\)\(^0\). Recently, a case of perforation of the small intestine after the introduction of lenvatinib in advanced HCC was reported\(^2\)\(^1\)\(^1\). Rapid shrinkage of the metastatic tumor in the small intestine was considered as the cause of the perforation\(^2\)\(^1\)\(^2\). In another case, recurrent gallbladder perforation occurred in a patient with HCC receiving lenvatinib\(^2\)\(^1\)\(^3\). Gallbladder metastasis was absent in this case, and lenvatinib was strongly considered as the cause of gallbladder perforation\(^2\)\(^1\)\(^4\). According to these studies, the possible relationship between fatal complications (e.g., fistula and perforation) and the use of mTKIs for HCC cannot be denied. In this case report, the precise mechanism of fistula recurrence remains unknown. We believe that the main cause of fistula formation might be the direct gastric invasion of HCC. However, it is difficult to completely deny the relationship between the administration of lenvatinib and fistula formation because severe inflammation, tumor shrinkage, and delayed healing might be attributed to fistula formation.

In other cancers, fistula formation is reported during administration of mTKIs, such as sorafenib\(^1\)\(^6\), regorafenib\(^1\)\(^7\), and lenvatinib\(^1\)\(^8\)\(^-\)\(^2\)\(^0\), which are used for HCC treatment. Fistulas related to lenvatinib have been reported in patients with thyroid cancer\(^1\)\(^8\)\(^-\)\(^2\)\(^0\). According to these reports, several reasons could be attributed to the increased number of fistula formation observed in patients with thyroid cancer during lenvatinib treatment. First, lenvatinib was approved for radioiodine-refractory thyroid cancer in 2015 and sufficient information is available regarding lenvatinib as it has been available for a longer period of time for the treatment of thyroid cancer compared to HCC. Second, the thyroid is surrounded by many other organs that can form fistulas (e.g., esophagus, trachea, and skin), and thyroid cancer can easily cause direct invasion or inflammation in other organs. Finally, the response rate of lenvatinib in thyroid cancer is 64.8\%\(^1\)\(^3\), which is higher than that in HCC\(^1\)\(^2\)\(^1\). In addition, lenvatinib is used at a higher dose in thyroid cancer (maximum 24 mg/day) compared with HCC (maximum 12 mg/day). However, it is difficult to compare the efficacy of lenvatinib in different types of cancers.

The second finding in our report is that an OTSC was useful for the treatment of recurrent hepatogastric fistula during lenvatinib administration for HCC. For the treatment of fistula related to HCC, the surgical approach has been reported to show good results\(^6\). However, patients with HCC are not always good candidates for surgery owing to the advanced stage of HCC and impaired liver functions. For the endoscopic approach, the use of through-the-scope clip closure\(^2\)\(^2\)\(^5\) and histoacryl injection\(^2\)\(^2\)\(^0\) have been reported. Despite these modes of treatment, gastrointestinal involvement in HCC is reported to have a poor prognosis\(^5\)\(^-\)\(^6\), and the treatment of hepatogastric fistula remains challenging.

In recent years, a novel endoscopic clipping device, the OTSC, has dramatically increased the possibility of endoscopic closure of the defect\(^3\)\(^1\). The success rate of the OTSC for closure of the digestive fistula is 71.4\%\(^3\)\(^4\) and the OTSC allows for closure of larger lesions using one clip and great-

| No. | Age | Sex | Size of HCC | Diagnosis                  | Treatment        | Treatment of fistula                  | Reference |
|-----|-----|-----|-------------|-----------------------------|------------------|--------------------------------------|-----------|
| 1   | 36  | M   | 190 mm × 130 mm | Hepatogastric fistula       | Sorafenib        | Transcatheter arterial embolization   | 7         |
| 2   | 59  | M   | 200 mm        | Hepatopulmonary fistula     | Sorafenib        | Preserved                            | 20        |
| 3   | 73  | M   | 58 mm × 52 mm | Hepatogastric fistula       | Lenvatinib       | Over-the-scope-clip closure          | Our case  |

HCC: Hepatocellular carcinoma; M: Male.
er compression force compared to the through-the-scope clip\(^{35}\). In the present case report, the OTSC was effective for recurrent hepatogastric fistula during lenvatinib therapy for HCC. Our experience shows that the OTSC is useful even in refractory cases. In addition, our patient survived for 11 months from the diagnosis of the initial fistula, which is similar to the outcomes obtained using the surgical approach\(^{36}\). The use of OTSC could be a considerable choice in patients who are not suitable candidates for surgery.

This study has several limitations. First, there is a lack of clinical information, such as the details of the esophagogastroduodenoscopy before the administration of lenvatinib, as this report is retrospective in nature. Second, we considered the direct gastric invasion of the HCC to be the main cause of fistula formation in this case, and lenvatinib might additionally contribute to fistula formation. However, we lack clinical data to prove the precise mechanism of fistula formation in this case. Finally, although we had repeated esophagogastroduodenoscopy, the present case experienced recurrence of fistula during lenvatinib treatment. Our clinical decision might be debatable, and clinicians should be aware that careful informed consent is required for decision making.

In conclusion, we report the first case of recurrent hepatogastric fistula during lenvatinib treatment for advanced HCC managed by OTSC closure. Clinicians should be aware of the fatal complications associated with HCC treatment.

**Acknowledgement**

The authors appreciate all the medical staff at the Chuno Kosei Hospital, who contributed to the treatment of the patient.

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