

Case Report

# A Case of Unresectable Combined Hepatocellular-Cholangiocarcinoma Successfully Treated with Lenvatinib

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## Keywords

Combined hepatocellular and cholangiocarcinoma · Systemic therapy · Lenvatinib

## Abstract

A 77-year-old man was referred to our hospital because of a hepatic tumor. Blood biochemistry showed elevated serum alfa-fetoprotein, protein induced by vitamin K absence-II, and carbohydrate antigen 19-9 levels. Gd-EOB-DTPA-enhanced magnetic resonance imaging revealed a 95-mm-sized tumor in liver S7. The tumor showed heterogeneous hyperintensity in the arterial phase, slightly washed out from the portal vein phase, and hypointensity in the hepatocellular phase. Post-enlargement segmental resection was performed, and the pathological diagnosis was combined hepatocellular cholangiocarcinoma. Seven months after surgery, multiple liver tumors were found, and biopsy revealed combined hepatocellular-cholangiocarcinoma. Hepatic arterial infusion chemotherapy with cisplatin was initiated. However, the patient developed a pulmonary abscess, which was treated with antibiotics. He then underwent treatment with lenvatinib, 11 months after surgery. At 8 weeks follow-up, a complete response (according to the modified Response Evaluation Criteria in Solid Tumors [RECIST]) and a partial response (RECIST version 1.1) was noted. To the best of our knowledge, thus far, only a single case of lenvatinib treatment of unresectable mixed liver cancer has been reported. In that case, lenvatinib was used as a third-line treatment. The present report is the

first to describe lenvatinib as a first-line therapy for unresectable combined hepatocellular-cholangiocarcinoma, which resulted in a meaningful response. This case provides useful insights into the choice of appropriate drug treatment in this disease in the absence of randomized controlled trials of drug treatment.

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## Introduction

Combined hepatocellular-cholangiocarcinoma is a relatively rare disease found in less than 5% of all liver cancers [1, 2]. Although its prognosis is worse than that of hepatocellular carcinoma (HCC) [1], standard systemic therapy for unresectable cases has not been established. Here, we report a case in which lenvatinib was effective in combined hepatocellular-cholangiocarcinoma.

## Case Report

A 77-year-old man with a right hypochondrial pain was admitted to our hospital for a large liver tumor on computed tomography (CT). There was no unusual history other than partial gastrectomy for gastric ulcer at the age of 21 years. He had a habit of drinking 14 g/day of ethanol. There were no cases of liver disease in relatives and family members living together. Laboratory blood findings revealed slight liver injury (Table 1). In addition, the patient had a history of hepatitis B virus infection (hepatitis B-core antibody-positive, hepatitis B surface antibody-positive, hepatitis B surface antigen-negative, hepatitis B virus-deoxyribonucleic acid undetectable). The tumor markers alfa-fetoprotein, protein induced by vitamin K absence-II, and carbohydrate antigen 19-9 were elevated. Gd-EOB-DTPA-enhanced magnetic resonance imaging revealed a single tumor 95 mm in size in liver S7. The tumor was unevenly stained at the margin and inside in the arterial phase (Fig. 1a), had some washout from the portal vein phase, low signal in the hepatocellular phase (Fig. 1h), and high signal in the diffusion-weighted image. Dynamic CT examination showed that the tumor was unevenly stained in the early phase and weakly washed out in the portal vein phase and the equilibrium phase.

Based on the above results, we diagnosed HCC or combined hepatocellular-cholangiocarcinoma with pT3N0M0, pStage IIIA (UICC TNM 8th edition) and performed extended posterior segmentectomy. There was no problem with the postoperative course, and the patient was discharged on the 13th postoperative day. In the pathological diagnosis of the surgical specimen, a mixture of cord-like HCC components with positive hepatocyte staining and a cholangiocarcinoma component that formed a glandular tube with abundant fibrous tissue and positive for CK19 staining were seen, so the patient was diagnosed with combined hepatocellular-cholangiocarcinoma (Fig. 2a–d). After discharge, the patient was followed up, and contrast-enhanced CT performed on the 127th day after surgery revealed multiple neoplastic lesions with partial hyperintensity in the early phase on both lobes of the liver. A percutaneous liver biopsy was performed for the lesion. HE staining revealed a histological image similar to poorly differentiated HCC, which grew in a cord-like, alveolar-like, and solid manner (shown in Fig. 2e). However, because no clear sinusoid-like structures or pseudoglandular cavity formation was observed, and it was atypical, immunostaining was also carried out with the result that the tumor cells were not stained with the hepatocyte (shown in Fig. 2f) but

**Table 1.** Laboratory data on admission

Laboratory studies	Results	Reference interval
<b>Hematology</b>		
WBC, / $\mu$ L	8,100	3,300–8,600
RBC, $\times 10^4$ / $\mu$ L	502	435–555
Hb, g/dL	14.7	13.7–16.8
Ht, %	44.7	40.7–50.1
PLT, $\times 10^4$ / $\mu$ L	16.5	15.8–34.8
<b>Coagulation</b>		
PT, %	117.3	70–130
APTT, s	29.3	26.9–38.1
ATIII, %	80	80–130
<b>Chemistry</b>		
TP, g/dL	6.9	6.6–8.1
Alb, g/dL	4.2	4.1–5.1
T-Bil, mg/dL	0.9	0.4–1.5
AST, U/L	42	13–30
ALT, U/L	34	10–42
LDH, U/L	233	124–222
ALP, U/L	346	38–113
$\gamma$ -GTP, U/L	224	13–64
BUN, mg/dL	18	8–20
CRE, mg/dL	0.72	0.65–1.07
HbA1c, %	5.8	4.6–6.2
NH <sub>3</sub> , $\mu$ g/dL	43.5	12–66
<b>Serological test</b>		
CRP, mg/dL	0.37	0–0.14
HBs-Ag	(–)	
HBs-Ab	(+)	
HBe-Ab	(+)	
HCV-Ab	(–)	
<b>Genetic test</b>		
HBV DNA	Not detected	
<b>Tumor marker</b>		
AFP, ng/mL	11.9	0–7
PIVKA-II, mAU/mL	168	0–40
CEA, ng/mL	2.4	0–5.68
CA19-9, U/mL	591	0–37

Hematology: WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Ht, hematocrit; PLT, platelets.

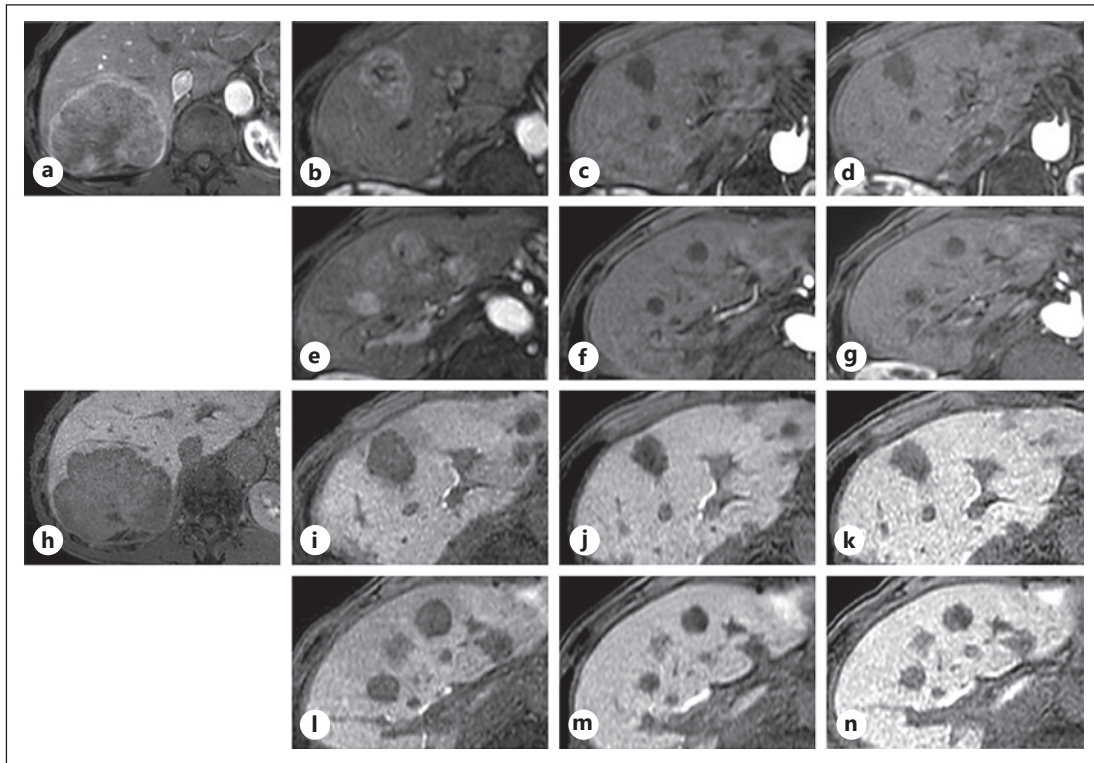
Coagulation: PT, prothrombin time; APTT, activated partial thromboplastin time; ATIII, antithrombin III.

Chemistry: TP, total protein; Alb, albumin; T-Bil, total bilirubin; AST, aspartate transaminase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase;  $\gamma$ -GTP,  $\gamma$ -glutamyl transpeptidase; BUN, blood urea nitrogen; CRE, creatinine; HbA1c, hemoglobin A1c; NH<sub>3</sub>, ammonia.

Serological test: CRP, C-reactive protein; HBs-Ag, hepatitis B surface antigen; HBs-Ab, hepatitis B surface antibody; HBe-Ab, hepatitis B-core antibody; HCV-Ab, hepatitis C virus antibody.

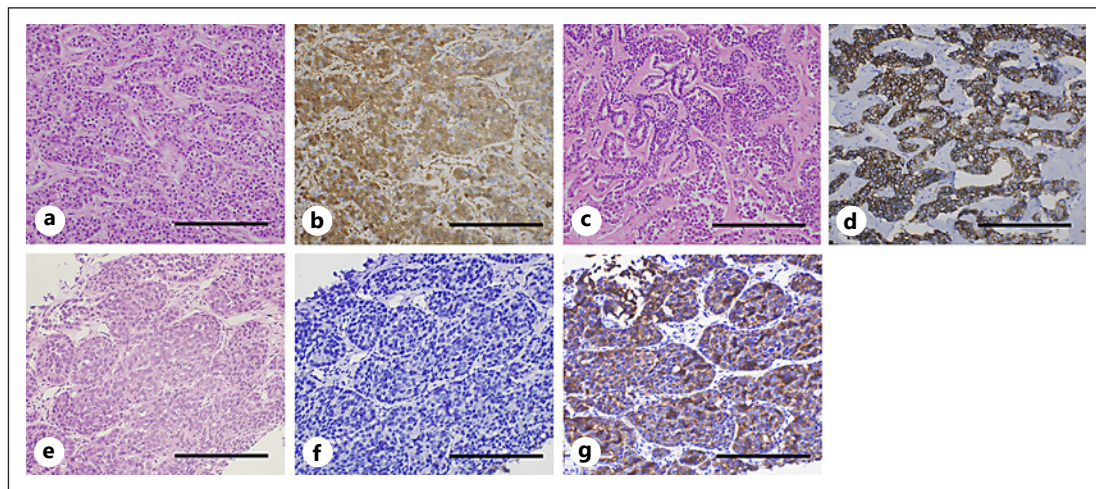
Genetic test: HBV DNA, hepatitis B virus deoxyribonucleic acid.

Tumor marker: AFP, alfa-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

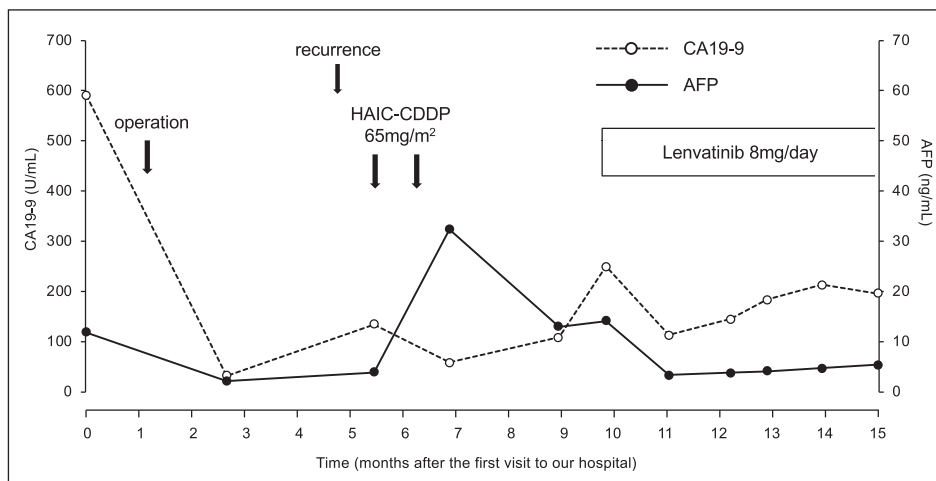


**Fig. 1.** Early phase (a–g) and hepatocellular phase (h–n) of EOB-MRI preoperatively (a), at the start of treatment (b, e, i, l), 8 weeks (c, f, j, m), and 16 weeks (d, g, k, n) later. After 8 and 16 weeks of treatment, hyperintensity disappeared in both tumors in the early phase, and CR was diagnosed by mRECIST. In the hepatocellular phase, the low signal area showed a reduction of 30% or more and thus a PR by RECIST version 1.1. EOB-MRI, Gd-EOB-DTPA-enhanced magnetic resonance imaging; CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

strongly with CK19 (shown in Fig. 2g). The tumor was considered to have acquired the trait of cholangiocarcinoma, and the recurrence of combined hepatocellular-cholangiocarcinoma was diagnosed based on the findings of this biopsy specimen and previous surgical specimens. Because standard treatments for unresectable combined hepatocellular-cholangiocarcinoma have not been established, intra-arterial infusion chemotherapy, which has been reported to be effective for combined hepatocellular-cholangiocarcinoma, was performed (using cisplatin, which is used for both HCC and cholangiocarcinoma). However, after 2 cycles of intra-arterial infusion chemotherapy, a *Pseudomonas aeruginosa*-induced lung abscess developed. Although improved by administration of antibiotics, the abscess cavity remained visible on imaging, and it was considered that this precluded further administration of the cytotoxic drug. Because the tumor was Child-Pugh class A, we decided to introduce lenvatinib, which the patient started taking 10 months after his first visit. Eight weeks after the start of lenvatinib, evaluation was performed by Gd-EOB-DTPA-enhanced magnetic resonance imaging (shown in Fig. 1b–g, i–n). In the early phase, no hyperintensity was observed in any of the lesions, and a complete response was diagnosed according to the modified Response Evaluation Criteria in Solid Tumors. The hypointensity in the hepatocellular phase was reduced by more than 30%, which resulted in assigning a partial response according to Response Evaluation Criteria in Solid Tumors version 1.1. This state has been maintained 7 months after the start of lenvatinib, and treatment is ongoing (shown in Fig. 3).



**Fig. 2.** Pathological findings of surgical specimens (a–d) and specimens obtained by percutaneous liver biopsy for lesions that occurred after surgery (e–g). Pathological findings of surgical specimens revealed a mixture of cord-like HCC components (HE staining (a), positive hepatocyte staining (b)) and cholangiocarcinoma component (HE staining (c), positive CK19 staining (d)), proliferating as a glandular tube with abundant fibrous tissue, diagnosed as combined hepatocellular cholangiocarcinoma. e Pathological findings of specimens obtained by percutaneous liver biopsy revealed that tumor cells proliferated in a cord-like, alveolar-like, and solid manner and showed a histological image similar to poorly differentiated HCC. In immunostaining, tumor cells were not stained with the hepatocyte (f) but strongly stained with CK19 (g) (scale bar, 200  $\mu$ m).



**Fig. 3.** Change of tumor markers (CA19-9 and AFP) through the pre- and postoperative course. AFP, alpha-fetoprotein; CA19-9, carbohydrate antigen 19-9.

## Discussion

Because combined hepatocellular-cholangiocarcinoma is a rare disease, its pathophysiology has not been fully elucidated. Resection is recommended for resectable lesions, but the risk of recurrence has been reported to be higher than for HCC [1, 2]. Therefore, the selection of treatment for postoperative recurrence of unresectable combined hepatocellular-cholangiocarcinoma as in the present case seems to be extremely important clinically.

**Table 2.** Observational studies of systemic drug therapies as first-line treatments for combined HCC

Study design	n	Systemic chemotherapy (1st-line), n (%)	OS, months	PFS, months	Reference	
Retrospective	30	GEM + L-OHP	18 (60.0)	16.2	9.0	[3]
		GEM + L-OHP + bevacizumab	9 (30.0)			
		GEM + CDDP	3 (10.0)			
Retrospective	36	GEM + CDDP	12 (33.3)	10.2	3.0	[4]
		5-FU + CDDP	11 (30.5)	11.9	3.8	
		Sorafenib	5 (13.8)	3.5	1.6	
		Other	8 (22.2)	8.1	2.8	
Retrospective	68	GEM + CDDP/L-OHP	41 (60.3)	11.5	8.0	[5]
		GEM±5-FU	16 (23.5)	11.7	6.6	
		Sorafenib	7 (10.3)	9.6	4.8	
		Other	4 (5.9)	N/A	N/A	
Retrospective	99	Sorafenib	62 (62.6)	10.7	4.2	[6]
		Cytotoxic drug	37 (37.4)	10.6	2.9	

OS, overall survival; PFS, progression-free survival; GEM, gemcitabine; L-OHP, oxaliplatin; CDDP, cisplatin; 5-FU, fluorouracil; N/A, not available.

However, there is very little evidence for systemic drug therapy, which is an unmet need. Therefore, treatment regimens for HCC or cholangiocarcinoma have often been used as the first-line systemic drug therapy for combined hepatocellular-cholangiocarcinoma. There are no prospective clinical trials such as randomized controlled trials for drug therapy for this, and only four retrospective observational studies are available [3–6] (Table 2). Sorafenib, used as a standard treatment for HCC, was previously reported to be less effective in treating combined hepatocellular-cholangiocarcinoma than cytotoxic drugs which are used as standard treatments for cholangiocarcinoma [4, 5]. However, a recent study with more cases [6] reported that there was no difference in their therapeutic effects. Therefore, it cannot be concluded which of the molecular-targeted or cytotoxic agents is most useful.

Lenvatinib is a multikinase inhibitor of vascular endothelial growth factor receptor 1–3, fibroblast growth factor receptor 1–4, platelet-derived growth factor receptor  $\alpha$ , stem cell factor receptor, and rearranged during transfection and exerts angiogenesis-suppressing and antitumor effects. Lenvatinib was noninferior to sorafenib in the first-line treatment of unresectable HCC in the REFLECT randomized phase III clinical trial. In that trial, lenvatinib yielded a significantly higher response rate than sorafenib, suggesting a greater tumor shrinkage effect [7]. Therefore, it is currently the most frequently used first-line treatment for HCC, along with atezolizumab/bevacizumab combination therapy. To the best of our knowledge, only 1 case report of lenvatinib treatment of combined hepatocellular-cholangiocarcinoma has appeared. In that report, unlike in our patient, lenvatinib was used as a third-line treatment, yielding a good therapeutic effect on brain metastasis, suggesting its effectiveness for combined hepatocellular-cholangiocarcinoma [8]. A phase II study of lenvatinib as a second-line treatment for gemcitabine-refractory cholangiocarcinoma has also been reported, with a favorable response rate of 11.5% and a median overall survival of 7.35 months [9]. The dose of lenvatinib in that clinical trial was 24 mg day regardless of body weight, which is different from the dose for HCC (<60 kg: 8 mg/day, 60 kg or more: 12 mg/day). However, the fact that lenvatinib may also be effective against cholangiocarcinoma components appears to be an important finding.

It has been reported that combined hepatocellular-cholangiocarcinoma often appears similar to typical HCC on imaging and that it often develops from chronic hepatitis and cirrhosis as does HCC [2]. Therefore, it is possible that if treated without performing a liver biopsy, some cases of supposed HCC were in fact unresectable combined hepatocellular-cholangiocarcinoma. Recently, due to requirements for confirmation of microsatellite instability-high and for genomic medicine, histological diagnosis is increasingly being performed even for unresectable liver tumors. It is therefore likely that in future the diagnosis of combined hepatocellular-cholangiocarcinoma may increase as a proportion of all liver cancers [1]. In the absence of randomized controlled trials of drug treatments for unresectable combined hepatocellular-cholangiocarcinoma, the present case provides useful insights into the choice of appropriate drug treatment in this population which may increase in the future.

## Conclusions

We presented a case in which lenvatinib was an effective first-line treatment for unresectable combined hepatocellular-cholangiocarcinoma. This may be considered a reference case for treatment selection for this the malignant disease for which there is no effective evidence-based treatment thus far.

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## Statement of Ethics

Ethical approval is not required for this study in accordance with national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

Takahiro Osuga, Koji Miyanishi, and Ryo Ito: collected and analyzed data and wrote and edited the manuscript; Shingo Tanaka, Kota Hamaguchi, Hiroyuki Ohnuma, Kazuyuki Murase, Kohichi Takada, and Junji Kato: involved in the patient's care (mainly systemic therapy) and the acquisition, analysis, and interpretation of data for this case; Minoru Nagayama, Yasutoshi Kimura, and Ichiro Takemasa: involved in the patient's care (mainly surgical therapy) and the

acquisition, analysis, and interpretation of data for this case; Taro Sugawara, Shintaro Sugita, and Tadashi Hasegawa: involved in pathological diagnosis and creating figures from a histopathological photograph.

### Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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