Multimodal treatment involving molecular targeted agents and on-demand transcatheter arterial chemoembolization for advanced hepatocellular carcinoma: A case report and review of the literature

KYOKO OURA, KEI TAKUMA, MAI NAKAHARA, TOMOKO TADOKORO, KOJI FUJITA,
SHIMA MIMURA, JOJI TANI, ASAHIRO MORISHITA, HIDEKI KOBARA and TSUTOMU MASAKI

Department of Gastroenterology and Neurology, Kagawa University, Miki, Kita, Kagawa 761-0793, Japan

Abstract. Formulating sequential therapeutic strategies based on the pathological conditions of patients and by using molecular targeted agents (MTAs) and transcatheter arterial chemoembolization (TACE) is crucial for the treatment of unresectable advanced hepatocellular carcinoma (HCC). The current report presents the case of a patient with HCC involving a large intrahepatic primary tumor and lung metastases, and discusses treatment strategies for advanced HCC based on the current literature. Sequential therapy with MTAs was effective after TACE. Lenvatinib was effective for treating the metastases in the lungs and spleen. Only the progressing intrahepatic tumor was additionally treated with TACE. The patient has been alive for 3 years and continued lenvatinib treatment without HCC progression or decline in liver function. In conclusion, although multiple MTAs introduced into the clinic have been gradually replacing TACE, on-demand TACE in the multidisciplinary treatment of advanced HCC may be effective for intrahepatic hypervascular tumors resistant to MTAs, including lenvatinib. It may be possible to re-initiate lenvatinib treatment with good efficacy against distant metastatic lesions, thereby contributing to long-term survival.

Introduction

Liver cancer is the fifth most common cancer and second most common cause of cancer-related fatalities worldwide (1). Hepatocellular carcinoma (HCC) accounts for approximately 90% of primary liver cancers. HCC has one of the worst prognoses among cancers due to late diagnosis, resistance to chemotherapy, tumor recurrence, and metastasis (2). In HCC, vascular invasion or extrahepatic metastasis is considered as an advanced disease stage and is classified as stage C in the Barcelona Clinic Liver Cancer (BCLC) staging system (3). Although the expected median survival of patients with advanced HCC is 7-9 months (4), the effectiveness of molecular targeted agents (MTAs), including sorafenib, lenvatinib, regorafenib, cabozantinib, and ramucirumab for treatment of advanced HCC has been reported, and these MTAs are in clinical use worldwide (1). The number of drugs for the treatment of advanced HCC is expected to increase in the future, and application of transcatheter arterial chemoembolization (TACE), a crucial treatment approach currently, is expected to decrease. However, TACE might be more effective in certain situations, for example, in cases of large HCC where MTAs cannot produce an immediate effect, or in cases of intrahepatic tumors resistant to multiple MTAs. Thus, it is important to formulate a sequential therapeutic strategy involving MTAs and TACE for advanced HCC based on the pathological condition of the patient.

Here, we present a case of a patient with advanced HCC who had a large intrahepatic tumor along with extrahepatic metastases. Sequential therapy with MTAs was effective after the control of the large intrahepatic tumor through drug-eluting beads (DEB)-TACE. Lenvatinib was effective for the extrahepatic metastases including those in the lungs and spleen. Conventional-TACE (C-TACE) was performed on demand for lenvatinib-resistant intrahepatic radical tumors. This strategy prolonged the long-term survival of the patient. Here, we discuss the effectiveness of a multimodal treatment strategy

including MTAs and TACE for long-term survival in advanced HCC.

Case report

The patient was a 57-year-old Japanese woman with a history of hepatitis C virus infection. Thirteen years prior to this study, a sustained biological response was reported in her after successful treatment with peginterferon alfa-2a. Although she showed no disease symptoms, a large mass was noted in the right lobe of the liver on abdominal ultrasonography performed at our hospital for screening. Contrast-enhanced computed tomography (CE-CT) examination revealed a tumor that was 140 mm in diameter with an uneven high density in the early arterial phase (Fig. 1A). The tumor had a washout appearance in the delayed phase, mainly in the posterior segment (Fig. 1B). In addition, eight metastatic lesions up to 10 mm in diameter were detected in both lungs (Fig. 1C and D). The liver showed no signs of cirrhosis. The level of the tumor marker des-γ-carboxy prothrombin (DCP) was 63,589 mAU/ml, which was considered to be remarkably high, whereas that of α-fetoprotein (AFP) was 9 ng/ml, which was within the prescribed range. The clinical diagnosis was stage IVb hepatocellular carcinoma according to the Tumor-Nodule-Metastasis classification based on the criteria of the Liver Cancer Study Group of Japan (5). Laboratory data showed no significant abnormalities (Table I). The Child-Pugh score was 5, which indicated that liver function was well maintained, and the Eastern Cooperative Oncology Group performance status (ECOG-PS) score of the patient was 0. The carcinoma was classified as advanced stage C with extrahepatic metastasis according to the BCLC criteria, and the guidelines recommended systemic therapy, such as with MTAs, as the initial treatment. As the large primary tumor in the posterior segment of the liver was progressing rapidly and small lung metastases were observed, TACE was planned to suppress the growth of the large primary tumor.

First, DEB-TACE with 82 mg epirubicin was performed for the large primary tumor in the liver. After 6 weeks, C-TACE with 62 mg cisplatin was additionally performed for the surrounding residual lesion. Following the two sessions of TACE, DCP levels were almost normalized and CE-CT revealed that most of the treated intrahepatic tumors were necrotic (Fig. 2A). Considering that growth suppression of the primary intrahepatic tumors was achieved, treatment with MTA was planned as a systemic therapy.

At 2 months post-diagnosis (2 weeks after c-TACE), serum transaminase decreased to normal levels, and liver reserve was completely restored. The patient was administered 400 mg sorafenib daily, which was the only MTA approved in Japan as first-line therapy for advanced HCC at that time. After initiating the sorafenib treatment, DCP levels, which had been almost normalized earlier, increased gradually. However, tumor assessment was performed via CE-CT every 8 weeks to confirm disease progression.

At 1 year post-diagnosis (10 months after initiation of sorafenib treatment), CE-CT revealed an increased hyper-enhancement at the site of the primary intrahepatic tumor in the early arterial phase, indicating tumor progression in the marginal area; however, the lung metastases showed no change relative to their states before the start of the treatment.

Due to the progression of HCC, the patient discontinued sorafenib for two weeks, and she was administered 160 mg regorafenib daily for three weeks, followed by no drug administration for one week.

At 1.5 years post-diagnosis (6 months after initiation of regorafenib treatment), DCP levels increased slowly and were in the range of 357-873 mAU/ml. Although no change was observed in the lung metastases on the CE-CT, viable residual marginal lesions of the primary liver tumor progressed. In addition, new intrahepatic metastatic lesions 20 mm in size appeared in the S7 segment (Fig. 2B), and multiple metastases 10 mm in size were observed in the spleen (Fig. 2C). The therapeutic effect was evaluated as progressive disease based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (6) and RECIST version 1.1 (v1.1) (7). At this point, there were no significant abnormalities in the laboratory parameters (Table I), and the clinical data showed that the Child-Pugh score was 5 and the ECOG-PS score was 0. Regorafenib was discontinued for two weeks, and the patient was administered 8 mg of lenvatinib daily, which had just been approved for use in Japan. During the clinical course, the patient suffered from mild fatigue and anorexia equivalent to Grade 1 according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (8), with no serious adverse effects. Although DCP levels gradually increased from 1,045 to 1,734 mAU/ml over 2-5 months, CE-CT findings showed that the primary tumor in the posterior segment and that in the S7 segment changed from a high density to iso-density in the early arterial phase, suggesting that lenvatinib could have a positive effect.

At 2.5 years post-diagnosis (one year after initiating the lenvatinib treatment), DCP levels slightly decreased (918 mAU/ml). However, CE-CT revealed that both intrahepatic tumors had high density in the early arterial phase, and the tumor sizes had also increased (Fig. 2D). Notably, the lung and spleen metastases were downsized or disappeared on CE-CT analysis. The intrahepatic metastases became more resistant to lenvatinib later in the course of the treatment, whereas lenvatinib was effective against extrahepatic metastases even after 1 year. After discontinuing lenvatinib for 2 weeks, C-TACE with 70 mg of cisplatin was performed for both intrahepatic tumors, namely, the radical marginal lesions of the primary tumor in the posterior segment and the growing tumor in the S7 segment. Two weeks after TACE, recovery of the liver function was confirmed, and lenvatinib administration was re-initiated because previous lenvatinib treatment had been effective for extrahepatic metastases in the lungs and spleen. During the course of this treatment, the patient developed hypothyroidism equivalent to Grade 2 according to the CTCAE v5.0 due to lenvatinib; hence, oral levothyroxine was administered.

At 3 years post-diagnosis (5 months after re-initiation of lenvatinib treatment), the patient's DCP levels decreased to 290 mAU/ml, and AFP was 9 ng/ml, which was considered to be within the prescribed range. CE-CT revealed that the primary tumors in the posterior segment and S7 segment had downsized (Fig. 3A and B), and no obvious intrahepatic lesions or recurrence was observed. In addition, the extrahepatic metastases in the lungs and spleen remained undetectable (Fig. 3C and D). Since good liver function and good performance status were maintained, with a Child-Pugh score of 5 and ECOG-PS score of 0, the lenvatinib treatment was

Table I. Laboratory data at the time of diagnosis and at the start of lenvatinib treatment.

Laboratory data	Value at diagnosis	Value at start of lenvatinib treatment
Biochemistry		
Total protein, g/dl	7.2	6.8
Albumin, g/dl	4.7	4.0
Total bilirubin, mg/dl	0.4	0.5
Direct bilirubin, mg/dl	0.1	0.2
AST, U/l	28	21
ALT, U/l	21	18
LDH, U/l	220	282
ALP, U/l	238	188
GGTP, U/l	91	31
BUN, mg/dl	14.8	15.3
Creatinine, mg/dl	0.58	0.64
Sodium, mmol/l	143	142
Potassium, mmol/l	3.6	4.3
Chloride, mEq/l	108	108
Cholinesterase, U/l	347	339
CRP, mg/dl	0.05	0.42
Coagulation		
PT, %	147	109
APTT, sec	23.8	27.6
Fibrinogen, mg/dl	286	
Antithrombin III, %	111	
D-dimer, μg/ml	2.1	
FDP, μg/ml	5.9	
Hematology		
White blood cells, /μl	4,120	4,400
Red blood cells, x10^4/μl	410	344
Hemoglobin, g/dl	12.5	10.9
Platelet count, x10^4/μl	18.6	16.0
Endocrinology		
TSH, μU/ml	3.240	2.560
Free T3, ng/dl	2.96	2.45
Free T4, pg/ml	1.24	1.12
Fibrosis markers		
Hyaluronic acid, ng/ml	71.9	
Type IV collagen, ng/ml	4.1	
Tumor markers		
AFP, ng/ml	9	3
AFP-L3, %	0.5	0.5
DCP, mAU/ml	68,036	873
Hepatic virus		
HBs antigen	(-)	
HBc antibody	(-)	
HCV antibody	(-)	
HCV-RNA	Undetected	

AST, aspartate transaminase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; GGTP, g-glutamyl transpeptidase; BUN, blood urea nitrogen; CRP, C-reactive protein; PT, prothrombin time; APTT, activated partial thromboplastin time; FDP, fibrinogen and fibrin degradation products; TSH, thyroid stimulating hormone; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; HBs, hepatitis B surface; HBc, hepatitis B core; HCV, hepatitis C virus.
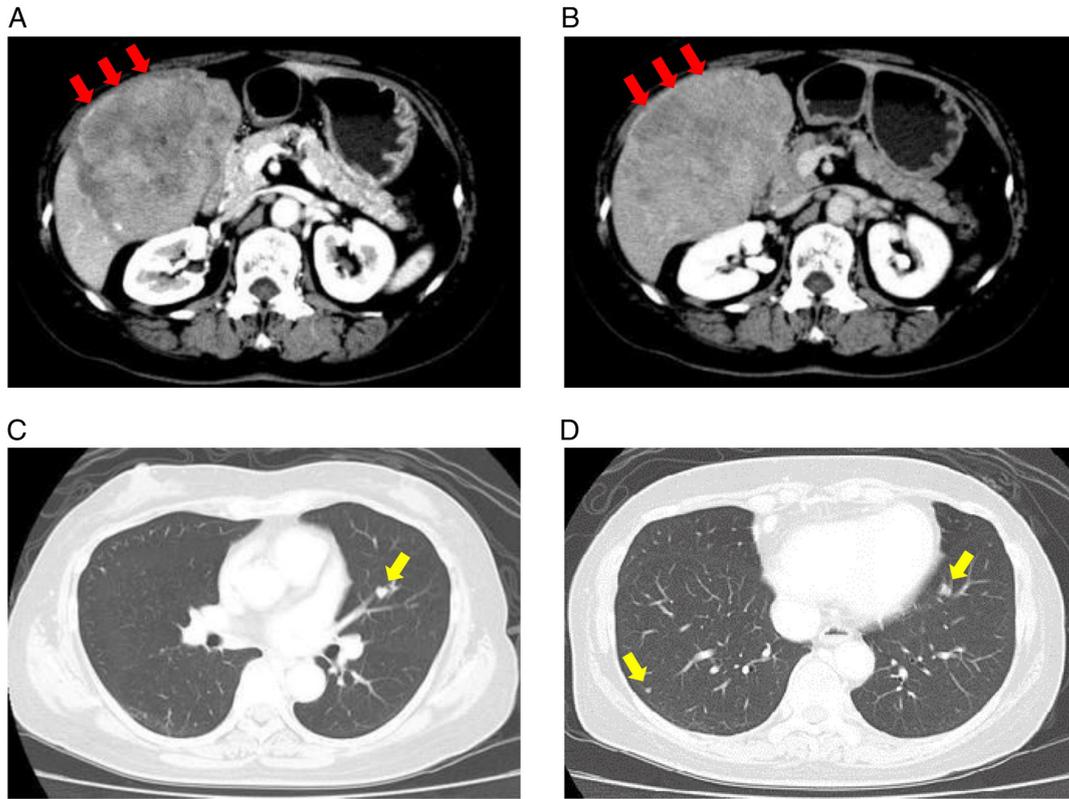
Figure 1. Contrast-enhanced computed tomography findings at diagnosis. (A) The intrahepatic tumor was 140 mm in diameter and had an uneven high density in the early arterial phase, mainly in the posterior segment. (B) The primary tumor displayed a washout appearance in the delayed phase. (C) The largest metastatic lesion of 10 mm was found in the left lung. (D) A total of eight metastatic lesions up to 10 mm in diameter were found in both lungs. Red arrows indicate the primary lesion diagnosed as hepatocellular carcinoma, and yellow arrows indicate lung metastases.
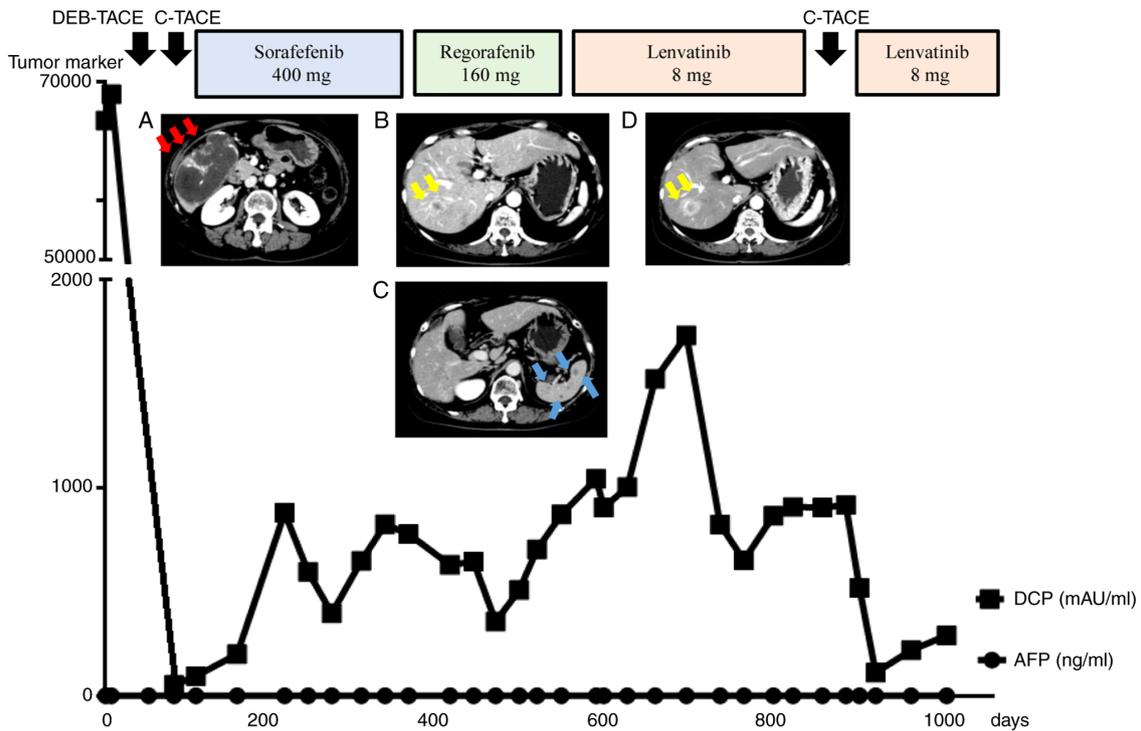
Figure 2. Clinical course with all treatment regimens. (A) After two sessions of TACE, most of the treated intrahepatic tumor was necrotic. (B) At 1.5 years post-diagnosis, new intrahepatic metastatic lesions 20 mm in size appeared in S7, and (C) multiple metastases 10 mm in size appeared in the spleen during regorafenib treatment. (D) At 2.5 years post-diagnosis, the S7 lesion progressed in the early arterial phase, and the tumor size increased during lenvatinib treatment. Viable tumor growth was also observed around the primary tumor in the posterior segment. Red arrows indicate the primary lesion in the liver, yellow arrows indicate other intrahepatic metastases, and blue arrows indicate splenic metastases. TACE, transcatheter arterial chemoembolization; DEB, drug-eluting beads; C, conventional; DCP, des-γ-carboxy prothrombin; AFP, α-fetoprotein.
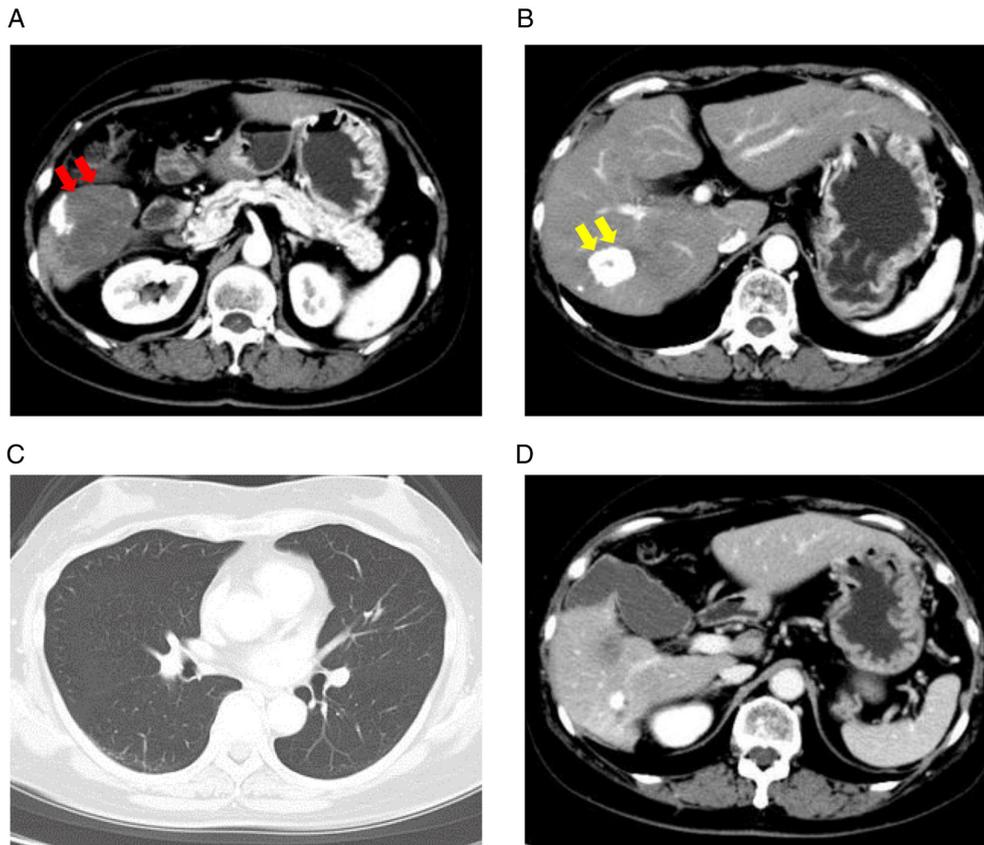
Figure 3. Contrast-enhanced computed tomography findings at 3 years post-diagnosis. (A) The primary lesion in the posterior liver segment was downsized with no recurrence. (B) The intrahepatic lesion in the S7 was also downsized with no obvious intrahepatic tumors or recurrence. (C) The extrahepatic metastases in the lungs remained undetectable. (D) The metastases in the spleen also remained absent. Red arrows indicate the primary lesion in the posterior liver segment, and yellow arrows indicate other intrahepatic metastases.

continued till date (December 2020), without serious adverse effects during the course of treatment of 3 years.

Discussion

For unresectable advanced HCC, sequential therapy using multiple MTAs alongside TACE can confer long-term survival. It is important to select an appropriate method from the multiple treatment options available and switch to the next option at an appropriate time to improve the prognosis. In addition to the many effective clinical applications of various MTAs worldwide (1), several clinical studies on the use of MTAs and immune checkpoint inhibitors (ICIs) are ongoing, and combination therapies with MTAs and ICIs are likely to play a central role in the treatment of advanced HCC (9).

For patients with HCC and extrahepatic metastases classified as stage C according to the BCLC staging system, administration of MTA as a systemic therapy is recommended. However, in the present case, the large primary tumor in the posterior segment of the liver progressed rapidly and small lung metastases were observed; therefore, TACE was performed for the large primary liver tumor to reduce its volume followed by sorafenib treatment. Sorafenib prolongs survival by suppressing tumor growth; however, reduction in tumor size cannot be expected, and the complete response rate is 3% (10,11). Therefore, even in cases of extrahepatic metastasis, prior treatment with TACE to downsize a large intrahepatic tumor is beneficial before administering an MTA such as sorafenib. In contrast, although lenvatinib has a better effect on tumor reduction than sorafenib (12), it has been reported to cause hemorrhage in the tumor through necrosis because of the rapid blockage of the feeding circulation. TACE before lenvatinib might prevent tumor hemorrhage and rupture in large HCC.

Maintaining good liver function is the most important factor in improving the long-term prognosis of patients with HCC because all MTAs are only recommended for patients with good liver function. Losing further treatment opportunities with MTAs due to decreased liver function is detrimental to patients with HCC. Hence, excessive embolization causing widespread hepatic ischemia should be avoided during TACE treatment. To maintain liver function, it is important to perform contrast CT angiography with the catheter placed in the hepatic artery during TACE treatment and identify the exact location between the HCC and the feeding arteries to be treated. Selective catheterization of the tumor feeders and injection of embolic materials should be performed. DEB-TACE, an endovascular treatment based on the use of microspheres to release chemotherapeutic agents within the target lesion, may downsize large intrahepatic tumors. As the antitumor drug loaded in DEB remains in the tumor at a high concentration and does not pass into the peripheral blood, DEB-TACE is less likely to cause adverse effects such as liver damage and post-embolization syndrome compared to C-TACE (13,14). In the present case as well, sequential therapy with MTAs, including sorafenib, regorafenib, and lenvatinib,

could be continued while maintaining good liver function after selective DEB-TACE.

Sorafenib, which prolonged the survival of patients with advanced HCC, was the first MTA used clinically and the only systemic chemotherapeutic drug indicated for HCC for a long time (11). In the later stages of the RESORCE and REFLECT trials, regorafenib (15) and lenvatinib, respectively, were found to be efficacious in patients with advanced HCC (12); these drugs were approved in Japan in 2017 and 2018, respectively. Shortly thereafter, the usefulness of other MTAs, such as ramucirumab and cabozantinib, was also demonstrated (16,17). Since the time when there were only classical treatments such as radiofrequency ablation, TACE, and hepatic arterial infusion chemotherapy, the medical treatment of HCC has dramatically changed due to the increase in treatment options.

Lenvatinib is a multi-kinase inhibitor targeting vascular endothelial growth factor receptor (VEGFR) 1-3, fibroblast growth factor receptor (FGFR) 1-4, platelet-derived growth factor receptor α, rearranged during transfection receptor, and tyrosine kinase receptor, thereby suppressing neo-vessel assembly and maturation, and decreasing the vascular permeability of the tumor microenvironment (18). In the REFLECT trial mentioned above, lenvatinib was shown to be equally effective as sorafenib. The overall survival of the patients treated with lenvatinib was similar to that with sorafenib (13.6 vs. 12.3 months). Notably, the antitumor effect of lenvatinib treatment vs. sorafenib treatment in mRECIST resulted in a response rate, disease control rate, and progression-free survival of 40.6 vs. 12.4, 73.8 vs. 58.4%, and 7.3 vs. 3.6 months, respectively, showing that lenvatinib was significantly better than sorafenib (12). The high response rate of lenvatinib also promises a therapeutic strategy for conversion to resection, which is challenging with sorafenib. Among the adverse events after lenvatinib treatment, hypertension, urinary protein excretion, and hypothyroidism were more common, whereas hand-foot syndrome and diarrhea were less frequently observed compared to treatment with sorafenib. It is important to understand the characteristics of each MTA and manage its adverse effects. In addition, lenvatinib has a stronger inhibitory effect on the angiogenic factors VEGFR1-3 and FGFR-1-4 than sorafenib (19), and it is expected to strongly suppress angiogenetic factors that cause recurrence after TACE.

Drug resistance remains the major cause of failure in MTA therapy (20) and is an important issue when switching between MTAs. As in the present case, even though the strongest antitumor effects are observed when using multiple MTAs for advanced HCC, intrahepatic lesions, especially primary tumors, often show resistance to MTAs as indicated by a partial increase in size on CE-CT analysis. It is necessary to understand the mechanisms underlying drug resistance. In general, tumor heterogeneity causes primary resistance and clonal evolution, eventually leading to drug resistance (21). According to recent findings, cancer stem cells are implicated in drug resistance and are the main factors associated with distant metastases through epithelial-mesenchymal transition (EMT) (22). A study on patient-derived sorafenib-resistant, poorly differentiated thyroid cancer cells has revealed that lenvatinib alongside the histone deacetylase inhibitor HNHA blocks EMT through interference with FGFR signaling (23). Although the molecular mechanism involved in EMT regulation has not been fully elucidated, several studies focusing on EMT in stem cell models have indicated

that both p21 and p53 activation play key roles in suppressing EMT (24). Although there are some reports on the efficacy of lenvatinib in a multidrug-resistant setting, most patients also develop resistance to lenvatinib, particularly in cases of HCC. Although a few preclinical studies have highlighted the role of the c-MET/PI3K/AKT cascade in thyroid cancer (25) and mTOR in renal cancer (26), the mechanism of lenvatinib resistance in HCC remains unclear.

The treatment options for HCC resistant to multiple MTAs are limited. In our case, TACE was performed on-demand for the intrahepatic radical tumors that were resistant to multiple MTAs and was successful after lenvatinib treatment. Despite the current mainstream therapy with MTAs, on-demand TACE is an effective treatment option for intrahepatic tumors resistant to sequential therapies with multiple MTAs. However, it should be noted that TACE might reduce liver function if a wide range of embolization or frequent procedures are performed (27). Currently, the available MTAs for HCC are recommended only for patients with good liver function, especially Child-Pugh class A. To continue sequential treatment with MTA later, unnecessary repetition of TACE should be avoided to preserve liver function. In the present case, no progression of HCC was observed after re-administration of lenvatinib. Furthermore, the patient is still alive, showing no severe adverse effects or decline in liver function. To the best of our knowledge, this is the first report showing the responsiveness of metastatic advanced HCC to re-initiation of lenvatinib treatment after TACE, although the primary intrahepatic tumor had become resistant to initial sorafenib, regorafenib, and lenvatinib regimens. However, one limitation is that multimodal treatment of advanced HCC is often based on the experience of the attending doctor, and the strategy differs depending on the case and medical institute. There is still ambiguity on many factors, such as the timepoints to change the treatment course and to re-initiate MTA treatment after TACE. Therefore, it is necessary to accumulate evidence over long periods, including MTA treatment periods, in future studies.

In conclusion, although multiple MTAs introduced into the clinic have been gradually replacing TACE, TACE can improve the multimodal treatments for advanced HCC. In particular, on-demand TACE in the multidisciplinary treatment of advanced HCC is effective for intrahepatic hypervascular tumors resistant to MTAs, including lenvatinib. By performing on-demand TACE with adequate precautions to preserve liver function, it is possible to re-initiate lenvatinib treatment with good efficacy against distant metastatic lesions, thereby contributing to long-term survival.

Authors' contributions

KO and TM designed the study and wrote the manuscript. KO, KT, MN and TT analyzed and interpreted the patient's clinical data for the manuscript. KO, KF, SM, JT, AM, HK and TM contributed to collecting the relevant literature and to data analysis, and reviewed and critically interpreted the information. KO and TM are responsible for confirming the authenticity of the data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Approval was obtained from the Ethics Committee of Kagawa University Hospital (Kagawa, Japan) (approval no. 2019-238). Informed consent for participation in the study or use of the clinical data was obtained from the patient.

Patient consent for publication

The patient provided written informed consent for the publication of any data.

Competing interests

The authors declare that they have no competing interests.

References

1. European Association for the Study of the Liver. Electronic address easloffice@easloffice.eu; European Association for the Study of the liver: EASL clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 69: 182-236, 2018.
2. Altekruse SF, Henley SJ, Cucinelli JE and McGlynn KA: Changing hepatocellular carcinoma incidence and liver cancer mortality rates in the United States. Am J Gastroenterol 109: 542-553, 2014.
3. Forner A, Reig M and Bruix J: Hepatocellular carcinoma. Lancet 391: 1301-1314, 2018.
4. Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, Brú C, Rodés J and Bruix J: Natural history of untreated nonsurgical hepatocellular carcinoma: Rationale for the design and evaluation of therapeutic trials. Hepatology 29: 62-67, 1999.
5. Kudo M, Kitano M, Sakurai T and Nishida N: General rules for the clinical and pathological study of primary liver cancer, nationwide follow-up survey and clinical practice guidelines: The outstanding achievements of the liver cancer study group of Japan. Dig Dis 33: 765-770, 2015.
6. Lencioni R and Llovet JM: Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 30: 52-60, 2010.
7. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
8. National Cancer Institute (NCI): Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50. Accessed May 18, 2020.
9. Kudo M: Combination cancer immunotherapy with molecular targeted Agents/Anti-CTLA-4 antibody for hepatocellular carcinoma. Liver Cancer 8: 1-11, 2019.
10. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359: 378-390, 2008.
11. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, et al: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10: 25-34, 2009.
12. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, et al: Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. Lancet 391: 1163-1173, 2018.
13. Golfieri R, Giampalma E, Renzulli M, Cioni R, Bargellini I, Bartolozzi C, Breatta AD, Gandini G, Nani R, Gasparini D, et al: Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 111: 255-264, 2014.
14. van Malenstein H, Maleux G, Vandecaveye V, Heye S, Laleman W, van Pelt J, Vaninbroukx J, Nevens F and Verslype C: A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie 34: 368-376, 2011.
15. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, et al: Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 389: 56-66, 2017.
16. Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, Assenat E, Brandi G, Pracht M, Lim HY, et al: Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 20: 282-296, 2019.
17. Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, Cicin I, Merle P, Chen Y, Park JW, et al: Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 379: 54-63, 2018.
18. Koyama N, Saito K, Nishioka Y, Yusa W, Yamamoto N, Yamada Y, Nokihara H, Koizumi F, Nishio K and Tamura T: Pharmacodynamic change in plasma angiogenic proteins: A dose-escalation phase 1 study of the multi-kinase inhibitor lenvatinib. BMC Cancer 14: 530, 2014.
19. Tohyama O, Matsui J, Kodama K, Hata-Sugi N, Kimura T, Okamoto K, Minoshima Y, Iwata M and Funahashi Y: Antitumor activity of lenvatinib (e7080): An angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. J Thyroid Res 2014: 638747, 2014.
20. Marin JJG, Macias RIR, Monte MJ, Romero MR, Asensio M, Sanchez-Martin A, Cives-Losada C, Temprano AG, Espinosa-Escudero R, Reviejo M, et al: Molecular Bases of Drug Resistance in Hepatocellular Carcinoma. Cancers (Basel) 12: 1663, 2020.
21. McGranahan N and Swanton C: Clonal heterogeneity and tumor evolution: Past, present, and the future. Cell 168: 613-628, 2017.
22. Zhang Y and Weinberg RA: Epithelial-to-mesenchymal transition in cancer: Complexity and opportunities. Front Med 12: 361-373, 2018.
23. Lee YS, Kim SM, Kim BW, Chang HJ, Kim SY, Park CS, Park KC and Chang HS: Anti-cancer effects of HNHA and lenvatinib by the suppression of EMT-mediated drug resistance in cancer stem cells. Neoplasia 20: 197-206, 2018.
24. Lamouille S, Xu J and Derynck R: Molecular mechanisms of epithelial-mesenchymal transition. Nat Rev Mol Cell Biol 15: 178-196, 2014.
25. Saji M and Ringel MD: The PI3K-Akt-mTOR pathway in initiation and progression of thyroid tumors. Mol Cell Endocrinol 321: 20-28, 2010.
26. Ghidini M, Petrelli F, Ghidini A, Tomasello G, Hahne JC, Passalacqua R and Barni S: Clinical development of mTor inhibitors for renal cancer. Expert Opin Investig Drugs 26: 1229-1237, 2017.
27. Hiraoka A, Kumada T, Kudo M, Hirooka M, Koizumi Y, Hiasa Y, Tajiri K, Toyoda H, Tada T, Ochi H, et al: Hepatic function during repeated TACE procedures and prognosis after introducing sorafenib in patients with unresectable hepatocellular carcinoma: Multicenter analysis. Dig Dis 35: 602-610, 2017.