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Illuminating and Instructive Clinical Case

Dramatic Response to Cabozantinib in a Patient with Refractory Hepatocellular Carcinoma with c-*MET* Amplification

Yun Beom Sang[1#], Gwangil Kim[2#], Sohyun Hwang[2,3], Haeyoun Kang[2] and Hong Jae Chon[1,3*]

[1]Department of Medical Oncology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam-si, Gyeonggi-do, Korea; [2]Department of Pathology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam-si, Gyeonggi-do, Korea; [3]CHA Future Medicine Research Institute, CHA Bundang Medical Center, Seongnam-si, Gyeonggi-do, Korea

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Abstract

We report a case of a patient with c-*MET* amplified hepatocellular carcinoma (HCC) who had a dramatic response to cabozantinib despite being refractory to four previous lines of systemic therapy. The patient had previously received regorafenib plus nivolumab as first-line treatment, lenvatinib as second-line, sorafenib as third-line, and ipilimumab plus nivolumab as fourth-line treatment in sequence. However, all regimens showed early progression within 2 months. The patient's HCC was well-controlled, with a partial response (PR) of over 9 months after beginning cabozantinib treatment. Although there were mild adverse events such as diarrhea and elevated liver enzymes, they were tolerable. Next-generation sequencing (NGS) of the patient's previous surgical specimen indicated amplification of c-*MET* genes. Although it is well known that cabozantinib has excellent effectiveness for inhibiting c-*MET* at the preclinical level, to the best of our knowledge this is the first case of dramatic response to cabozantinib in a patient with advanced HCC with c-*MET* amplification.

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Introduction

Hepatocellular carcinoma (HCC) is a major cause of cancer mortality worldwide.[1] As many patients are diagnosed at an advanced stage, they receive systemic therapy. Currently, either atezolizumab plus bevacizumab, sorafenib, or lenvatinib are considered as frontline therapy. Subsequent treatment options for advanced HCC, include cabozantinib, regorafenib, ramucirumab, and nivolumab plus ipilimumab.[2,3] Therefore, it is crucial to select the optimal treatment considering of the efficacy and toxicity of the agents, tumor extent, liver function, and biomarkers. Cabozantinib is a multikinase inhibitor that targets tyrosine kinases such as vascular endothelial growth factor 2 and mesenchymal-epithelial transition factor (c-*MET*).[4] In the phase 3 CELESTIAL trial, cabozantinib treatment led to a median 5.2 months of progression-free survival and 10.2 months of overall survival in patients who had received up to two previous systemic treatments, including sorafenib.[5] However, in the CELESTIAL study, the efficacy evaluation of cabozantinib did not include c-*MET* status of patients, and no studies have reported the efficacy of cabozantinib in patients with c-*MET* amplification.[6] Here, we report a patient with HCC and c-*MET* amplification who had a dramatic response to cabozantinib despite being refractory to the previous four lines of systemic therapy.

Case report

In December 2020, a 57-year-old woman with advanced-stage HCC visited our institute. She had a history of hypertension (HTN), diabetes mellitus (DM), chronic hepatitis B diagnosed in young adulthood, and HCC. She was started on entecavir soon before being diagnosed with HCC. Her mother had the same medical history (i.e. HTN, DM, and hepatitis B), and her brother died of HCC at 32 years of age. She had never smoked or drank alcohol. In September 2020, she experienced abdominal pain and visited a local hospital where she was diagnosed with HCC rupture in the liver segment 2/3. The initial treatment was emergency transarterial chemoembolization (TACE) on September 23, 2020, and was followed by a left extended hepatectomy on October 5, 2020. The tumor was 14 × 14 × 5 cm in size and pathologic stage T4 based on the American Joint Committee on Cancer staging system, eighth edition. The tumor pathology was HCC with Edmondson grade 3 differentiation. There was no metastasis to regional lymph nodes, and the resection margin was clear. On a follow-up CT performed in November 2020, 1 month after surgery, multiple metastases were found in other parts of liver segment 7, the resected area of the liver,

Keywords: Hepatocellular carcinoma; c-*MET* amplification; Cabozantinib; Dramatic response; Next-generation sequencing.
Abbreviations: HCC, hepatocellular carcinoma; NGS, next-generation sequencing; RECIST, response evaluation criteria in solid tumors.
[#]Contribute equally to this work.
[*]**Correspondence to:** Hong Jae Chon, Medical Oncology, CHA Bundang Medical Center, CHA University School of Medicine, 59 Yatap-ro, Bundang-gu, Seongnam 13496, Korea. ORCID: https://orcid.org/0000-0002-6979-5812. Tel/Fax: +82-31-780-7590, E-mail: minidoctor@cha.ac.kr

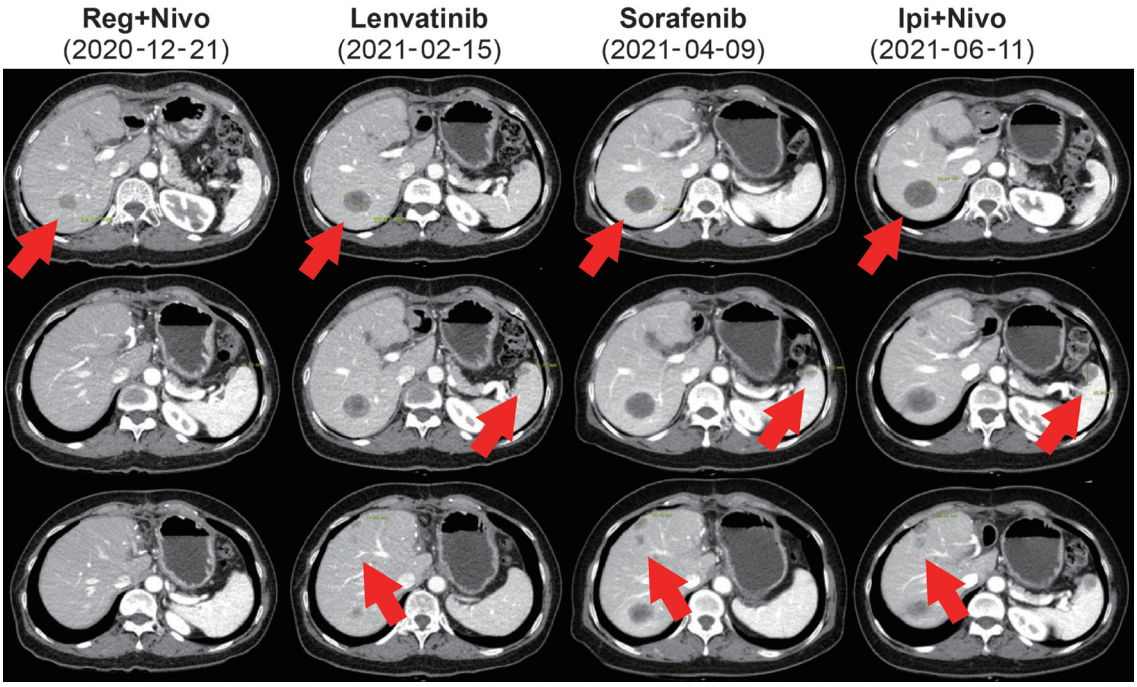

Fig. 1. Changes in baseline tumor size during four lines of treatment prior to cabazantinib. Ipi, ipilimumab; Nivo, nivolumab; Reg, regorafenib.

subdiaphragm, perisplenic areas, lungs, and peritoneum. After consultations to determine the need for systemic therapy for advanced HCC, she visited our institute.

She initially wished to be enrolled in a clinical trial (NCT04310709) and started a combination treatment of regorafenib and nivolumab as first-line systemic therapy. Unfortunately, a Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 follow-up after two cycles of treatment, found progressive disease (PD) involving the target lesion in liver segment S7 and metastasis of non-target lesions, including other liver segments. Subsequent treatment was with a multikinase inhibitor lenvatinib as second-line and sorafenib as third-line therapy. However, both treatments showed PD in a RECIST evaluation after about 2 months. The tumor markers alpha-fetoprotein (AFP) and prothrombin-induced by vitamin K absence or antagonist-II (PIVKA-II) were elevated. The patient was given a combination of nivolumab and ipilimumab as fourth-line treatment, but two cycles of the combination immunotherapy were not effective, with the patient experiencing PD. Despite the previous four lines of treatment, her HCC was refractory to all regimens and showed early progression. Her performance status deteriorated from European Cooperative Oncology Group 1 (ECOG 1) to ECOG 2, and symptoms such as abdominal pain began to worsen. Changes in baseline tumor size and a history of the dose, cycles, and other characteristics of the treatment regimens can be found in Figure 1 and Supplementary File 1.

After treatment with cabozantinib as fifth-line systemic therapy, the patient's tumor was well-controlled. The patient's first response was a partial response (PR) in RECIST, which was maintained for over 9 months. At the beginning of cabozantinib treatment, considering her poor ECOG 2 performance status, she initiated treatment with 40 mg cabozantinib once daily instead of 60 mg on August 11, 2021. Next-generation sequencing (NGS) was performed using formalin-fixed paraffin-embedded tissue from her liver surgery in October 2020 to find any targetable genetic alterations that could guide subsequent treatment. The Oncomine Comprehensive Assay Plus (Thermo Fisher Scientific, Waltham, Massachusetts United States), covering over 500 unique genes.

About 1 week after receiving cabozantinib, the patient experienced Common Terminology Criteria for Adverse Events (CTCAE 5.0) grade 2 diarrhea. Her laboratory test results showed elevation of aspartate aminotransferase (AST 350 IU/L, grade 3) and alanine aminotransferase (ALT 110 IU/L, grade 1). She discontinued cabozantinib for about 5 days, and was given supportive care with the administration of hepatic drugs such as ursodeoxycholic acid and antidiarrheal drugs such as loperamide. Thereafter, her diarrhea resolved and the AST/ALT levels decreased to their normal ranges. Cabozantinib was restarted without a dose reduction. After 2 months of treatment with cabozantinib, her performance status recovered from ECOG 2 to ECOG 1 and her abdominal pain was relieved. AFP dramatically decreased from 47,340 ng/mL to 675 ng/mL. The RECIST 1.1 response evaluation found a 61.5% reduction of the summed target lesion diameters, indicating a partial response. CT (Fig. 2) performed on July 27, 2021, before starting cabozantinib, indicated an initial sum of target lesion diameters of 113.7 mm. The most recent CT on March 14, 2022, indicated a sum of 43.8 mm (liver S7 26.1 mm + liver S4 10.7 mm + spleen 7 mm).

The results of the patient's NGS test performed when she started cabozantinib were available when the first response evaluation of cabozantinib was performed. The NGS test result revealed c-*MET* amplification (copy number: 5.65). Microsatellite instability (MSI) status was low (0.37), and tumor mutation burden was 5.71 mutations/Mb. The NGS results can be found in details in Supplementary Table 1. Previous studies have reported that non-small cell lung cancer patients with oncogene-specific driver mutations, such as epidermal growth factor receptor or anaplastic lymphoma kinase, were refractory to targeted therapies or immunotherapy.[7,8] In that perspective, the results of this case study can

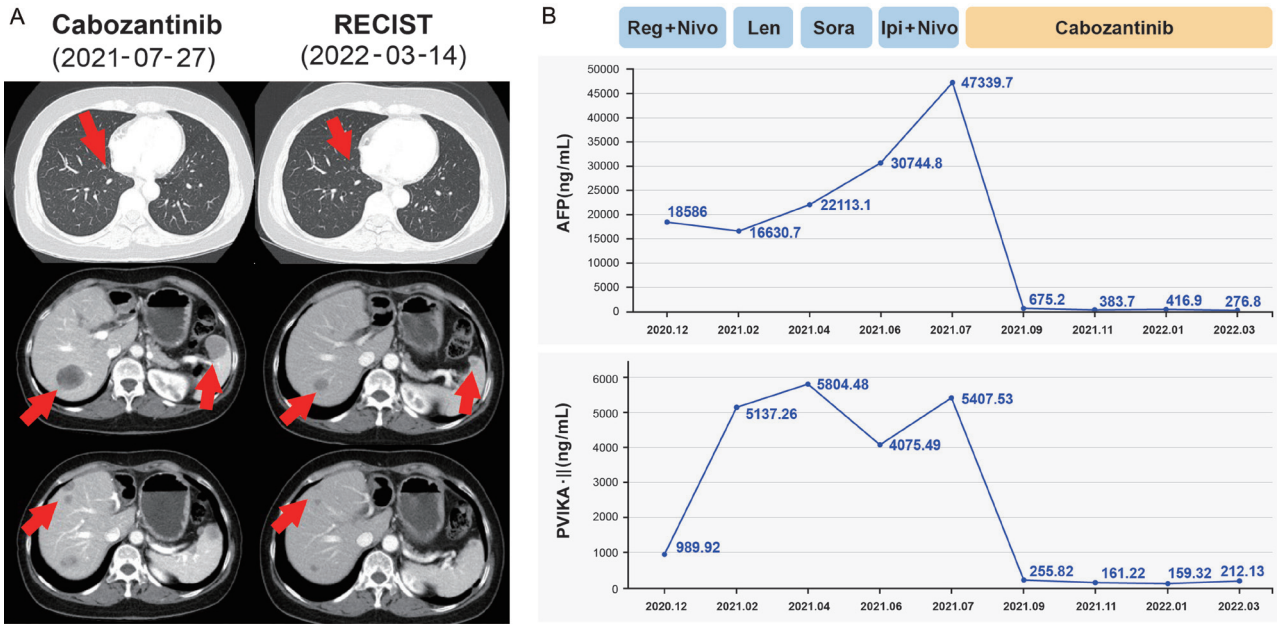

Fig. 2. (A) Representative CT images of tumor burden before introducing cabozantinib, a continuing partial response to cabozantinib was observed. (B) Treatment course and levels of the tumor markers AFP and PIVKA-II. AFP, alpha-fetoprotein; Ipi, ipilimumab; Len, lenvatinib; Nivo, nivolumab; PIVKA-II, prothrombin-induced by vitamin K absence or antagonist-II; RECIST, response evaluation criteria in solid tumors; Reg, regorafenib; Sora, sorafenib.

be interpreted as consistent with c-*MET* gene amplification acting as a strong driver genetic alteration that rendered the patient refractory to the previous treatments but sensitive to cabozantinib. Although preclinical studies have reported inhibition of c-*MET* by cabozantinib,[9] to our knowledge, there are no literature reports of a strong response to cabozantinib in patients with advanced HCC with *c-MET* amplification.

Discussion

c-MET is a tyrosine kinase receptor with hepatocyte growth factor (HGF) as a ligand. c-MET is expressed on the surfaces of various cells, including epithelial cells, endothelial cells, hematopoietic cells, and hepatocytes.[10] In normal cells, HGF/c-MET has a key role in embryogenesis, tissue regeneration, and wound healing.[11] In tumor cells, activation of multiple down-

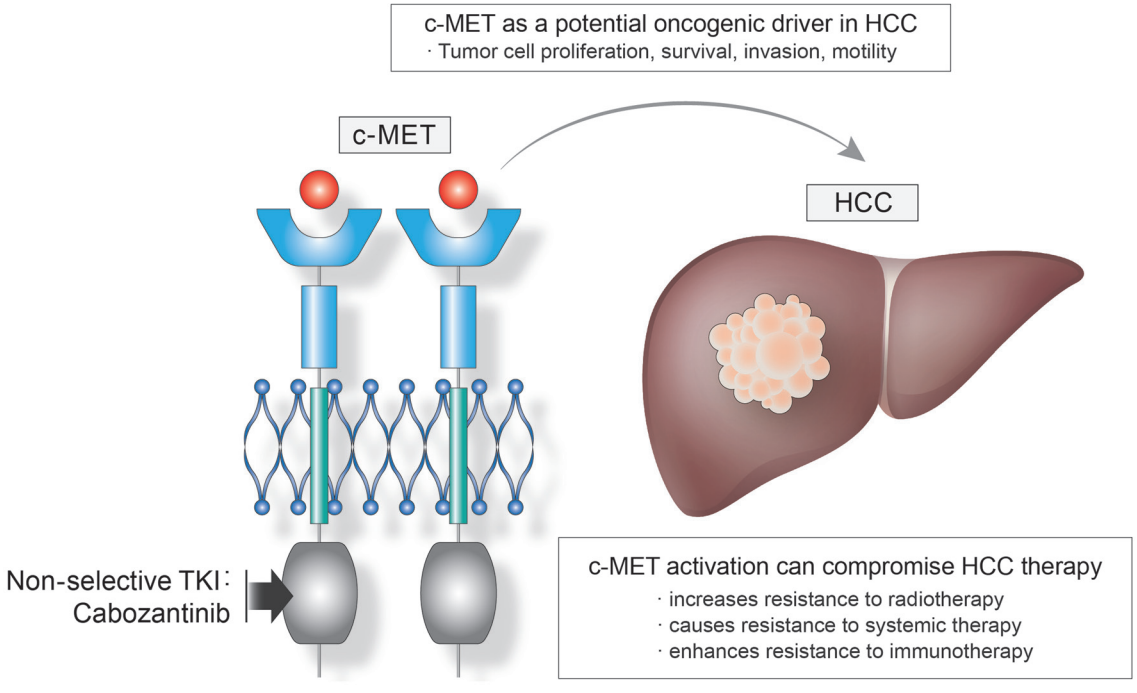

Fig. 3. Effects of c-MET on the development and treatment of HCC. HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibitor.

stream cascades, including PI3K/AKT and MAPK/ERK leads to angiogenesis, cell proliferation, survival, invasion, motility, and epithelial-mesenchymal transition.[12] c-Met activation may also confer resistance to radiotherapy and systemic therapy in HCC (Fig. 3).[13–16] HGF/c-MET signaling can be activated by c-*MET* gene amplification, and c-*MET* amplification has been reported in multiple carcinomas.[17] But c-*MET* amplification was rarely detectable in patients with HCC, 0% by single-nucleotide polymorphism (SNP) genotyping array, defined as a copy number of >ploidy +2[18] and 4.5% by SNP genotyping array, defined as a copy number ≥3.[19] The varying incidence of c-*MET* amplification in HCC in the literature may be due to differences in sample size, detection method, and cutoff settings.

In HCC patients, a liver biopsy is not mandatory for diagnosis and is frequently avoided because of the risk of bleeding and seeding.[20] However, lack of a tissue sample leads to difficulty in studying targeted therapy based on genetic analysis. As HCC treatment options such as various targeted and immunotherapies are increasing, genetic analyses such as NGS through biopsies should be performed more frequently in order to select the optimal treatment for each patient. More clinical results are warranted to identify c-*MET* amplification as a robust predictive biomarker for finding c-*MET* inhibitors.

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Conflict of interest

HJC has received honoraria from Eisai, Roche, Bayer, ONO, MSD, BMS, Celgene, Sanofi, Servier, AstraZeneca, Sillajen, Menarini, GreenCross Cell, Boryung Pharmaceuticals, Dong-A ST, and has received research grants from Roche, Dong-A ST, Boryung Pharmaceuticals. The other authors have no conflict of interests related to this publication.

Author contributions

Supervised the study, obtained funding, and drafted the manuscript (HJC). responsible for the study concept and design (YBS, GK, SH, HK, HJC), performed data analysis (YBS, GK, HJC). generated the figures and wrote the manuscript (YBS, GK, HJC). All authors read and approved the final manuscript.

Ethical statement

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

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