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CASE REPORT

Tepotinib in Cholangiocarcinoma with MET Amplification: A Case Report

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Abstract: Cholangiocarcinoma is a malignant tumor that affects the bile ducts and is usually aggressive with poor prognosis. The treatment of cholangiocarcinoma depends on the stage and location of the tumor as well as the patient's overall health status. Systemic therapy, such as chemotherapy using gemcitabine and cisplatin, is the first choice for patients with cholangiocarcinoma who were inoperable. After no response to first-line chemotherapy, second-line chemotherapy or targeted therapy focusing on signaling pathway inhibition are subsequent treatment. The present report described a case of cholangiocarcinoma involving bilateral lobes of liver. He received one cycle of chemotherapy with gemcitabine plus cisplatin and exhibited rapid progression. Next-generation sequencing was performed, and the results showed that MET amplification had a gene copy number of 68. After that, he underwent tepotinib and tumor shrinkage occurred. After a follow-up period of 12 months, the treatment response was partial response, and the benefit of tepotinib is ongoing. The development of precision medicine has expanded the paradigm of targeted therapies to increasingly favorable options in the second line and beyond, and prolong overall survival. Detecting druggable mutations (mutations potentially amenable to treatment with) for identifying a landscape of therapeutic options is imperative for managing cholangiocarcinoma.

Keywords: cholangiocarcinoma, tepotinib, MET amplification, NGS

Introduction

Cholangiocarcinoma is a malignant tumor that affects the bile ducts. It can occur anywhere along the bile duct, from the liver to the small intestine. Based on location, cholangiocarcinoma is classified into intrahepatic, extrahepatic, and gallbladder cancers. Cholangiocarcinoma is rare; its incidence varies widely worldwide and is more common in Asia than in Western countries. The incidence of cholangiocarcinoma is also higher in individuals with certain medical conditions such as primary sclerosing cholangitis, a chronic liver disease that causes inflammation and scarring of the bile ducts, choledochal cysts, exposure to certain chemicals such as thorium dioxide or dioxin, and a history of biliary tract surgery or liver transplantation.

The treatment of cholangiocarcinoma depends on the stage and location of the tumor as well as the patient's overall health. Surgery is the preferred treatment for early-stage cholangiocarcinoma. However, cholangiocarcinoma is often diagnosed at a late stage when the tumor has already spread to other parts of the body involving extensively the extraductular tissues, or local and distant draining nodes, or distant metastases, and the prognosis is poor. Therefore, systemic therapy plays an important role in the management of advanced and metastatic cholangiocarcinoma.

Gemcitabine and cisplatin are the most commonly used chemotherapeutic agents for advanced cholangiocarcinoma. In the ABC-02 trial, the combination of gemcitabine and cisplatin improved the overall survival (OS) compared to gemcitabine alone in patients with advanced cholangiocarcinoma.[1] Recently, durvalumab plus gemcitabine and cisplatin

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has been approved as first-line systemic therapy based on its superior objective response rate, progression-free survival (PFS), and OS compared to gemcitabine and cisplatin in the TOPAZ-1 trial.[2]

After no response to first-line chemotherapy, signaling pathway inhibition has emerged as a promising therapeutic option for treating cholangiocarcinoma. The ClarIDHy trial showed that ivosidenib increased OS in patients with chemotherapy-refractory cholangiocarcinoma with an *IDH1* mutation.[3] In contrast, fibroblast growth factor receptor (*FGFR*)2 fusions or rearrangements are present in a subset of patients with cholangiocarcinoma. Pemigatinib, a selective oral inhibitor of FGFR1, FGFR2, and FGFR3, has shown an objective response rate (ORR) of 36% with a median PFS of 6.9 months in patients with previously treated cholangiocarcinoma.[4] In addition, several studies have demonstrated that many therapeutic agents target genetic aberrations common in solid tumors, including Her-2, RET fusions, B-RAF V600E, tropomyosin receptor kinase fusions, and high tumor mutational burden.[5] Therefore, searching the tumor genome for treatable mutations with precision targeting appears to be a useful and viable option for cholangiocarcinoma.

Case Report

A 43-year-old man had a history of chronic hepatitis B viral infection without medication. He was in his usual state of health until May, 2022, when he visited the oncology clinic of our hospital because of multiple liver tumors found accidentally on surveillance sonography of his abdomen. Upon examination, the patient was asymptomatic, without abdominal pain, fullness, or appetite changes. Computed tomography (CT) of the liver revealed multiple poorly enhanced tumors involving the left liver section (S4 and S8), up to 8.1 cm of the biggest one, with one enlarged lymph node up to 1.9 cm over the right paracardial region; no vessel or biliary tract invasion was noted. Blood levels of carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), alpha-fetoprotein (AFP), and protein induced by vitamin K absence or antagonist-II (PIVKA-II) were normal, as were the results of liver- and kidney-function tests, including aspartate aminotransferase (AST), alanine transaminase (ALT), direct/indirect/total bilirubin, gamma glutamyl transpeptidase (γGT), and creatinine. Esophagogastroduodenoscopy and colonoscopy were performed to exclude the possibility of upper and lower gastrointestinal malignancies. We performed a core liver biopsy and diagnosed poorly differentiated adenocarcinoma, favoring cholangiocarcinoma (Figure 1).

Because of the unresectable status, chemotherapy with gemcitabine plus cisplatin was prescribed on July, 2022, and August, 2022. However, the patient presented with nausea, vomiting, poor appetite, and fatigue after chemotherapy, and the severity of these symptoms did not improve. Therefore, CT of the abdomen was performed immediately, revealing disease progression of multiple liver tumors, the biggest growing from 8.1 cm to 10.7 cm, and new onset of multiple nodules involving the right lobe of the liver.

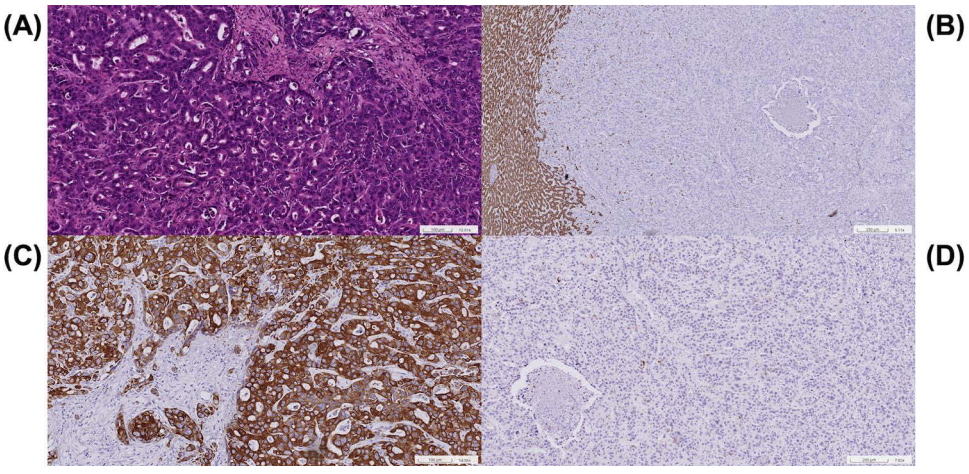

Figure 1 Histopathological findings of cholangiocarcinoma. (**A**) The tumor cells were distributed in nests (hematoxylin and eosin staining); (**B**) Immunostaining for hepatocyte specific antigen (HSA) shows a negative reaction; (**C**) Immunostaining for CK19 shows a positive reaction; (**D**) Immunostaining for glypican 3 shows a negative reaction.

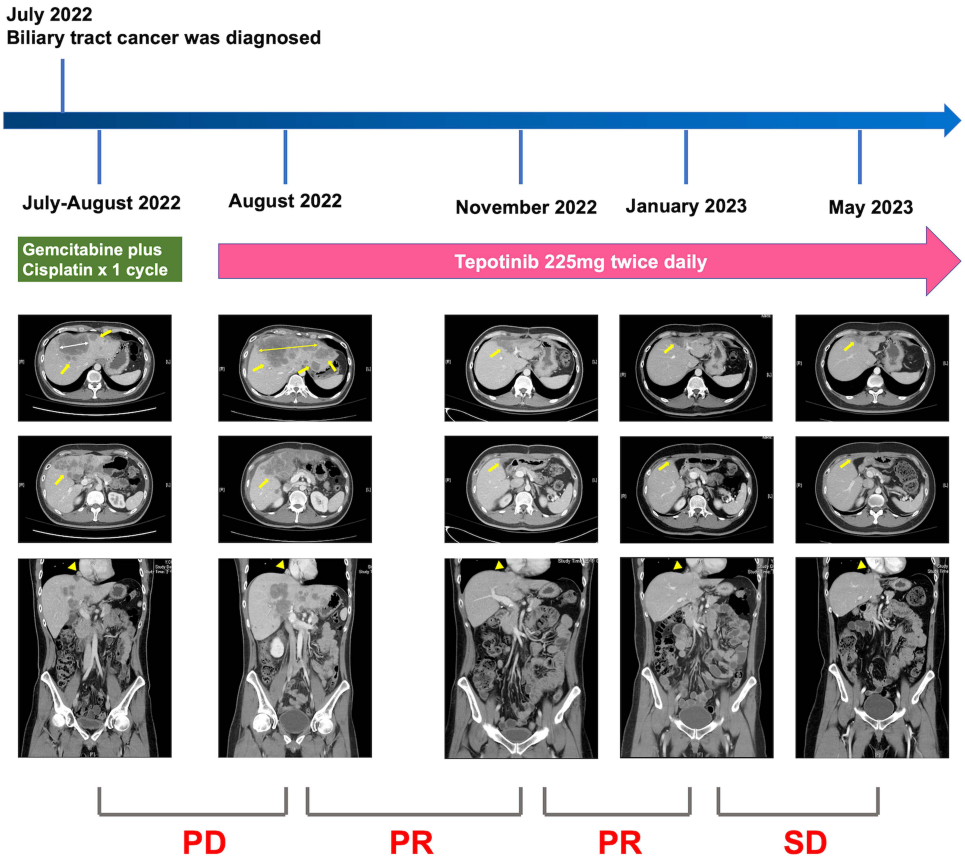

Figure 2 The course of treatment for this patient with cholangiocarcinoma. Double arrow (white): the biggest liver tumor with a size of 8.1 cm; double arrow (yellow): the biggest liver tumor with a size of 10.7 cm; arrow (yellow): liver tumors; arrowhead (yellow): right paracardial lymph node.
Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease.

Next-generation sequencing (NGS) was used to identify druggable mutations, and the results showed that MET amplification had a gene copy number of 68. Subsequently, tepotinib was prescribed at 450 mg/day (225 mg/tablet, orally, twice daily) on August, 2022. Subsequently, the severity of his symptoms gradually decreased, and no further vomiting was noted. His appetite also increased, and fatigue subsided. Follow-up abdominal CT revealed partial regression of multiple liver tumors in both lobes of the liver on November, 2022. Grade 1 peripheral edema was reported without other adverse events, including nausea, vomiting, diarrhea, creatinine increase, or AST/ALT increase. Tepotinib was continued, and an abdominal CT on January, 2023, found a partial response compared to the last CT scan of the abdomen. Currently, tepotinib has been prescribed for 15 months, and its benefits continue. The treatment course was summarized in Figure 2.

Discussion

The MET receptor, encoded by the *MET* oncogene, is a tyrosine kinase that plays a crucial role in cell proliferation, migration, and survival. MET is activated by its ligand hepatocyte growth factor (HGF), which is secreted by stromal cells in response to tissue injury or inflammation. MET signaling is essential for normal development and tissue repair; its dysregulation is implicated in the pathogenesis of several types of cancers.[6] Overexpression of MET or its ligand HGF has been observed in a variety of solid tumors, including lung, breast, colon, and gastric cancers. Activation of the MET pathway can promote cancer cell proliferation, invasion, and metastasis by stimulating cell motility, angiogenesis, and the epithelial–mesenchymal transition through activating multiple signal transduction pathways, including the PI3K–AKT pathway, the mitogen-activated protein kinase (MAPK) pathway, the signal transducer and activator of transcription

(STAT), and NF-κB pathway.[7,8] In addition, MET pathway activation can confer resistance to targeted therapies and chemotherapy, making it an attractive therapeutic target for cancer treatment.

Several approaches have been developed to inhibit MET signaling in cancer. These include small-molecule inhibitors of the MET kinase domain, and monoclonal antibodies targeting the MET receptor or its ligand, HGF. MET exon 14–skipping mutations occur in approximately 3–5% of patients with non-small cell lung cancer (NSCLC) and are associated with a poor prognosis; MET amplification is reported in 1–6% of patients with NSCLC.[9] Recently, tepotinib and capmatinib have been approved for patients with NSCLC harboring MET exon 14–skipping mutations based on their superior OS.[10,11] MET amplification is an important mechanism involved in resistance to first-, second-, and third-generation tyrosine kinase inhibitors, including gefitinib, erlotinib, afatinib, and osimertinib. In addition, tepotinib may be considered in patients with high-leverage MET amplification. Cohort B of the VISION trial enrolled 24 patients with NSCLC harboring high-level MET amplification without MET exon 14–skipping mutations and showed an ORR (complete response rate plus partial response rate) of 42%, which was particularly pronounced in the first-line setting.[12] A Phase I trial investigating the response to tepotinib in patients with advanced solid tumors harboring MET amplification showed that only two of nine patients had stable disease, with a disease control rate (DCR) of 22.2%.[13] In the present case, the patient with cholangiocarcinoma showed rapid progression to standard chemotherapy with gemcitabine and cisplatin. However, NGS showed high-level MET amplification (68 gene copies); therefore, he received tepotinib with a durable response of at least 9 months, and the benefit continues. Gallbladder cancer may also be amenable to treatment with such agents, but its epithelium and mucosa/submucosa differs from that of the bile ducts.

Cholangiocarcinoma remains a deadly disease with a poor prognosis. The development of precision medicine has expanded the paradigm of targeted therapies to increasingly favorable options in the second line and beyond. In the future, NGS will play an important role in determining the ideal treatment course for each patient. Detecting druggable mutations for identifying a landscape of therapeutic options is imperative for managing cholangiocarcinoma.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request. The sequence data from this study have been submitted to NCBI BioProject (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1096850) under BioProject number PRJNA1096850.

Ethics

This case report was approved by the Institutional Review Board of Chang Gung Medical Foundation (202300257B0) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for the publication of potentially identifiable images or data included in this article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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