Complete Response for Adding Pyrotinib to Pembrolizumab and Lenvatinib for HER2 Positive Advanced Intrahepatic Cholangiocarcinoma

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Case Report

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Abstract

Background: Intrahepatic cholangiocarcinoma (ICC) is a highly lethal hepatobiliary cancer. Only very few patients could undergo surgery. The prognosis of advanced ICC is poor, especially for patients who progressed after first-line chemotherapy, leaving median overall survival less than 10 months. To date, no case has been reported to achieve complete response by targeted therapy and immunotherapy for advanced ICC.

Case presentation: In this study, a 64-year-old male was diagnosed with advanced ICC with HER2 3+ amplification determined by tissue-based testing, and was confirmed by the next-generation sequence. He was treated with adding pyrotinib to pembrolizumab and lenvatinib after progressed with pyrotinib and tegafur and responded very well to regression of tumor on imaging as well as normalization of tumor marker levels without serious adverse events. The recent PET-CT showed a complete response. Up to now, the disease is stable, and the progress free time of 2nd line treatment has reached 26 months.

Conclusion: Adding pyrotinib to pembrolizumab and lenvatinib offered a chemotherapy-free option and could achieve complete tumor suppression with no serious AEs for this BTC patient with HER2 amplification.

Introduction

Intrahepatic cholangiocarcinoma (ICC), a subgroup of cholangiocarcinoma, is the second most common primary liver malignancy with increasing global incidence. Because of the frequent absence of symptoms, only 22% of patients have the opportunity to undergo surgery[1]. In cases with advanced biliary tract cancer (BTC), the current standard of care is systemic chemotherapy. However, chemotherapy is usually complicated with more adverse events, and for patients with metastatic BTC, who experience progression even undergoing chemotherapy, there aren't efficacious protocols as the second line treatment[2].

Anti-HER2 molecular targeted agents are established for treating cancers with HER2 gene amplification and are mostly employed in breast cancer[3]. A combination of two HER2-targeted agents also demonstrated to have clinical efficacy in advanced HER2-positive metastatic gastric and colorectal cancers.[4] Recently, pertuzumab and trastuzumab for HER2-positive, metastatic BTC (n = 39) are reported to have a 23% objective response rate (ORR) and no treatment-related serious adverse events or death cases.[5] To develop an efficacious second line treatment for BTC, combine HER2 targeted therapy with others might be a good solution.

Our previous reports had shown that pembrolizumab combined with lenvatinib showed a good response in advanced BTC, with ORR of 25% and disease control rate of 78.1%[6]. Recently, an article published in *Nature* had revealed that EGFR activation limits the response of liver cancer to lenvatinib in HCC[7]. And combination therapy of lenvatinib and geftinib received meaningful clinical responses in patients with

EGFR high HCCs. HER2 is one of the human epidermal growth factor receptor family numbers. We assumed that HER2 amplification limited the response of levatinib for BTC. In our case, combining HER2-targeted therapy and levatinib for refractory BTC achieved a satisfying response, which may prove our assumption.

Case Report

On 5 November 2019, a 64-year-old Chinese male patient was admitted to Peking Union Medical College Hospital, because of discovering liver tumor by ultrasound in physical examination and manifested no positive symptoms. The patient had a history of hepatitis B virus infection for 29 years. Magnetic resonance imaging (MRI) showed a 6 cm tumor in the right liver. The liver function test was normal. The serum tumor marker showed that cancer antigen199 (CA199) was 103.9 U/ml (normal range was < 34 U/ml), carcinoembryonic antigen (CEA) was 7.1 ng/ml (normal range was < 5 ng/ml), and alpha-fetoprotein (AFP) was 12.5 ng/ml (normal range was < 20 ng/ml). The patient was not a candidate for surgical intervention, because PET-CT showed bilobar disease with innumerable liver lesions and metastatic lymph nodes. After a biopsy of the tumor, pathological diagnosis confirmed poorly differentiated adenocarcinoma, with immunohistochemical staining of CK7(+), CK19(partly+), Her-2 (3+). (Figure 1) Next-generation sequencing verified the amplification of the Her-2 gene. As the result, the patient was diagnosed as poorly differentiated ICC with multiple lymph nodes metastases (hilar, posterior pancreatic head, paraaortic, and diaphragmatic angle of right heart lymph nodes) harboring Her-2 amplification (cT2N1M0, stage IIIb).

Platinum-based chemotherapy was recommended. Because the patient was worried about adverse events of chemotherapy, he received the pyrotinib (administered orally each day at a dose of 400 mg per day) and tegafur (administered orally each day at a dose of 40 mg per day). But after six months of treatment, PET-CT showed enlargement of primary lesions and metastatic lymph nodes, with appearing of bone metastasis in the lumbar spine and pubis, the disease was evaluated progressed. (Figure 2). The progress free time of first-line treatment was 6 months. The patient developed grade 3 adverse reactions including skin rash, hypertension, and increased bilirubin concentration, but no grade 4 or 5 adverse reactions were observed.

After discussion with the patient and his families, second-line pyrotinib (administered orally each day at a dose of 80 mg per day) and lenvatinib (administered orally each day at a dose of 12 mg per day) coexisting with pembrolizumab (administered 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks) were applied. After two months, the lesions in the liver were found to have increased by MRI, but tumor markers decreased. We reevaluated the efficacy of treatment with a multi-disciplinary team including surgery, internal medicine oncology, and radiology department. Pseudo-progression was suspected based on the performance improvement and decrease in tumor markers, so the patients continued the treatment.

Four months later, the PET-CT showed that the primary lesions had shrunk, accompanied by CA 199 and CEA response (CA 199 level decreased from 185 U/ml to 57.3 U/mL, CEA level decreased from 8.1ng/mL to 2.6 ng/mL). This evaluation of efficacy was a partial response. In June 2020, lenvatinib was reduced to 8 mg per day because of increased bilirubin. The recent response evaluation by PET-CT in May 2021, was a complete response. The progress free time of second-line treatment is 26 months up to now. The patient developed grade 3 adverse reactions after using three drugs including fatigue, irregular bowel movement, skin rash, hypertension, and increased bilirubin concentration, but no grade 4 or 5 adverse reactions were observed. Written informed consent to publish the case details was obtained from the patient.

Discussion

Compared with the published literature, this is the first report to show a complete response for advanced BTC progressed case after first-line therapy. The combination therapy of adding pyrotinib to pembrolizumab and lenvatinib identified here may present a promising strategy for advanced BTC who have a high level of HER2. Our patient received second-line therapy without chemotherapy, and achieved a complete response. Now the disease is stable and the patient has lived for about 20 months since he was diagnosed.

At present, gemcitabine combined with cisplatin is widely used as the first-line treatment in patients with advanced ICC[8]. However, the prognosis is very poor (median overall survival was 11.7 months and median progress free time was 8 months) and 70.7% of patients had grade 3 or 4 toxic effects[8]. Our patient worried about the adverse events of chemotherapy and received the pyrotinib and tegafur as the first-line line treatment and the progress free time of it was 6 months, with no serious adverse events. HER2 targeted therapy provided another choice for patients in first-line therapy with HER2 amplification, with comparable progress free time and fewer adverse events.

Currently, there is no standard second-line treatment for advanced BTC. The ABC-06 clinical trial with FOLFOX chemotherapy reported a median progress free time of 4.0 months and a median OS of 6.2 months[9]. HER2-targeting antibody is recognized as a new therapeutic option against advanced BTC recently. Dual-HER2 targeted therapy for HER2-positive metastatic BTC has the median progress free time of 4.0 months, and the median OS of 10.9 months[5]. Compared with chemotherapy, HER2 targeted therapy appeared as a better scheme for HER2-positive metastatic BTC. However, both results were significantly shorter than the 26 months in our study. Our patient achieved complete response with combination therapy, indicating that he acquired an effective treatment. In conclusion, HER2 targeted therapy combined with pembrolizumab and lenvatinib was probably effective for HER-2 amplification ICC.

The human epidermal growth factor receptor (ERBB or HER) family includes HER1 (also known as EGFR), HER2 (ERBB2), HER3, and HER4. The combination of the EGFR inhibitor geftinib and lenvatinib displayed potent anti-proliferative effects in HCC tumors.[7] Inhibition of fibroblast growth factor receptor (FGFR) by

lenvatinib treatment leads to feedback activation of the EGFR–PAK2–ERK5 signaling axis in EGFR high patients.[7] HER2 could also combine with EGFR and activate the EGFR–PAK2–ERK5 signaling axis. Thus, HER2 amplification could be another resistance mechanism of lenvatinib. The good response in our patient suggested that a combination of HER2-targeted therapy and lenvatinib was a potentially effective treatment for HER-2 amplification cholangiocarcinoma. The more specific mechanism needs further clinical studies and basic studies to prove.

Pseudo-progression is the unique response pattern of immune checkpoint inhibitors manifesting an increase in the size of tumor lesions with tumor necrosis, before a subsequent decrease in tumor burden[10]. The response after an increase in total tumor burden and the presence of new lesions were associated with favorable survival in pseudo-progression. Although our patient had increased tumor burden after using immunotherapy, he had improvement of the performance and decrease in tumor markers. As a result, he was suspected to have pseudo-progression after immune checkpoint inhibitors. The pseudo-progression indicated a favorable response to immunotherapy in our patient. It could be explained by the inhibition of angiogenesis by targeting VEGF/VEGFR enhances the antitumor efficacy of immunotherapy. Moreover, preclinical data showed that dual HER2 and PD-1 inhibition also had synergistic effect.[11,12]

In summary, adding pyrotinib to pembrolizumab and lenvatinib offered a chemotherapy-free option and could achieve complete tumor suppression with no serious AEs for this BTC patient with HER2 amplification.

Abbreviations

ICC: intrahepatic cholangiocarcinoma; BTC: biliary tract cancer; ORR: objective response rate; MRI: Magnetic resonance imaging; CA199: cancer antigen199; CEA: carcinoembryonic antigen; AFP: alpha-fetoprotein; CR: complete response

Declarations

Ethics approval and consent to participate

Since it was a case report, the ethics approval is not applicable. Written consent was obtained from the patient for publication of this case report. The patient gave consent for his clinical details as well as any identifying images to be published in this study.

Consent for publication:

All authors consent to the publishing of this case report.

Availability of data and material:

All data generated or analysed during this study are included in this published article.

Competing interests:

The authors disclose no conflict of interest.

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Authors' contributions

Z.J and Y.X. wrote the manuscript. All authors read and approved the final manuscript.

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Figures

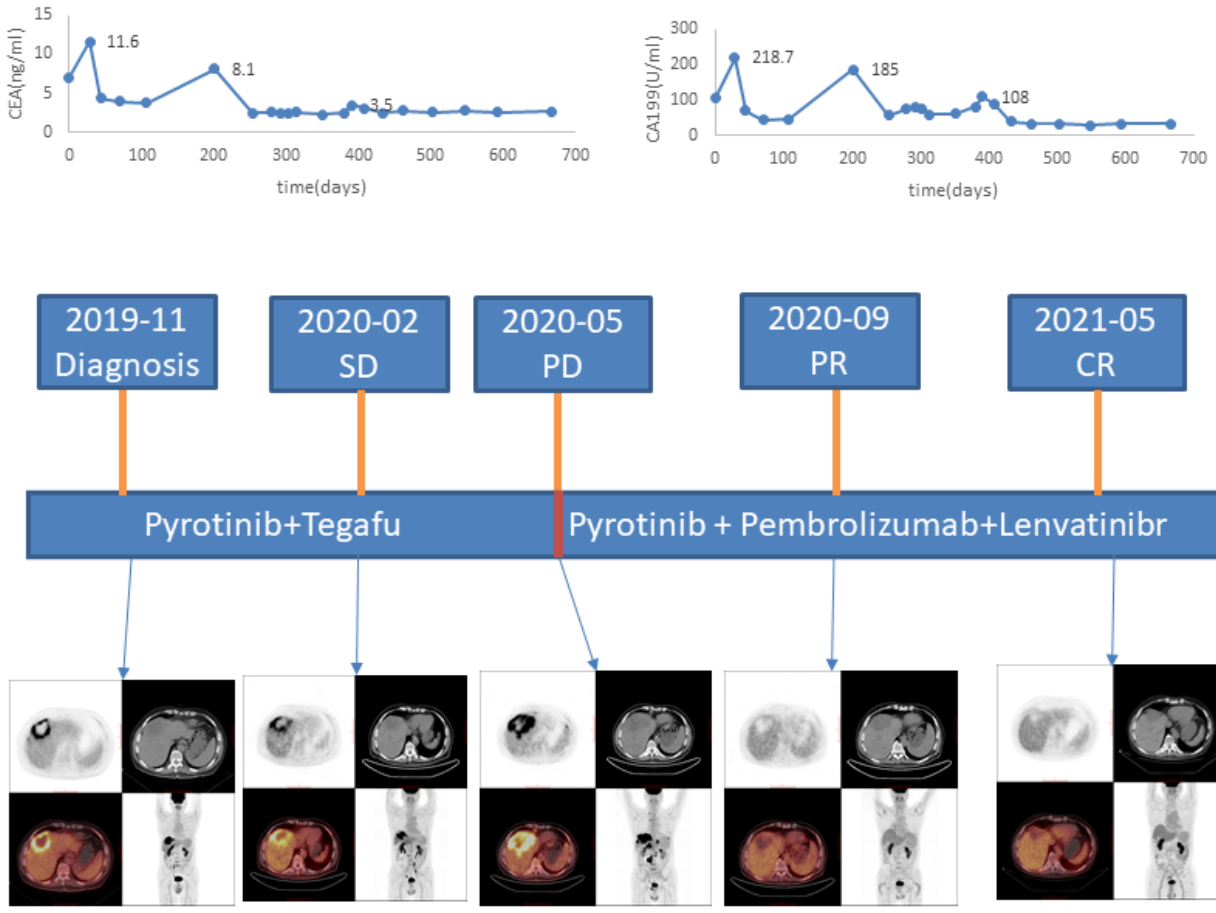

Figure 1

Images of patient during treatment, and preoperative and postoperative tumor maker results: carcinoembryonic antigen (CEA)、carbohydrate antigen 199 (CA199).

Abbreviation: SD: stable disease; PD: progressive disease; PR: partial response; CR、complete response.

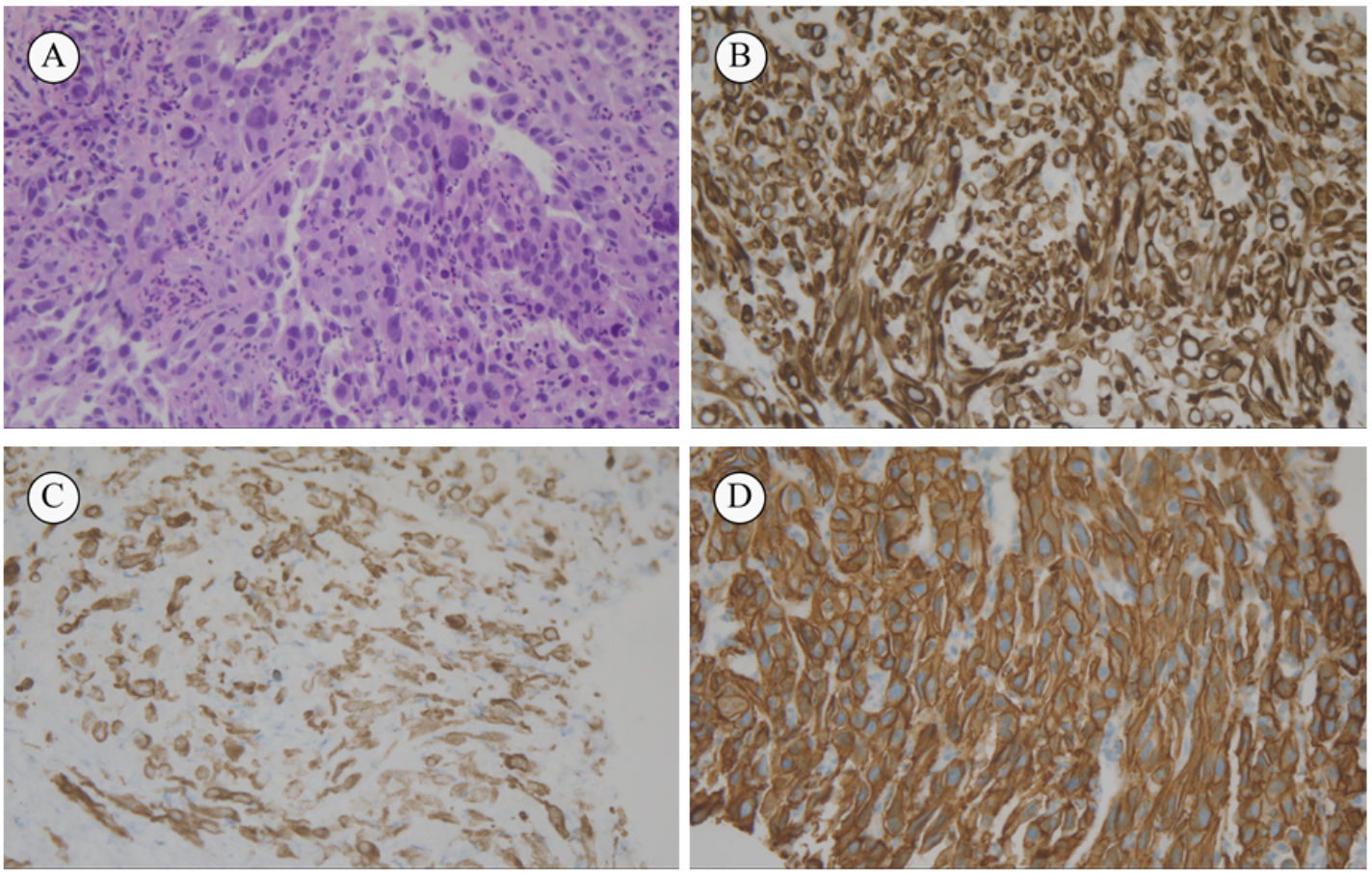

Figure 2

Pathological examination of the reported case. (A) Hematoxylin and Eosin (200×); (B) CK7(+)(200×),(C) CK19(partly+)(200×),(D) HER2(3+)(200×).