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Case Report

Successful Long-term Treatment with Modified Dose Pemigatinib in FGFR2-BICC1 Intrahepatic Cholangiocarcinoma: A Case Report

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Abstract

Patients with advanced intrahepatic cholangiocarcinoma (iCCA) have a poor prognosis. Recent advances in molecular profiling offer hope by enabling targeted treatment for those with specific mutations, potentially increasing survival rates. Pemigatinib targets fibroblast growth factor receptor 2 (FGFR2) fusions or rearrangements, providing a promising avenue for treatment. Here, we report the case of a 70-year-old woman diagnosed with advanced iCCA, characterized by FGFR2-Bicaudal family RNA binding protein 1 (BICC1) fusion, who received pemigatinib therapy. Despite adverse effects including mucositis and nail changes, she continued treatment following dose adjustments for over 18 months. This report highlights the importance of dose optimization in maintaining patients on therapy and preventing treatment discontinuation. Real-world patients are often more fragile than those in clinical trials, necessitating tailored dose adjustments. However, the literature on alternative dose modifications remains limited. This case represents the longest documented successful treatment of advanced iCCA with pemigatinib in Taiwan, emphasizing the potential efficacy of pemigatinib treatment in a real-world setting.

Keywords: Cholangiocarcinoma, fibroblast growth factor receptor 2, pemigatinib

Introduction

Currently, infusional 5-fluorouracil combined with leucovorin and oxaliplatin (FOLFOX) is considered the standard preferred regimen for the second-line treatment of advanced/metastatic cholangiocarcinoma. However, the objective response rate (ORR) with this regimen is only 5%,[1] and survival remains poor for those with advanced or metastatic cholangiocarcinoma. With advances in molecular biology and genome sequencing, the European Society for Medical Oncology recommends next-generation sequencing (NGS) for patients with advanced cholangiocarcinoma to identify

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actionable molecular aberrations.[2] Pemigatinib, a fibroblast growth factor receptor 2 (FGFR2) inhibitor, is the first targeted therapy for cholangiocarcinoma. Here, we present a patient who received prolonged pemigatinib treatment for cholangiocarcinoma and showed a sustained response despite dose reduction. This is the first case report demonstrating the effectiveness of pemigatinib at a dose of 4.5 mg every other day in a fragile patient.

Case Report

A 70-year-old Taiwanese woman was admitted to our hospital because of a 2-week history of abdominal fullness and jaundice. Magnetic resonance imaging showed a 10.8 cm × 10.2 cm lobulated mass lesion with diffusion restriction at the right liver, causing obliteration of the right portal vein [Figure 1]. No distant organ metastasis was detected. She underwent surgery, including extended right hepatectomy, S1 segmentectomy, cholecystectomy, and hepatic hilum lymph node dissection in July 2020. The pathological diagnosis confirmed intrahepatic cholangiocarcinoma (iCCA) (pT3N1M0). Four months after surgery, contrast-enhanced computed tomography (CT) disclosed some enlarged lymph nodes along the common hepatic artery, left paraaortic, aortocaval regions, and metastatic lymphadenopathy and recurrent cholangiocarcinoma were considered. Due to her older age, poor performance, and fragile status, she received gemcitabine (800 mg/m^2) infusion on day 1 plus S-1 (80 mg/day) on days 1–10 from December 2020 as the first-line systemic treatment.[3] This regimen was repeated every 2 weeks. The tumor specimen was profiled using NGS, which identified *FGFR2-BICC1* fusion. After 14 cycles, she switched to S-1 monotherapy for 2 cycles, then chemotherapy was discontinued upon her request.

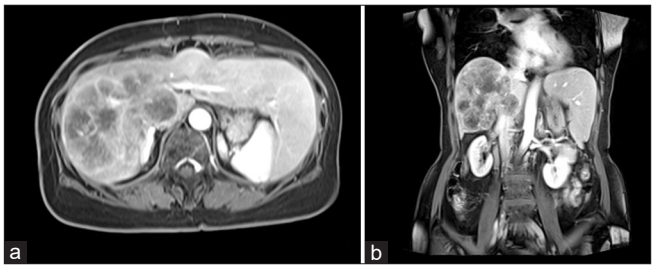

Figure 1: Magnetic resonance imaging revealed a large, lobulated mass in the right lobe of the liver, as shown in the axial view (a) and coronal view (b)

A follow-up CT scan in July 2022 revealed two new liver nodules, indicating possible cancer progression. Due to economic constraints, she started oral 13.5 mg pemigatinib every other day as a second-line treatment in August 2022. Figures 2 and 3 show the CT image and timeline of events in her clinical course, including a partial response after 2 months of pemigatinib treatment. Before pemigatinib treatment, ophthalmic problems were ruled out, and baseline serum phosphate was normal (3.7 mg/dL). During the course of treatment, we routinely monitored side effects, particularly retinal pigment epithelial detachment, but no issues were detected. However, hyperphosphatemia (6.2 mg/dL) occurred within 1 month of pemigatinib treatment, which was managed with a low-phosphate diet and nonabsorbed phosphate-binding agents with sevelamer carbonate. The patient also developed paronychia, along with painful sensations, blisters, and desquamation over the fingers [Figure 4]. Despite applying topical corticosteroids and supportive care, the symptoms persisted, prompting a dosage reduction of pemigatinib to 9 mg and eventually to 4.5 mg once every other day, resulting in symptomatic relief. A subsequent CT scan in January 2024 indicated stable disease. She is currently still receiving pemigatinib treatment without grade 3 or 4 adverse effects and has achieved a response duration of over 18 months.

Discussion

Fibroblast growth factor (FGF) signaling is involved in a variety of biological functions, including cell metabolism, growth, proliferation, and differentiation. Dysregulation of the FGFR pathway can lead to an abnormal cascade of transduction pathways, including signal transducer and activator of transcription, mitogen-activated protein kinase, and phosphoinositide-3-kinase/Akt pathway, gradually leading to tumor formation.[4] Several studies identified *FGFR* genomic alterations in approximately 10%–20% of iCCAs.[5,6] To block the potential of FGF/FGFR signaling in carcinogenesis, several novel FGFR inhibitors which target the FGF/FGFR pathway have been developed, some of which are used in clinical practice.

Pemigatinib, an oral FGFR inhibitor, selectively targets FGFR1, FGFR2, and FGFR3. In the FIGHT-202 trial, pemigatinib demonstrated efficacy in advanced cholangiocarcinoma patients harboring *FGFR2* fusions or rearrangements.[7] The trial reported an ORR of approximately 35.5% and a median

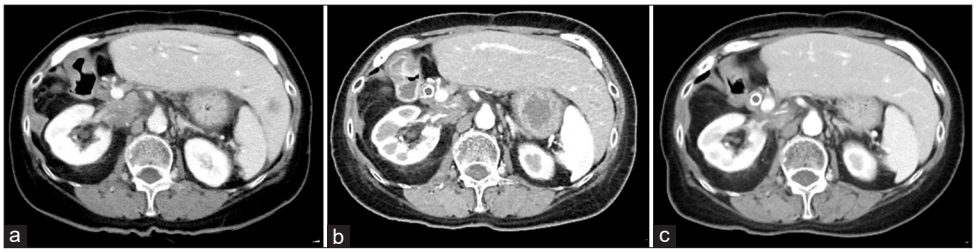

Figure 2: Computed tomography image showed hepatic metastasis before pemigatinib treatment (a), a partial response was observed after 2 months (b) and cancer regression occurred after 1 year of treatment (c)

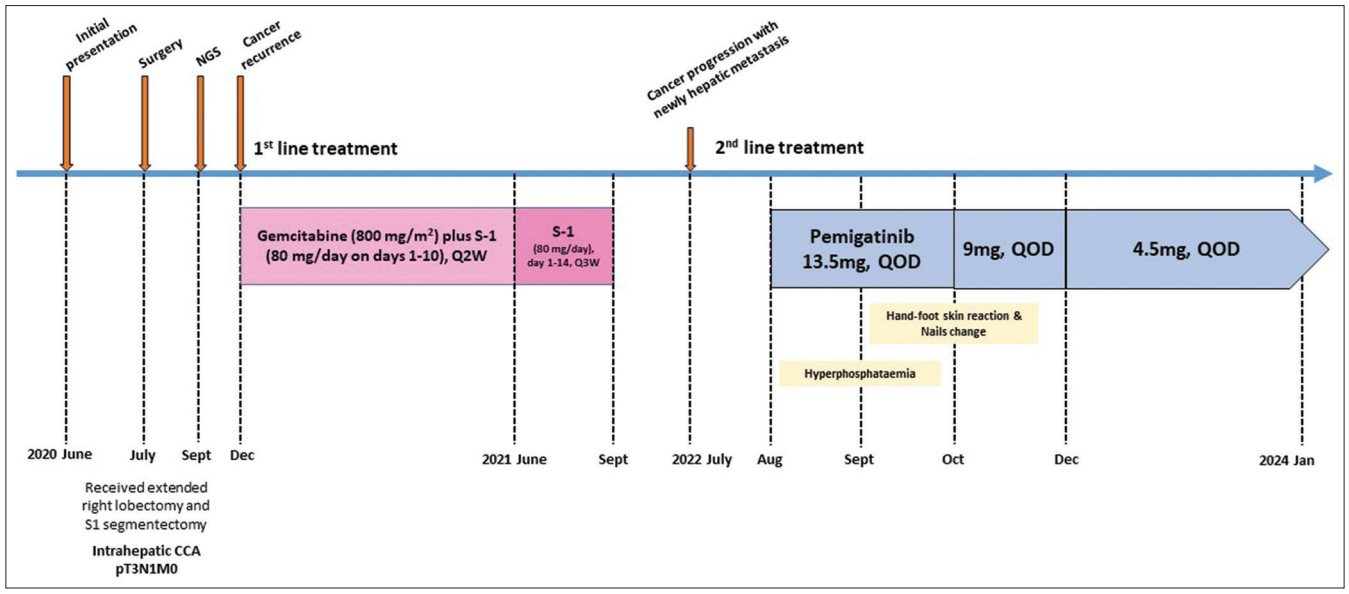

Figure 3: Timeline of events from symptoms to pemigatinib treatment. CCA: Cholangiocarcinoma, NGS: Next-generation sequencing

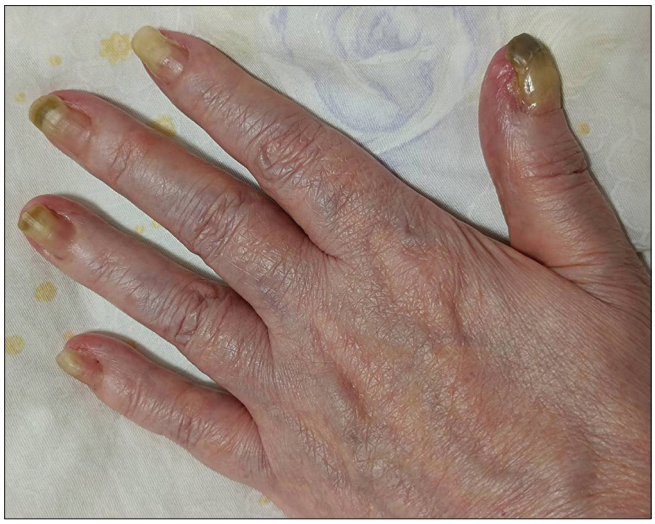

Figure 4: Nail toxicity induced by pemigatinib

duration of response of 7.5 months, leading to Food and Drug Administration approval for the treatment of previously treated, locally advanced, or metastatic *FGFR2*-fusion or rearrangement cholangiocarcinoma. Ongoing trials such as FIGHT-302 are evaluating the efficacy of pemigatinib compared to standard chemotherapy in treatment-naïve patients with *FGFR2*-rearrangement-positive cholangiocarcinoma.[8] Despite the promising efficacy of pemigatinib, reports of toxicities persist. Hyperphosphatemia has been reported to be the primary treatment-related adverse effect in FGFR inhibitor trials, along with hand-foot skin reactions, dermatologic toxicities, ophthalmic issues, and gastrointestinal upset.[7,9] Managing hyperphosphatemia involves various strategies, including a low-phosphate diet, traditional phosphate-lowering agents, adjusting the dosage, or discontinuing the FGFR inhibitor based on blood phosphate levels.[9] Regarding ocular toxicity, ophthalmic examinations are advised before starting pemigatinib. Regular eye check-ups during treatment can promptly identify central serous retinopathy and retinal pigment epithelial detachment and allow for the timely cessation of the medication to prevent further vision loss.[10]

In our case, deviating from the FIGHT-202 protocol, the patient initially received 13.5 mg of pemigatinib every 2 days. However, due to financial limitations and the emergence of associated adverse effects including hyperphosphatemia, dermatologic issues, and fingernail changes, we gradually reduced the dosage to 4.5 mg once every other day. This lower dosage was both safe and maintained efficacy in our patient. Although this is a single case report, it highlights the differences in management between real world and clinical trial patients. The prognosis for advanced cholangiocarcinoma is poor, and precision medicine has gradually become a mainstream of management. Our case report illustrates the successful implementation of a dose-reduction regimen with pemigatinib, resulting in the long-term survival. It is important to optimize treatment based on the patient's economic situation, drug toxicities, and treatment effectiveness. Additional studies assessing the effectiveness and safety of pemigatinib in the real-world settings are warranted.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Acknowledgment

We extend our sincere thanks to the patient and her family for their invaluable contributions to this research.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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