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CASE SERIES

Clinical experience with pemigatinib for previously treated metastatic cholangiocarcinoma: practical considerations from clinical cases

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Abstract

The management of advanced cholangiocarcinoma (CCA) is challenging. In patients with advanced CCA, gemcitabine/cisplatin combination is the standard frontline chemotherapy, with 5-fluorouracil-based regimens preserved for subsequent lines; however, the expected survival is poor. Pemigatinib was approved for locally advanced or metastatic CCA with *FGFR2* fusions or rearrangement. Pemigatinib has a manageable safety profile and achieves a durable response. Nearly 50 patients with CCA have been treated with pemigatinib in the United Kingdom. However, clinical experience with pemigatinib is lacking. We present our experience with three clinical cases to illustrate the position of pemigatinib in the management of CCA and related toxicities.

Keywords: cholangiocarcinoma, *FGFR2* fusion, metastatic disease, pemigatinib.

Citation

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Background

Molecular targeted therapy, that is, molecules targeting specific receptors, antigens or pathways according to the underlying molecular or genetic abnormalities, has resulted in paradigm shifts in treatment across a wide spectrum of malignancies.[1] Targeted agents mainly work by inducing apoptosis of tumour cells, modulating the tumour microenvironment and/or directly inhibiting specific oncogenic drivers.[2] Thus, they have the potential to halt tumour progression and invasion, as well as overcome resistance to chemotherapy.[3] Several types of targeted therapies exist, including small molecules, monoclonal antibodies and cancer vaccines.[4] The current treatment landscape of non-small-cell lung cancer (NSCLC) represents a blueprint for the survival benefits targeted therapy can provide according to the unique genomic profile of the patients;[5] pivotal clinical trials showed that targeted molecules doubled the survival of patients with NSCLC.[6,7]

The evolution of precision medicine in NSCLC opened the gate for investigating the feasibility of targeted therapy in other cancer types. Cholangiocarcinoma (CCA) is a heterogeneous group of malignancies of the bile ducts that represents a promising candidate for targeted therapy due to its diverse molecular features.[8] Although the incidence of CCA is low in the Western world, roughly 0.35 to 2 per 100,000 per year, its global incidence has steadily increased over the last 30 years.[9,10] Anatomically, CCA is classified into perihilar, distal and intrahepatic subtypes.[11] Hepatobiliary resection and adjuvant chemotherapy form the backbone of treatment options for CCA in the early resectable stage, with a 5-year overall survival (OS) of 25–40%.[12] The role of neo-adjuvant therapy for CCA remains unclear. Clinical trials in this area are ongoing; however, data are still limited.[13] However, the majority of patients with CCA present with unresectable, locally advanced or metastatic disease in which systemic therapy combinations (gemcitabine/cisplatin and 5-fluorouracil/oxaliplatin (FOLFOX) regimens) are the mainstay management lines.[14] Despite the ongoing investigations of first-line chemotherapeutic combinations with immune-checkpoint inhibitors or nucleotide analogues, locally advanced or metastatic CCA continues to have a poor prognosis and a 5-year OS of <10%.[15,16]

The advances in molecular profiling led to the identification of actionable mutations in patients with CCA, including *IDH1* and *IDH2* and fusions of *FGFR2*.[17] Genetic alterations in *FGFR2* – mainly fusions and rearrangements – are present in up to 16% of patients with intrahepatic CCA (iCCA).[18] Malignant cell angiogenesis, survival, migration and proliferation result from ligand-independent activation of numerous signalling networks triggered by clonal *FGFR2* gene fusions in CCA.[19] The current evidence suggests a prognostic role of *FGFR2* rearrangements and, possibly, for *FGFR2* or *FGFR3* alterations in patients with iCCA.[20] Early clinical trials showed limited antitumour activity of non-selective FGFR tyrosine kinase inhibitors in CCA.[21–23] However, the introduction of selective FGFR inhibitors has significantly improved the response and survival of patients with advanced CCA with *FGFR2* fusion or rearrangement. Pemigatinib is a selective FGFR1–3 inhibitor with potent antitumour activities and inhibition of FGFR-mediated tumour invasion and progression.[24,25] In the FIGHT-202 trial, once-daily pemigatinib at a dose of 13.5 mg during the first 14 days of the 21-day cycle was investigated in previously treated locally advanced or metastatic CAA with *FGFR2* fusions or rearrangements. The results showed that pemigatinib led to an objective response rate of 37% (95% CI 27.94–46.86%), a median duration of response of 9.13 months (95% CI 6.01–14.49 months) and a disease control rate of 82% (95% CI 74–89%). The treatment was well tolerated, with a manageable safety profile.[26,27] The promising results of this trial led to the ongoing phase III FIGHT-302 trial assessing pemigatinib in the first-line setting.[28]

In 2019, the FDA approved pemigatinib as the first targeted therapy for locally advanced or metastatic iCCA with *FGFR2* fusions or rearrangement. This was followed by a 'conditional approval' of pemigatinib for the same indication in the United Kingdom in April 2021. To date, nearly 50 patients with CCA have been treated with pemigatinib in the United Kingdom. However, experience with pemigatinib in real-world practice is still lacking, and oncologists have limited experience with pemigatinib use in later lines of the management of locally advanced or metastatic CCA. This manuscript presents real-world experience with three clinical cases to illustrate the position of pemigatinib in the management algorithm of CCA and the management of pemigatinib-related toxicities.

Case description

This article was prepared in concordance with the CARE Case Report Guidelines.[29] Signed patient consent was not required as the details have been de-identified.

Pemigatinib provides symptomatic relief and improved QoL in advanced metastatic CAA

Case 1

A female patient in her 30s initially presented with pelvic and perineal pain, fatigue, unintentional weight loss and abdominal distension. The patient had no relevant medical or family history. Upon physical examination, palpable ascites with no abdominal masses was noted. The pelvic and rectal exemptions also revealed extrinsic peritoneal nodularity. In September 2020, CT demonstrated a large solitary liver lesion and extensive peritoneal and omental metastases. An ultrasound-guided liver biopsy confirmed a moderate-to-poorly differentiated adenocarcinoma, which was CK7 and CK19 positive, and CK20 and CDX2 negative, in keeping with a metastatic iCCA. Laboratory examinations showed modestly elevated C-reactive protein and a normal albumin level.

The patient started cisplatin 25 mg/m^2 plus gemcitabine 1000 mg/m^2 on day 1 and day 8 of a 21-day cycle for six cycles. In January 2021, the CT revealed partial response; however, another follow-up CT in May 2021 showed significant progression of the primary tumour, peritoneal metastases, omental deposits and progressive ascites. Thus, the patient started capecitabine 1000 mg/m^2 on days 1–14 plus oxaliplatin 130 mg/m^2 on day 1 of a 21-day cycle. This was stopped after two cycles due to early progression and deteriorating performance status (PS) in June 2021.

Following the confirmation of the presence of *FGFR2* fusion, the patient started pemigatinib 13.5 mg once daily on days 1–14 of a 21-day cycle in July 2021. At the time of pemigatinib initiation, the patient had PS 2, with symptoms of sub-acute bowel obstruction, including early satiety, unintentional weight loss, nausea, vomiting and bloating/abdominal distension. Symptomatic benefit was noted within 3 weeks of starting pemigatinib, including improvement in ascites, appetite, early satiety and nausea. The PS improved from 2 to 1 after 6 weeks of beginning pemigatinib. The CT scans at cycles 3 and 7 showed stable disease, coupled with significant symptomatic improvement. Pemigatinib was continued for ten cycles. In February 2022, radiological and clinical progressions were noted with progressive disease in the omentum and liver and worsening ascites. Pemigatinib treatment was stopped, and the patient started symptomatic management.

Regarding safety, the serum phosphate rose from a baseline level of 0.96 mmol/L to 2.45 by day 7 and 2.76 by day 14, falling back to 0.97 after the 'rest week'. Hyperphosphataemia was initially managed with a low-phosphate

diet but this was poorly tolerated. Calcium acetate was then administered during the second cycle of pemigatinib. Recurrent hyperphosphataemia was noted in cycles 2 and 3 despite the administration of calcium acetate and low-phosphate diet attempts; therefore, the pemigatinib dose was reduced to 9 mg daily from cycle 4 onwards. After dose reduction, serum phosphate levels did not rise above 1.63 mmol/L during the remainder of pemigatinib therapy. Other noted adverse events were grade 1 arthralgia managed with oral analgesia, and skin induration in both axillae with no specific management. Nonetheless, the patient reported no issues with treatment compliance and tolerability during the 3-weekly monitoring reviews.

In April 2022, the patient deceased due to the progression of the disease.

Case 2

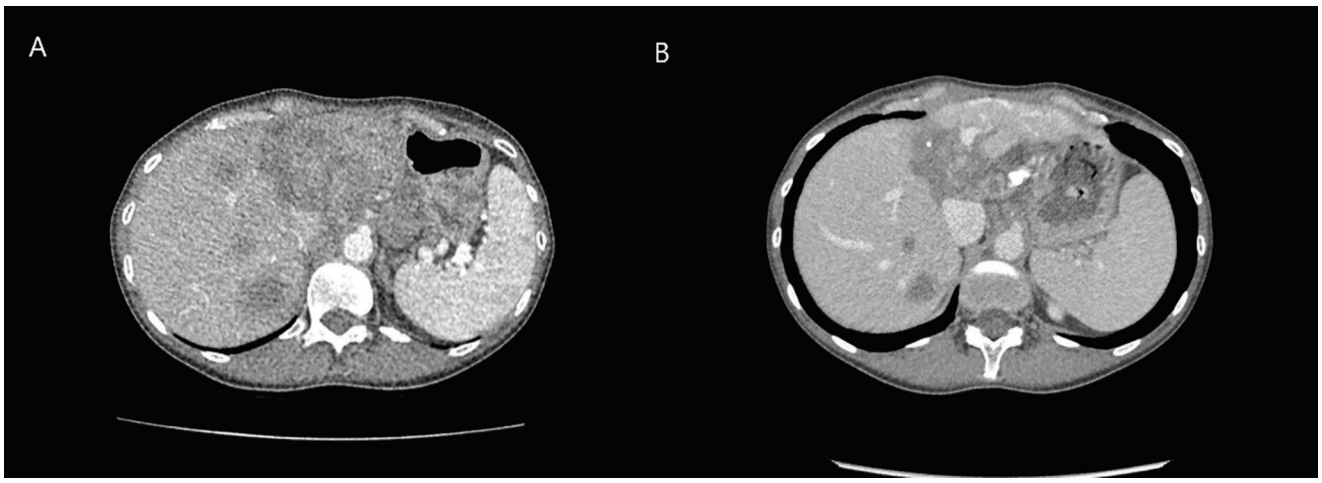
A female patient in her 40s with a history of hypertrophic obstructive cardiomyopathy presented early in the COVID-19 pandemic with back pain, which did not respond to analgesia and physiotherapy and was subsequently found to have a right upper quadrant abdominal mass. In August 2020, a CT scan revealed a large liver mass, hepatic and pulmonary metastasis, and enlarged para-aortic lymph nodes. The ultrasound-guided liver biopsy confirmed the diagnosis of poorly differentiated metastatic iCAA. The immunohistochemical examination showed positive AE1/AE3 and CK7. The serum carbohydrate antigen (CA19-9) level was markedly elevated (1204 U/mL).

In September 2020, the patient started cisplatin 25 mg/m^2 plus gemcitabine 1000 mg/m^2 on day 1 and day 8 of a 21-day cycle for six cycles. The chemotherapy regimen led to significant symptomatic improvement and serum CA19-9 reduction to 373 U/mL. A CT scan in November 2020 showed a reduction in the tumour mass, suggestive of partial response. The patient completed the sixth cycle of cisplatin plus gemcitabine in January 2021, and the serum CA19-9 level continued to fall to reach 187 U/mL. A CT scan in February 2021 showed a sustained tumour response in the liver but progression of lung metastases. Therefore, *FGFR2* fusion testing was arranged and showed *FGFR2* gene rearrangement.

The patient started pemigatinib 13.5 mg once daily on days 1–14 of a 21-day cycle in April 2021 due to recurrent abdominal pain and radiological evidence of significant disease progression. The treatment led to rapid resolution of abdominal pain within 3 days and restoration of daily activities, with an observed improvement in quality of life (QoL). The serum CA19-9 level decreased from 4262 to 946 U/mL after one cycle. A CT scan in June 2021 showed a partial response (Figure 1). In September 2021, the patient developed new neck and left shoulder pain, and an MRI scan showed progression involving the seventh cervical vertebra, causing nerve root compression. Thus, pemigatinib was stopped, palliative radiotherapy was given to the cervical spine, and FOLFOX was initiated in October 2021. The FOLFOX was discontinued after two cycles only due to poor tolerability.

Pemigatinib was well tolerated in this case with development of grade 1 toxicities only, including hair thinning, dry skin and fatigue. The routine blood monitoring showed no elevation in serum phosphate level, and the patient was compliant with the treatment according to the 3-weekly monitoring reviews.

Figure 1. A contrast-enhanced CT scan of the abdomen. (A) Axial image showing the hepatic mass at the time of pemigatinib initiation in April 2021. (B) Axial image in June 2021 showing a partial response.



Management of pemigatinib-related toxicities

Case 3

A 67-year-old man was incidentally diagnosed with iCCA when he presented with gallstone pancreatitis in March 2020. There was no relevant medical or family history. He proceeded to have a left hemihepatectomy and cholecystectomy in April 2020; histology confirmed this was a complete resection of a pT2 NX R0 iCCA. This was not followed by adjuvant chemotherapy.

He was diagnosed with metastatic CCA when MRI and CT imaging in October 2020 confirmed recurrence in the liver and lung. He was enrolled into a clinical trial in December 2020 to receive cisplatin plus gemcitabine, with or without immunotherapy. At the time of enrolment, the patients had PS 0 and normal hepatic and renal functions. Four months after enrolment, in April 2021, a CT scan showed stable lung disease but progressive hepatic disease. The patient's molecular profiling showed negative *HER2* and *NTRK* mutations, intact mismatch repair and positive *FGFR2* fusion. Thus, the patient started pemigatinib 13.5 mg once daily on days 1–14 of a 21-day cycle in July 2021, alongside supportive medications: topical emollient, antiemetic and antidiarrhoeal agents.

Before the start of cycle 2 (29 July 2021), the serum phosphate level increased to 2.06 mmol/L and the patient presented with grade 1 dry mouth, mucosal dryness and diarrhoea. One month later, grade 1/2 toxicities were reported in the form of diarrhoea, abdominal pain, hair loss and nail discolouration. Therefore, the pemigatinib dose was reduced to 9 mg daily at cycle 3, significantly improving grade 2 diarrhoea and dry mouth. However, the nail changes persisted, and the patient was referred to a podiatrist. Aside from the observed toxicities, the patient showed partial response in the CT scan 2 months after treatment, and the serum CA19-9 decreased to a normal level.

In November 2021, the patient suffered from nasal congestion and rash/erythema with induration over the right shin, which responded to topical steroids. Two weeks later, the patient reported abdominal discomfort and mild constipation. Thus, the decision was made to introduce a phosphate binder. A CT scan in January 2022 (6 months of treatment) showed stable disease, with a mild increase in the liver and pulmonary metastases. The serum CA19-9 increased to 161 U/mL. At the same time, the painless toenail changes were persistent, and the patient reported a painful heel during walking, suggestive of plantar fasciitis. Dermatological review noted diffuse destruction of the toenails with onycholysis and subungual haematoma; the fingernails presented with distal onycholysis only (Figure 2). Due to the persistent nail changes, a 2-week treatment break was decided, and pemigatinib was continued at a reduced dose of 9 mg. Following the re-initiation of pemigatinib, the patient reported improved plantar fasciitis; however, nail discolouration worsened. The serum CA19-9 has dropped to 74 from 240 U/mL. A CT scan on 28 February 2022 showed stable disease.

Figure 2. Pemigatinib fingernail-related changes. Fingernails show diffuse destruction, onycholysis and subungual haematoma.

One week after the CT scan, the patient reported grade 2/3 generalized abdominal pain and persistent nail discolouration. Thus, a 3-week break was commenced, leading to the resolution of abdominal pain but with ongoing nail changes. Pemigatinib 9 mg was restarted, and a CT scan in May 2022 showed stable pulmonary metastasis and a decrease in the size of hepatic metastases. Nonetheless, the patient reported heartburn and nizatidine was initiated. The patient then continued pemigatinib, with a supportive H2 blocker, an antidiarrhoeal agent and emollients. In August 2022, the patient showed improved nail changes with no signs of infection and stable grade 1 diarrhoea. A CT scan in September 2022 showed multifocal progression in the known hepatic and lung disease with new nodal and lung metastasis, and pemigatinib was discontinued, leading to a duration of benefit of 14 months. During pemigatinib therapy, the patient was able to maintain routine daily activities as most related toxicities were grade 1 or 2.

Discussion

Advanced unresectable CCA (accounting for nearly 70% of CCA cases at presentation[30]) represents a management challenge for oncologists and usually carries a high symptomatic burden, limited response to standard systematic chemotherapy, high treatment-related

toxicities, impaired QoL, and an overall poor prognosis.[31] In these patients, systemic chemotherapy is administered as palliative treatment in fit patients with PS ≤2. Robust clinical evidence supports the gemcitabine/cisplatin combination as the standard frontline chemotherapy for advanced CCA; however, the response rate to frontline chemotherapy is modest, and the expected progression-free survival is only 8 months.[30] Upon progression on frontline therapy, 5-fluorouracil-based chemotherapy has become the standard second-line option based on the results of the phase III ABC-06 trial.[32] However, the survival benefit with FOLFOX is modest compared to active symptom control. With the evolution in understanding of the molecular heterogeneity of CCA, several targeted therapies have been proposed and shown promising antitumour activities.[33] Pemigatinib is the first approved targeted therapy for locally advanced or metastatic CCA with *FGFR2* fusions or rearrangement.

Patients with unresectable CCA often suffer from a high symptomatic burden and treatment-related toxicities, affecting their physical function and emotional well-being. As the management is mainly for palliative intent, controlling symptomatic burden and improving QoL should be primary management goals during the later lines of treatment.[34] In our experience, pemigatinib led to durable symptomatic benefit in all three cases, even when the radiological evaluation showed stable disease. The duration of benefit ranged from 6 to 14 months, highlighting the benefit of pemigatinib in achieving a response as durable as the standard gemcitabine/cisplatin regimen during later lines of metastatic CCA management. The symptomatic relief in the three cases was reflected in their QoL. Our experience in clinical practice is in line with the reported benefits in the FIGHT-202 trial, which showed a median duration of response of 9.13 months, an objective response rate of 37% and a disease control rate of 82%.[27] In a recent real-world study, three cases with advanced iCCA with *FGFR2* fusions or rearrangements received pemigatinib and showed a trend towards improved OS.[35]

Treatment-related time toxicity has emerged as a relevant indicator of palliative treatment benefits in incurable diseases, including advanced cancers. Time toxicity in cancer can refer to the timing of toxic side-effects resulting from cancer treatment and the associated need for medical attention/hospitalization, as well as the time spent in the hospital for treatment administration or routine monitoring.[36] In the context of advanced cancers, oral therapies may represent more convenient alternatives that are not associated with the need to go to the hospital for infusion visits. Pemigatinib can potentially reduce time toxicity due to fewer hospital visits and no chair time required for a well-tolerated oral anticancer therapy. With the utilization of phone and video consultations and courier service to deliver medications locally, the first case, a resident of a remote area, required only six direct contacts with secondary care over 7 months. Her primary care team delivered the remainder of her investigations and treatment at home.

Pemigatinib has a manageable safety profile. In the phase I FIGHT-101 trial, the most commonly observed grade ≥3 adverse events were hyponatraemia (7%) and pneumonia (7%). No dose-limiting toxicities were observed, whilst the treatment discontinuation rate due to adverse events was 10.2%.[37] In the FIGHT-202, grade ≥3 adverse events were observed in 64% of patients and the treatment discontinuation rate due to adverse events was 9%.[26] In our cases, there was no recorded incidence of grade ≥3 adverse events or treatment discontinuation due to adverse events, reflecting the tolerable safety profile of pemigatinib. Common adverse events related to pemigatinib include hyperphosphataemia, fatigue, diarrhoea, nausea, dysgeusia and dermatological manifestations.[26,37] Therefore, monitoring of serum phosphate levels should be conducted during pemigatinib therapy. In a few cases (4.8% in the FIGHT-202 trial), serous retinal detachment may occur, leading to an impaired outer retinal barrier due to inhibition of the MAPK pathway.[38] Therefore, the pemigatinib therapy protocol should include a baseline ophthalmological examination followed by a routine examination every three cycles.[24]

Hyperphosphataemia is widely considered an on-target effect of FGFR inhibitors due to the downregulation of FGFR1 signalling in the renal tubule. FGFR1 regulates urine excretion of phosphate and phosphate homoeostasis through a cascade of endocrine feedback mechanisms.[39] In patients receiving pemigatinib, hyperphosphataemia occurs early during the first cycle and is suggested to be a marker of exposure. A low-phosphate diet can be initiated in mild hyperphosphataemia (serum phosphate ≤7 mg/dL). If serum phosphate increases up to 10 mg/dL, phosphate-binding therapy should be started; in case of persistent elevation of serum phosphate levels or recurrent hyperphosphataemia despite phosphate-binding therapy, a 2-week treatment break can be attempted. A dose reduction should be tried when restarting pemigatinib if the serum phosphate level recurs to >7 mg/dL. In severe persistent hyperphosphataemia (>10 mg/dL), pemigatinib should be stopped permanently.[24] In our experience, a pemigatinib dose reduction to 9 mg daily was effective in treating recurrent hyperphosphataemia without the need for permanent treatment discontinuation.

Whilst the efficacy and safety of pemigatinib have been established in phase II trials, several gaps still exist in our current understanding of its role in CCA. To date, there is a lack of prospective studies investigating the

predictive biomarkers for response to pemigatinib. Efforts have been made to correlate molecular markers, such as non-coding RNA and cell surface molecules, with the therapeutic response in CCA,[40] yet linking the efficacy of pemigatinib with predictive molecular and genetic markers is an area of further research.[41] According to the FIGHT-207 trial, pemigatinib showed a response in patients with infrequent FGFR alterations and patients with coalterations, such as BAP1 coalterations.[42] Previous reports have also demonstrated the development of acquired resistance to FGFR inhibitors.[43] The genetic alterations that lead to the development of resistance mechanisms remain unclear. Research is ongoing to unravel these mechanisms and develop novel therapeutic strategies. With the emergence of next-generation sequencing and advanced molecular biology techniques, we anticipate gaining deeper insights into the complex mechanisms of resistance, which can help tailor more effective and durable therapeutic strategies. Additionally, the role of liquid biopsies and circulating tumour DNA in the early detection of resistance mechanisms and optimizing patient care is still under investigation.[41] Further research to investigate the long-term safety of pemigatinib in the treatment of CCA is also warranted.

Although the present study provides real-world clinical experiences of treating iCCA with pemigatinib, there are potential limitations. Whether other treatments or patient-specific factors affected patient response to treatment is unclear. Another limitation is the possibility of selection bias, as case series often include patients with more remarkable or unusual outcomes, potentially leading to overestimating treatment effectiveness. Furthermore, evaluation of the safety profile of pemigatinib may be constrained in a case series setting, with rare but potentially severe adverse events not being observed due to the limited number of patients.

Conclusion

In conclusion, patients with extensive metastatic CCA with *FGFR2* fusion or rearrangement can benefit from late-line pemigatinib therapy. In our practice, a significant and durable symptomatic benefit was obtained in patients receiving pemigatinib, even without a radiological response. The symptomatic benefit was associated with improved QoL of the patients, especially with the reduced time toxicity of oral pemigatinib therapy. However, pemigatinib is generally associated with a manageable safety profile. Routine treatment monitoring should be commenced, including evaluation of serum phosphate level, ophthalmological examination and 3-weekly clinical reviews. In our experience, pemigatinib was associated with few significant toxicities that can be managed with dose reduction and supportive measures. None of our cases discontinued treatment due to toxicity. Further real-world evidence is needed to reflect the outcomes of pemigatinib in patients with advanced CCA.

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