Review Article

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Response To Pemigatinib In A Patient With FGFR2 Y375C Mutation – A Case Report And Review Of Literature

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1. Abstract:

1.1 Background: Cholangiocarcinoma (CCA) is a malignancy of the biliary tree epithelium which constitutes 15% of all primary liver tumors. Anatomically, CCAs can be intrahepatic, perihilar and distal CCA. Of the three types, the perihilar CCA is the most common type in the USA and accounts for 50-60% of all CCAs. These CCAs are associated with several epigenetic alterations which act as targets for new therapeutic agents such as those targeting active gene fusions of FGFR2 and IDH mutations.

1.2 Case discussion: Here we present a case of a 65-year-old man with metastatic intrahepatic CCA with FGFR2 Y375C mutation. The patient's initial abdominal ultrasound revealed liver cirrhosis and a mass in the left hepatic lobe which was confirmed on a PET CT scan. He further underwent CT guided biopsy of the liver mass which showed a moderately differentiated adenocarcinoma, positive for pancytokeratin, CK 7 and MOC-31. He was started with Gemcitabine and Cisplatin over one month with swift progression of disease as evidenced by worsening right upper quadrant pain, increasing CA19-9 levels and image findings. Therefore, treatment was switched to FGFR2 inhibitor Pemigatinib as the qualitative next-generation sequencing of the pathological specimen showed FGFR2 Y375C mutation. The initial dose of Pemigatinib was lowered from 13.5 mg to 9 mg with better patient tolerance. Subsequent abdominal imaging showed decreased size of the heterogeneous mass in the left lobe of the liver with stable periportal adenopathy with decreasing CA19-9 levels. Over the last 13 months of treatment with Pemigatinib, the patient showed no progression of disease on imaging with favorable response and normalization of CA 19-9. His abdominal pain improved and he has maintained excellent quality of life.

1.3 Conclusion: When compared to the FIGHT-202 trial, none of the patients in the other FGRFR mutation cohort had a mutation similar to our patient. The Median PFS in FGFR2 fusions or rearrangements cohort of the FIGHT-202 trial was 6.9 months. In this case report, our patient with a rare FGFR2 Y375C mutation has demonstrated a prolonged clinical benefit with symptom improvement and stable disease on imaging studies over the last 13 months since starting therapy with Pemigatinib.

2 Introduction

Cholangiocarcinoma (CCA) comprises a group of malignancies arising from the epithelial cells of the biliary tree. CCA is the second most common primary hepatic malignancy after hepatocellular carcinoma (HCC) and constitutes about 15% of all primary liver tumours and 3% of gastrointestinal cancers [1,2,3]. Anatomically, CCAs are classified based on their site of origin: intrahepatic (iCCA), perihilar (pCCA) and distal (dCCA) CCA [1,4]. Intrahepatic CCAs arise above the second-order bile ducts. The transition from pCCA to dCCA occurs at the insertion site of the cystic duct and are therefore referred to as extrahepatic cholangiocarcinoma. The three main patterns of growth in iCCA are: mass-forming, periductal-infiltrating, and intraductal-growing[1,5]; pCCA and dCCA are usually flat or poorly defined nodular sclerosing tumours or, intraductal papillary tumours. These aggressive cancers limit treatment options as most of them are locally advanced at the time of diagnosis and hence, have a poor prognosis [1,6].

In the USA, pCCA is the most common and accounts for approximately 50–60% of all CCAs, followed by dCCA (20–30%) and iCCA (10–20%) [1,2,3]. The incidence of iCCA is higher in older people (≥45 years old) than in younger people and in Hispanic individuals than in non-Hispanic individuals, and is associated with a worse 5-year survival in both these populations [7]. Of the varied oncogenic alterations associated with CCA, the most common ones are those involving epigenetic processes [11]. *Several* targeted therapies are being developed and studied in phase III clinical trials with specific agents targeting alterations in *FGFR2* fusion-positive CCA [12, 13] and *IDH*-mutated CCA. The overexpression of FGFRs 1 to 4 via mutations, amplifications and chromosome translocations has been implicated in oncogenesis of iCCA. Among these, here we focus on discussing the FGFR2 inhibition therapeutic targeting with the help of a case. The FGFRs are membrane-bound receptor tyrosine kinases encompassing FGFR1, FGFR2, FGFR3, FGFR4, which are encoded by flg, bek, cek-2, and frek genes, respectively[14]. The FGF/FGFR complex activation participates in signal transduction by phosphorylating other receptors or effector molecules involved in specific pathways of cell

survival and proliferation, including RAS-MAPK, PI3K-AKT, PLCγ, and STAT[15-17]. FGFR signalling is one of the most commonly deregulated pathways in human cancers, through amplification, fusions, missense mutations in FGFR genes. This has been implicated in enhanced proliferation, survival and development of anticancer drug resistance as well as in promoting neoangiogenesis and immune system evasion in the tumor microenvironment[19, 20, 21,22,23]. FGFR2 variant Y375C is a missense gain of function mutation. Y375C lies within the extracellular juxta membrane domain of the FGFR2 protein. Herein, we present a case of a 65-year-old gentleman with metastatic intrahepatic CCA and FGFR2 Y375C alteration showing favourable response to Pemigatinib therapy.

3. Case Report

Our patient is a 65-year-old Caucasian gentleman who has a history of hepatitis C infection 20 years ago, treated with interferon and ribavirin and was in his normal state of health until August, 2021. Recently one of his friends died of "liver cancer", prompting him to undergo an extensive evaluation with his primary doctor, including blood test for alpha fetoprotein (AFP) which was undetectable. An ultrasound image of his abdomen during the same time revealed nodular hepatic changes suggesting cirrhosis and a mass in the anterior aspect of the right lobe of the liver with an estimated size of about 3.5 x 3.3 x 2.9 cm and a small amount of ascites surrounding the liver. An MRI of abdomen revealed a highly suspicious 6.3 x 5.3 x 5.7 cm mass in the posterior lateral aspect of the left hepatic lobe concerning for malignancy. A 16 mm T2 hypointense left renal mass was found which was suspicious for papillary neoplasm. A few periportal lymph nodes were enlarged up to 1.3 cm in greatest dimension. He then underwent a PET/CT scan which showed a hypermetabolic left hepatic mass and a 1.5 to 1.7 cm exophytic hypodense mass in the upper pole of the left kidney and splenomegaly. CT guided biopsy of the liver mass was done on September 8th, 2021 which showed a moderately differentiated adenocarcinoma, positive for pancytokeratin, CK 7 and MOC-31, but negative for HepPar-1, TTF-1 and PAX-8, S100 and other markers. A diagnosis of intrahepatic cholangiocarcinoma was made.

At the time the patient was seen by his oncologist at a different facility, his Hepatitis C antibody was positive but undetectable HCV RNA by PCR. The Hepatitis B viral panel was negative and CEA was normal. CA 19-9 was elevated at 75 units per milliliter (U/ml) (normal level:<37 U/ml). The patient subsequently underwent exploratory laparotomy which revealed peritoneal metastatic implants; therefore, liver resection was aborted. He was then treated with one cycle of Gemcitabine and Cisplatin chemotherapy, but his pain worsened in the right upper quadrant and the CA19-9 levels increased from 259 to 531 u/ml. Imaging showed disease progression. Therefore, his treatment was switched to FGFR2 inhibitor Pemigatinib since his tumor was found to have FGFR2 Y375C mutation on the FoundationOne CDx testing. On December 21, 2021, he was started on Pemigatinib 13.5 mg a day, two weeks on and one week off. He received a total of 4 cycles after which the CA 19-9 levels trended down to 243 on January 27, 2022. While on Pemigatinib 13.5 mg dose the patient developed bilateral lower extremity edema, fatigue, weight loss and decreased appetite. In addition, he had alternating episodes of constipation and diarrhea in the weeks he was on Pemigatinib and the week he was off, respectively. Hence pemigatinib dose was lowered to 9 mg per day 14 days on and 7 days off for a 21-day cycle, which was better tolerated.

On March 2nd, 2022, the CT scan of the chest, abdomen and pelvis showed stable heterogeneously enhancing infiltrating lesions in the left lobe of the liver with known history of cholangiocarcinoma and no chest metastatic disease (Fig 1). CEA (CA19-9?) levels significantly reduced to 35.7 u/ml before completely normalizing to 27.4 u/ml next visit a month later. He continued to tolerate the current dose of Pemigatinib well and remained symptom free. Subsequent imaging every 3 months continued to demonstrate stable disease. His last imaging done on 1/9/2023 (?) showed stable hypo-enhancing mass within the atrophic left hepatic lobe consistent with the patient's cholangiocarcinoma and CA 19-9 level remained within normal range (23 u/ml). Overall, the patient showed good response to Pemigatinib 9 mg regimen with imaging evidence of stable disease and well controlled clinical symptoms. He continues to be on Pemigatinib with regular follow up appointments for reassessment.

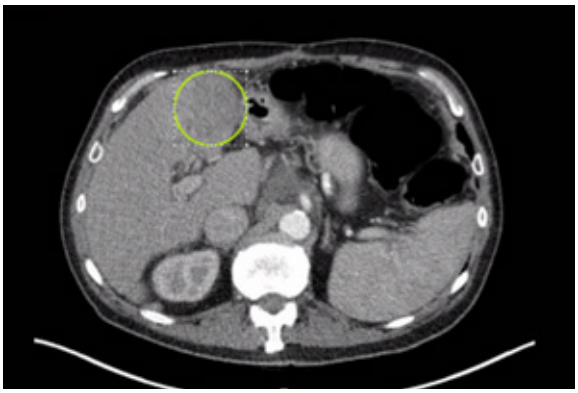

Fig 1 shows the initial CT Abdomen with an infiltrating lesion in the left lobe of the liver vs

4. Discussion

Although a relatively rare cancer, the incidence of cholangiocarcinoma (CCA) has shown a worldwide increase over the past few decades, with limited improvement in the 5-year mortality rate despite numerous therapeutic advances. The 5-year relative survival rate for CCA remains low at 2%[24]. Systemic therapy for intrahepatic CCA (iCCA) typically involves Gemcitabine and Cisplatin, which is considered the first-line choice over Gemcitabine alone, as shown in the ABC-02 Trial [25]. The addition of the immune checkpoint inhibitor durvalumab to gemcitabine and cisplatin has demonstrated superiority over gemcitabine/cisplatin alone, as evidenced in the TOPAZ-1 trial (Durvalumab or Placebo in Combination with Gemcitabine/Cisplatin in Patients With 1st Line Advanced Biliary Tract Cancer)[26]. Durvalumab-containing therapy significantly improved overall survival (median 12.8 versus 11.5 months, HR 0.8, 95% CI 0.66-0.97), and a higher proportion of patients were still alive at 24 months (24.9% versus 10.4%). The addition of durvalumab also

led to significantly longer progression-free survival (PFS) and a higher objective response rate (ORR) (26.7% versus 18.7%). Other regimens that have shown efficacy in trials include Gemcitabine and Oxaliplatin (phase II GEMOX Trial) and Capecitabine and Oxaliplatin (CAPOX Trial).

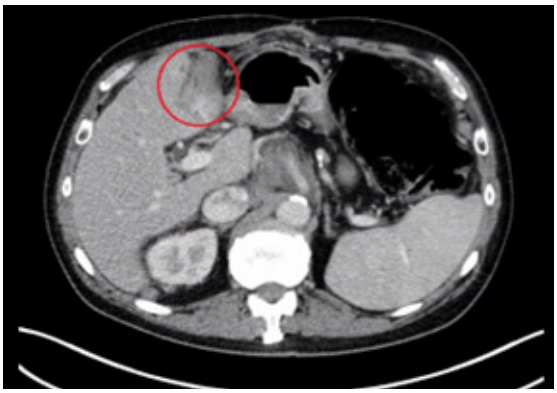

Fig 2 which shows the CT Abdomen taken 8 months later showing a decrease in the size of the left lobe lesion after Pemigatinib therapy.

Targeted therapies have been developed and are currently being studied to improve survival in CCA patients [28]. The most common alterations seen in iCCA involve gene fusions involving FGFR2, identified in 10–15% of patients, followed by activating mutations observed in 4% of patients. These alterations are mutually exclusive. Studies characterizing the genomic landscape of cholangiocarcinoma have shown that 12% of iCCA cases harbor an FGFR2 fusion, along with other oncogenic FGFR2 extracellular activating mutations such as p.F276C, p.C382R, and p.Y375C. FGFR2 translocations have been associated with a favorable prognosis in patients with iCCA. However, concurrent mutations in CDKN2A/B, PBRM1, or TP53 have been found to be associated with a statistically significant shorter PFS while on Pemigatinib.

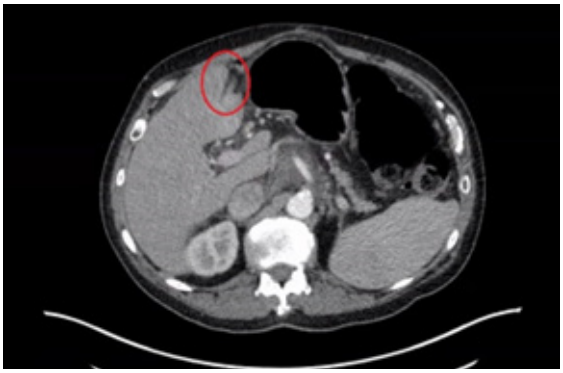

Fig 3 taken 11 months later, is the most recent CT image showing stable disease as per RECIST 1.1 with a 18.8% decrease in size of the primary lesion with no new lesions or lymph node involvement.

FGFR2 fusion or other rearrangements have been shown to confer sensitivity to FGFR inhibitors such as Pemigatinib [29,30], a selective oral inhibitor of FGFR 1, 2, and 3. The FIGHT-202 trial enrolled 146 patients with locally advanced or metastatic cholangiocarcinoma. Disease control was achieved in 80% of patients, with a median duration of response (DOR) of 7.5 months, a median PFS of 6.9 months, and a median overall survival (mOS) of 21 months. Based on this data, Pemigatinib has been approved by the United States FDA for adult patients with previously treated, unresectable, locally advanced, or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement as detected by an FDA-approved test. The approved dose is 13.5 mg once daily for 14 consecutive days followed by seven days off. Updated results from the FIGHT-202 trial after a median follow-up of 30.4 months showed an independent, centrally confirmed ORR of 37.0% and an mOS of 17 [31].

Recently, Futibatinib, a selective inhibitor of FGFR 1 to 4, has received approval for the treatment of locally advanced/metastatic intrahepatic cholangiocarcinoma (iCCA) with an FGFR2 gene fusion or rearrangement based on the phase II FOENIX-CCA2 study [34]. The study was a single-arm phase 2 trial where patients received a daily dose of 20 mg of futibatinib until disease progression. After a median follow-up of 25 months, 96 out of 103 patients had discontinued treatment. The objective response rate (ORR) was 42 percent, with a mean duration of response (DOR) of 9.5 months. There were no new safety signals, and the median progression-free survival (mPFS) was 8.9 months, with a 12-month PFS rate of 35.4%. The median overall survival (mOS) was 20.0 months, with a 12-month OS rate of 73.1% [35]. Based on this data, futibatinib has been granted accelerated approval for the treatment of locally advanced/metastatic iCCA with an FGFR2 gene rearrangement or fusion. In another phase 1 study of Futibatinib, which included patients with advanced solid tumors harboring FGF/FGFR aberrations, cholangiocarcinoma (CCA) comprised the largest tumor cohort (37.6%, mainly intrahepatic 35.9%). Objective responses were observed in 14% of patients, and more than 50% of all patients experienced tumor shrinkage. Notably, responses were observed in tumors harboring all FGFR aberrations, including those previously deemed insensitive to FGFR inhibition [35].

Infigratinib, an ATP-competitive FGFR1–3-selective oral tyrosine kinase inhibitor, was evaluated in a single-arm, phase II study for previously treated advanced CCA with FGFR fusions/rearrangements. Patients who had clinically progressed on at least one line of systemic therapy received 125 mg of infigratinib orally for 21 days of each 28-day cycle until unacceptable toxicity or disease progression. Updated results from the study, which included a total of 108 patients, showed an objective response rate (ORR) of 23.1% and a median duration of response (DOR) of 5.0 months. Among responders, 32.0% had a DOR of at least 6 months. The median progression-free survival (PFS) was 7.3 months. Based on this study, infigratinib was granted accelerated approval for patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement [32,33]. The ongoing FIDES-01 study (clinical trial NCT03230318) evaluated derazantinib, a potent anti-FGFR1-3 oral kinase inhibitor, in 28 patients with iCCA positive for FGFR2 mutations or amplifications who had received previous chemotherapy. The study analyzed various FGFR alterations, including missense point mutations (78%), other short variants

(11%), and amplifications (11%). Patients received 300 mg of derazantinib daily until disease progression, death, or intolerance. The primary endpoint was the number of patients who were alive and free of disease progression at 3 months. In the study, the best overall response was a partial response in 2 patients (8.7%) and stable disease in an additional 15 patients (65.2%), resulting in a disease control rate of 73.9%. The median progression. Other FGFR inhibitors, including RLY-4008, tinengotinib, erdafitinib, and Debio-1347, have shown promising results in ongoing phase I/II trials for metastatic cholangiocarcinoma with FGFR-2 fusion or rearrangement. These inhibitors have demonstrated clinically significant overall response rates [37-41].

Currently, there is limited data demonstrating the efficacy of FGFR TKIs for patients with FGFR mutations. In a preclinical study, seven tyrosine kinase inhibitors were evaluated for sensitivity and transforming activity in 160 FGFR mutations and ten fusion genes across various cancers using the mixed-all-nominated-in-one method. Among these inhibitors, pemigatinib, infigratinib, futibatinib, and erdafitinib showed half maximal inhibitory concentration (IC50) values of 4.65, 2.21, 4.26, and 5.15 nM, respectively, for FGFR2 Y375 alteration. This study suggested that cells expressing the FGFR2 Y375C mutation exhibited reduced cell viability and thus a potential response to treatment with Pemigatinib[27]. In this context, we present a case of a patient with metastatic intrahepatic cholangiocarcinoma carrying the FGFR2 Y375C alteration, who showed a prolonged response to the FGFR inhibitor Pemigatinib.

Initially, our patient received systemic chemotherapy with Gemcitabine and Cisplatin but experienced rapid disease progression. Subsequently, the patient was switched to Pemigatinib. Notably, none of the patients in the FIGHT-202 trial had a similar mutation (other FGFR mutation cohort) to that observed in this case. During the 13 months of Pemigatinib treatment, the patient exhibited no disease progression on imaging, demonstrated a favorable response, and experienced a decrease and subsequent normalization of CA 19-9 levels, even with a reduced dose regimen. The 9 mg dose was better tolerated by the patient and provided comparable benefits to the 13.5 mg dose.

The only side effects experienced by the patient were fatigue and anorexia, which gradually improved after the dose reduction. The patient continues to receive Pemigatinib therapy, having completed nine additional cycles with the 9 mg dose following the initial four cycles with the 13.5 mg dose. Regular monitoring of the patient's medical history, physical examination, imaging studies to assess disease status, and CA 19-9 levels is being conducted to monitor response and disease progression. It is worth noting that the median progression-free survival (PFS) in the FGFR2 fusions or rearrangements cohort of the FIGHT-202 trial was 6.9 months. However, in this case report, the patient has maintained stable disease over the past 13 months since initiating Pemigatinib therapy. This case report represents the first documented evidence of the clinically meaningful benefit of Pemigatinib in a patient with metastatic intrahepatic cholangiocarcinoma harboring a rare FGFR2 Y375C mutation.

5. Conclusion

While Pemigatinib has received FDA approval for patients with cholangiocarcinoma (CCA) exhibiting FGFR2 fusion/rearrangement, our case demonstrates that patients with rare mutations can also experience significant objective responses and benefit from progression-free survival. This finding has implications for therapeutic decision-making and suggests the potential expansion of Pemigatinib's approved usage to include patients with other mutations in the FGFR2 gene. Furthermore, promising results have been observed with other FGFR inhibitors such as futibatinib and derazantinib, specifically in diverse FGFR aberrations that were previously considered insensitive to currently available FGFR inhibition therapies, as demonstrated in phase I/II trials. Ongoing clinical trials aim to further establish the clinical significance of these treatments in managing rare FGFR aberrations in patients with unresectable locally advanced or metastatic cholangiocarcinoma.

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