

CASE REPORT

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Nivolumab in combination with dabrafenib and trametinib use in advanced cholangiocarcinoma with a BRAF V600E mutation and severe hepatic dysfunction: A case report and review of the literature

Aanika Balaji, Kayla Garzio, Kiyoko Oshima, Rachel Klein, Nilofer Azad, Chester Kao

ABSTRACT

Introduction: Cholangiocarcinomas (CCA) are rare, aggressive tumors often diagnosed in advanced stages with limited evidence guiding therapy on progression.

Case Report: We report a case of advanced CCA with rapid and aberrant progression, refractory to multiple lines of therapy, that resulted in severe hepatic dysfunction secondary to tumor burden with a BRAF V600E mutation and high tumor proportion score (TPS) of 99%. To our knowledge, this is the first reported use of BRAF/MEK inhibition to target BRAF V600E in a patient with severe hepatic dysfunction leading to rapid normalization of the patient's liver dysfunction within days. No adverse events were recorded during either initial titration or maintenance periods. Programmed death-1 (PD-1) inhibitor was added to BRAF/MEK inhibition, and the patient continues to have clinical therapeutic response.

Conclusion: This case highlights the use of BRAF/MEK inhibition in CCA with BRAF V600E mutations in

hepatic dysfunction due to tumor burden and the role of combining immune checkpoint inhibitors.

Keywords: BRAF/MEK inhibition, BRAF V600E, Cholangiocarcinoma, Immune-checkpoint inhibition, Targeted therapy

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INTRODUCTION

Cholangiocarcinoma (CCA) is a rare, aggressive tumor and comprises 2.2% of new cancer cases yearly [1]. Although uncommon, its incidence has been increasing worldwide [2]. These tumors are often asymptomatic early in the disease course. Therefore, they are often diagnosed in advanced stages, which portends a poor prognosis, with a five-year survival rate of 3.1% for unresectable, metastatic disease [1, 3].

Unresectable tumors are typically treated upfront with gemcitabine and cisplatin [4], but there are promising results for the addition of abraxane and more recently durvalumab based on TOPAZ-1 [5]. However, there is

limited evidence guiding therapy on progression. The only established salvage regimen based on phase III data is FOLFOX but has only modest survival benefit at the cost of quality of life [6]. There is emerging evidence for the use of immune checkpoint inhibitors (ICI) [7] such as programmed death-1 (PD-1) inhibitors in combination with tyrosine kinase inhibitors (TKI), chemotherapy, or targeted therapy depending on the molecular profile of the tumor [8, 9]. *BRAF*V600E is one targetable alteration seen in CCA, but recommendations for use of *BRAF*/MEK inhibitors such as dabrafenib and trametinib in moderate to severe hepatic dysfunction are currently unavailable in the literature.

Herein, we describe the use of dabrafenib and trametinib in a poorly differentiated carcinoma of biliary tract origin with a *BRAF* V600E mutation with severe hepatic dysfunction secondary to aggressive tumor growth, refractory to multiple lines of therapy. [10–12]. Given a high tumor proportion score (TPS) 99%, nivolumab was added to dabrafenib and trametinib resulting in sustained clinical response [10–12]. To our knowledge, this is the first published report describing the use of nivolumab, dabrafenib, and trametinib in CCA which highlights the safety and efficacy of a graded titration of *BRAF*/MEK inhibitors in severe hepatic dysfunction secondary to aggressive tumor growth and the sustained clinical response achieved with the addition of anti-PD-1 to *BRAF*/MEK inhibition.

CASE REPORT

Patient information

A 36-year-old woman with a history of paroxysmal supraventricular tachycardia with ablation, chronic cholecystitis status post cholecystectomy, and essential hypertension presented with worsening left-sided abdominal pain and weight loss in January 2021.

Diagnostic assessment

The patient's full disease course is presented in Table 1. In January 2021, an initial computed tomography (CT) of the abdomen/pelvis showed a 13 cm exophytic left-sided hepatic mass with satellite lesions abutting the stomach, mesenteric adenopathy, peritoneal implants, and significant lymphadenopathy with ascites. She underwent a diagnostic laparoscopy with liver biopsy that showed necroinflammatory tissue but no definite malignant calls. She then had an exploratory laparoscopy with left lateral hepatic segmentectomy in February 2021 which showed poorly differentiated carcinoma with immunohistochemical staining positive for diffuse pancytokeratin, AE1/AE3, CK7, CK19, vimentin, and patchy hCG (Figure 1). Mutation analysis showed *BRAF* p.V600E at a variant allele frequency (VAF) of 2.2% and PD-L1 staining with tumor proportion score (TPS) of 99% (Figure 2). The pathology and clinical impression were

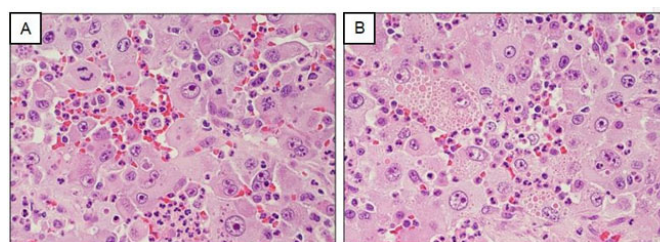


Figure 1: (A) Malignant cells are characterized by abundant pink cytoplasm and prominent nucleoli. Frequent mitosis and acute inflammation are also noted (Hematoxylin and Eosin stain $\times 400$). (B) Malignant cells contain unusual pink cytoplasmic globules (Hematoxylin and Eosin stain $\times 400$).

Coding Variants in Genes of Clinical Interest						
Notes	Chr.Pos	Base Change	Reference Database ID	Gene	AA_change	%VAF
1	chr7.140453136	A>T	COSM476	BRAF	p.V600E	29.4

Figure 2: Portion of complete mutation analysis of patient's tumor identifying the *BRAF* V600E mutation.

Abbreviations: Chr: chromosome; pos: position; AA: amino acid; VAF: variant allele frequency

most consistent with cholangiocarcinoma with aberrant hCG expression.

The patient started on gemcitabine/cisplatin/abraxane in March 2021. An initial restaging CT scan in May 2021 showed no evidence of disease. However, CT imaging in July 2021 showed a new sub-centimeter nodule along the hepatic lobe resection margin, but the patient was continued on therapy. Two months later, the soft tissue mass had grown to 3.7×3.3 cm. Second line liposomal irinotecan/leucovorin/continuous 5-fluorouracil was started in October 2021. Unfortunately, she tolerated this regimen poorly even with dose reductions with significant gastrointestinal symptoms including abdominal pain, nausea, and vomiting. After only completing two cycles, she had significant increase in her soft tissue mass to 7.8 cm with mass effect on the stomach. She opted for palliative surgery to alleviate the mass effect with pathology confirming her prior diagnosis. Repeat next generation sequencing showed *BRAF* p.V600E alteration with VAF of 29.4%.

Following surgical recovery, the patient's next CT imaging in January 2022 showed continued tumor growth to 9.6 cm at the site of hepatic resection with potential tumor invasion of the gastric antrum. She was planned for pembrolizumab and lenvatinib but only received one dose of pembrolizumab in late January 2022 before being admitted for gastric outlet and biliary obstruction. The patient's tumor growth occurred much more rapidly than predicted leading to severe acute hepatic dysfunction and biliary obstruction.

Therapeutic intervention

Due to the cancer's aggressive biology, decision was made to start off-label *BRAF* and MEK inhibitors,

dabrafenib, and trametinib, in a graded uptitration (Table 1) during the admission in the hopes of quicker disease control. There were plans to place biliary stents to relieve the biliary obstruction as a temporizing measure until systemic therapy could take effect and consideration for nivolumab after discharge if the patient achieved some normalization of her hepatic dysfunction.

The patient responded well with considerable improvement in her biliary obstruction (admission total bilirubin 6.8 to 1.4 mg/dL, as noted in Table 2), and, surprisingly, eliminated the need to place a biliary stent as originally planned to relieve the obstruction. She was continued on dabrafenib at 150 mg twice daily (BID) and trametinib at 2 mg daily upon discharge. No adverse events were noted during the period of uptitration despite

severe hepatic dysfunction. A subsequent CT scan showed a decrease in her liver lesions (largest lesion 7.4 × 6.7 cm) and nivolumab (480 mg) was added to her therapy given her high TPS score.

Follow-up

Currently, the patient continues on nivolumab, dabrafenib, and trametinib, with most recent CT imaging in May 2022 showing further decrease in hepatic masses (largest lesion 2.8 × 4.2 cm) after having completed four 28-day cycles (116 days of full dose trametinib and dabrafenib). The patient has not required hospital admission since starting this treatment regimen.

Table 1: Timeline of disease and therapy course from diagnosis in January 2021 to most recent review of data in May 2022

Day	Total bilirubin (mg/dL)	AST (U/L)	ALT (U/L)	Alkaline phosphatase (U/L)	Dabrafenib dose	Trametinib dose
1	6.0	211	148	974	75 mg qd	0.5 mg qd
2	5.7	177	138	922	75 mg qd	0.5 mg qd
3	3.5	122	121	1040	75 mg qd	0.5 mg qd
4	2.4	101	101	943	75 mg qd	0.5 mg qd
5	1.8	65	77	943	75 mg qd	0.5 mg qd
6	1.7	46	56	921	150 mg qd	1 mg qd
7	1.5	37	45	910	150 mg AM; 75 mg PM	1.5 mg qd
8	1.4	38	38	812	150 mg BID	2 mg qd
125	0.4	85	62	301	150 mg BID	2 mg qd

Table 2: Trend of liver enzymes and total bilirubin over an initial 8-day period with concurrent uptitration of dabrafenib and trametinib. The final row shows liver enzymes after having completed 4 cycles of full-strength combination BRAF/MEK targeted therapy

Date	Event
2021	
January	- Initial presentation with worsening abdominal pain and weight loss - Initial CT scan: large hepatic mass with satellite lesions within the peritoneum - Diagnostic laparoscopy - Liver biopsy showed necroinflammatory tissue
February	- Exploratory laparoscopy with L lateral hepatic segmentectomy - Pathology showed poorly differentiated carcinoma consistent with cholangiocarcinoma - Mutation analysis shows BRAF p.V600E mutation of tumor
March	1st line therapy: gemcitabine, cisplatin, and abraxane
May	Restaging CT scan: no evidence of disease
July	Follow-up CT scan: new hepatic nodule
October	- Follow-up CT scan: hepatic nodule growth 2nd line therapy: liposomal irinotecan, leucovorin, and continuous 5-fluorouracil
December	- Palliative surgery to remove hepatic mass - Next generation sequencing showed BRAF p.V600E mutation of tumor
2022	
January	Follow-up CT scan: increasing growth of hepatic mass with extension into stomach
February	Dabrafenib and trametinib started
March	- Follow-up CT scan: decrease in hepatic mass size - Nivolumab added to targeted therapy
May	Follow-up CT scan: decrease in hepatic mass size

Abbreviations: mg/dL: milligrams per deciliter; U/L: units per liter; qd: daily; BID: twice daily

DISCUSSION

BRAF/MEK inhibitors in CCA

An estimated 40–50% of patients with CCA have at least one genetic alteration that may be clinically actionable, of which *BRAF* gene alterations occur in approximately 5–7% [8]. Patients with unresectable or metastatic cholangiocarcinoma found to have *BRAF* V600E mutations in alignment with the ROAR trial can receive dabrafenib and trametinib as a subsequent line treatment option [8, 9].

Dabrafenib and trametinib target two kinases in the RAS/RAF/MEK/ERK pathway [10, 11]. Dabrafenib is an ATP-competitive inhibitor of RAF kinases, and targets mutated *BRAF*, such as *BRAF* V600E, which prevents constitutive activation of the oncogenic pathway and thus tumor proliferation. Dabrafenib works to downregulate MEK and ERK phosphorylation resulting in cell death [11]. Trametinib is an inhibitor of MEK1 and MEK2 [12]. Use of dabrafenib and trametinib concomitantly results in greater growth inhibition of *BRAF* V600E mutant tumors [13]. The ROAR trial was a phase II open-label, single-arm multicenter basket trial including 43 patients with *BRAF* V600E mutated advanced adenocarcinoma of the biliary tract or gallbladder lacking alternative treatment options. Treatment in patients with adequate organ function with dabrafenib 150 mg twice daily and trametinib 2 mg once daily yielded an overall response in 22 of 43 patients (51%, 95% CI: 36–67).

BRAF/MEK inhibitors in hepatic dysfunction

To our knowledge, use of dabrafenib and trametinib has not been studied in patients with severe hepatic dysfunction aside from a phase I pharmacokinetic single agent study with single agent trametinib. Evaluable dose limiting toxicities were assessed in four patients with severe liver dysfunction: three patients receiving trametinib 1 mg daily and one patient receiving 1.5 mg daily. There was one grade 3 dose limiting toxicity reported in the patient taking 1.5 mg daily which was an acneiform rash [13]. Acneiform rash, however, is an adverse event occurring in >20% of patients receiving trametinib in studies with normal hepatic function [12]. Pharmacokinetic data were limited to three patients with severe liver dysfunction, defined as bilirubin between >3× and ≤10× upper limit of normal (ULN); however, there were no significant differences observed between patients with normal hepatic function and those with severe hepatic dysfunction [13]. Prescribing information states that a recommended dose of trametinib has not been established for patients with moderate [bilirubin >1.5× to 3× ULN and any aspartate aminotransferase (AST)] or severe (bilirubin >3× to 10× ULN and any AST) hepatic impairment.

Trametinib *in vitro* is metabolized via deacetylation alone or with mono-oxygenation or in combination

with glucuronidation biotransformation pathways. It is excreted approximately 80% via the feces and approximately 20% via the urine [12]. Therefore, impact of severe liver dysfunction on trametinib was thought to be low. In our case, trametinib was started at 0.5 mg daily, 25% of target dose, in alignment with the phase I pharmacokinetic study previously described and was escalated according to response in transaminases and total bilirubin as demonstrated in Table 1. Dabrafenib is metabolized hepatically via CYP2C8 and CYP3A4 to active metabolites which are subsequently excreted in the bile predominantly, and urine [10, 11, 14]. Given hepatic metabolism and predominant biliary excretion, there may be higher concentrations present in the plasma than patients with normal hepatic function due to both the parent compound as well as active metabolites. However, dabrafenib has not been studied in patients with severe hepatic impairment. Given the severe hepatic impairment of the patient and concern for impact of hepatic metabolism and biliary excretion on the serum concentration of dabrafenib, it was started at 25% of the target dose and increased as demonstrated in Table 2 according to responding transaminases and total bilirubin. As described above, the patient's hepatic impairment and bilirubin normalized rapidly without any associated toxicities, suggesting that a carefully monitored graded titration of dabrafenib and trametinib can be a safe and viable strategy in CCA with *BRAF* V600E alterations in which hepatic impairment is primarily attributable to rapid tumor progression.

Role of immune-checkpoint inhibition with targeted therapy in CCA

Monotherapy ICI has limited activity in CCA with modest response rates. A single arm phase II study of nivolumab in CCA previously treated with systemic therapy showed an investigator assessed response rate of 22% but only 11% on central independent review [15]. Similar results were seen in both KEYNOTE-158 (phase II) and KEYNOTE-028 (phase IB) which evaluated safety and efficacy of pembrolizumab monotherapy in basket studies that included biliary tract cancers [16–19]. Objective response rate (ORR) was 5.8% in KEYNOTE-158 and 13.0% in KEYNOTE-028 [16–19]. Despite limited efficacy as monotherapy, the addition of ICI to chemotherapy has shown promising results in a phase III study, TOPAZ-1, with upcoming results from KEYNOTE 966 [5, 20]. In TOPAZ-1, the addition of durvalumab to chemotherapy significantly improved overall survival (OS), progression free survival (PFS), and ORR with 26.7% versus 18.7% for chemotherapy alone [odds ratio (OR) 1.60, 95% CI: 1.11–2.31] [5].

Immune-checkpoint inhibitors augment the activity of targeted therapies in multiple solid tumors. Combining ICIs with BRAF/MEK inhibition has been primarily studied in BRAF-mutant melanoma. It is suggested that targeted BRAF inhibition in BRAF-mutant melanoma

restores immune cell recognition of tumor cells, increasing the efficacy of ICIs [21, 22]. Several clinical studies have demonstrated favorable tumor response with combination ICI and BRAF/MEK targeted therapy. A retrospective review of 135 patients with *BRAF* V600-mutant melanoma by Haist et al. demonstrated that when compared to targeted therapy alone, ICIs followed by targeted therapy showed increased overall survival [23]. In a randomized phase II (KEYNOTE-022) trial, pembrolizumab and BRAF/MEK targeted therapy were compared against BRAF/MEK inhibition alone in 120 patients with advanced *BRAF*-mutant melanoma [24]. Combination BRAF/MEK inhibition with anti-PD-1 therapy provided a longer median duration of response (25.1 months for pembrolizumab and BRAF/MEK inhibition vs 12.1 months with BRAF/MEK inhibition alone), longer PFS at 24 months (41% for pembrolizumab and BRAF/MEK inhibition vs 16% for BRAF/MEK inhibition alone), but lower ORR (63% in pembrolizumab and BRAF/MEK inhibition vs 72% for BRAF/MEK inhibition alone, CI difference in rate –24.8 to 8.3%) [24].

Thus, extrapolating from the current literature for combined ICI and BRAF/MEK inhibition in melanoma, our case showcases the durable activity of adding nivolumab to dabrafenib/trametinib especially in the setting of a high TPS score of 99%. Programmed death ligand-1 (PD-L1) expression as measured by TPS or combined positive score (CPS) has conflicting predictive role for response to anti-PD-1/PD-L1 in different tumor types. One example of the utility of TPS for prediction of clinical benefit has been in non-small cell lung cancers (NSCLCs). Based on KEYNOTE-042, the FDA approved single agent pembrolizumab for NSCLC that have high PD-L1 expression as defined by TPS $\geq 1\%$ and demonstrated increasing overall survival benefit with higher TPS scores [25]. Though TPS score is not used as a formal predictive biomarker in CCA, the high TPS score of 99% in our patient encouraged the addition of ICI.

CONCLUSION

This case highlights the importance of next generation sequencing to identify actionable mutations amenable to targeted therapy, use of BRAF/MEK inhibition in a patient with severe hepatic dysfunction, and the utility of adding immune-checkpoint inhibition in advanced biliary tract cancers. Our patient had rapid progression on multiple lines of treatment and subsequently had severe liver impairment secondary to tumor burden. Despite limited evidence in severe liver injury, using dabrafenib and trametinib to target the *BRAF* V600E alteration achieved a clinical response as well as a rapid normalization of her liver impairment within days with no adverse events noted during the initial titration period. Though biliary stenting provides rapid alleviation of biliary obstruction and should be considered first line treatment for obstruction, treatment with BRAF/MEK

inhibition in this unique case of aberrant and aggressive growth demonstrated the potential for safe and rapid clinical response than with systemic therapy alone. Lastly, though monotherapy immune checkpoint inhibition has limited activity in CCA, ICI combined with BRAF/MEK inhibition can be a viable strategy for more durable responses in *BRAF* V600E altered tumors as evidenced by the melanoma literature.

Patient perspective

The patient reports that she is overall well since starting her new regimen and has returned to work full-time. Her energy levels have improved and was able to enjoy two international trips with family.

Declarations

Ethics approval and consent to participate:

No IRB approval was needed for this report, consent to participate available upon request

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Author Contributions

Aanika Balaji – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Kayla Garzio – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Kiyoko Oshima – Acquisition of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Rachel Klein – Acquisition of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Guarantor of Submission

The corresponding author is the guarantor of submission.

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Consent Statement

All institutional IRB guidelines were followed, and patient data were de-identified prior to publication.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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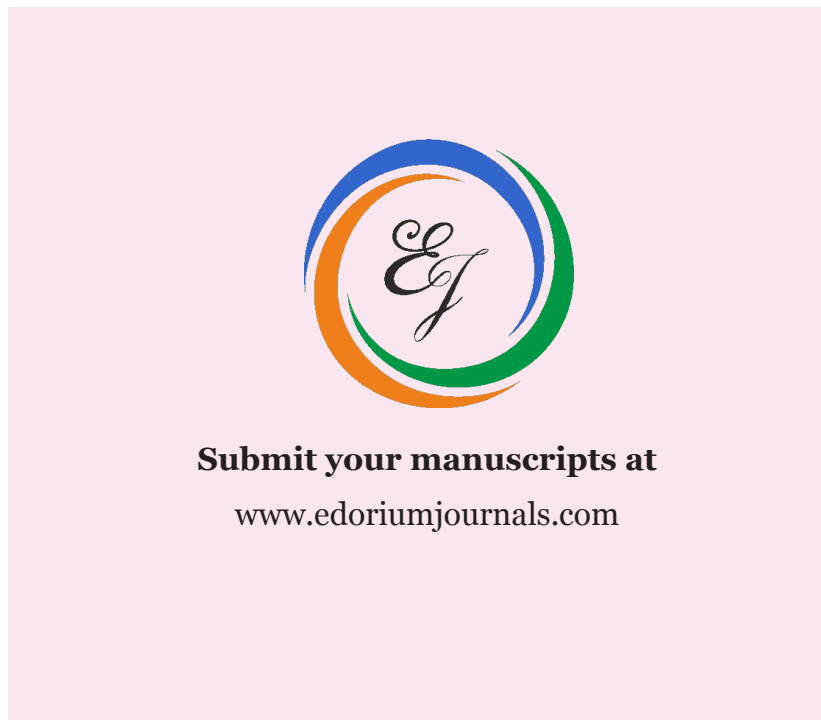
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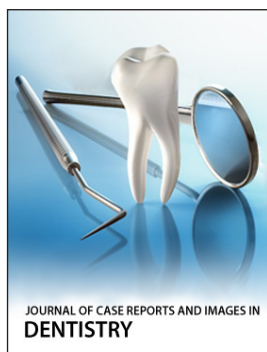
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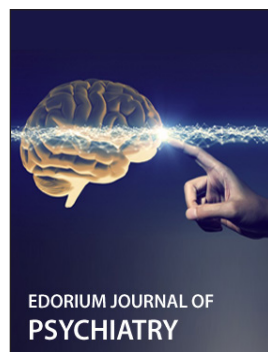
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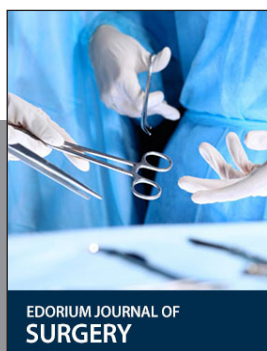
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