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Case Report

Corticosteroid-Refractory Myositis After Dual BRAF and MEK Inhibition in a Patient with BRAF V600E-Mutant Metastatic Intrahepatic Cholangiocarcinoma

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ABSTRACT

Intrahepatic cholangiocarcinoma is a rare malignancy, which is rich in actionable alterations. Genomic aberrations in the mitogen-activated protein kinase (MAPK) pathway are common, and *BRAF* exon 15 p.V600E mutations are present in 5–7% of biliary tract cancers (BTC). Dual inhibition of BRAF and MEK has been established for BRAF-mutated melanoma and lung cancer, and recent basket trials have shown efficacy of this combination in BRAF V600E-mutant BTCs. Here, we report on a patient with *BRAF* exon 15 p.V600E mutant metastatic intrahepatic cholangiocarcinoma who was started on BRAF and MEK inhibition with vemurafenib and combimetinib. Shortly thereafter, he developed debilitating myositis, which was refractory to corticosteroids, requiring therapeutic plasma exchange and intravenous immunoglobulin. We also review BRAF as a target in BTCs, relevant clinical trials, and adverse events associated with BRAF and MEK inhibition.

Keywords: cholangiocarcinoma, precision oncology, targeted therapy, myositis

INTRODUCTION

There has been growing interest in precision oncology, with the expectation that molecular profiling can help identify drivers of tumor growth, and thus, actionable alterations that can be targeted directly or indirectly with targeted therapy. It has been the hope that personalized cancer therapy with molecularly matched therapies will not only allow for greater antitumor efficacy but will also be less toxic. However, it should be noted that targeted therapies are associated with multiple adverse events, including those that are off-target, such as dermatologic reactions, hepatotoxicity, rhabdomyolysis, arthralgia, and ophthalmologic reactions as seen with BRAF and MEK inhibitors.[1–6]

Intrahepatic cholangiocarcinoma (ICC) is a rare malignancy that arises from the bile duct epithelial cells within the liver.[7] Unfortunately, many patients present with metastatic disease, and the 5-year survival for patients with unresectable ICC is less than 5–10%.[8,9] Increased molecular profiling of cholangiocarcinoma (CCA) has prompted evaluation of targeted therapies for these malignancies, which are rich in actionable mutations.[10] Large-scale sequencing studies have identified several targetable genetic alterations including *FGFR2*, *ERBB2*, *IDH1*, and *BRAF*, which have led to the development of various inhibitors currently under evaluation in multiple biomarker-selected clinical trials.[11–13]

BRAF, a serine/threonine protein kinase that activates the mitogen-activated protein kinase (MAPK) pathway, is an oncogenic driver in many human cancers.[14] Activating mutations at codon 600 results in constitutively active BRAF and aberrant MAPK signaling.[15] A recent multicohort basket study of the BRAF inhibitor vemurafenib in nonmelanoma *BRAF* V600E-mutant solid tumors in 172 patients with 26 unique cancer types, reported an overall response rate of 33% and median duration of response of 13 months.[16] Responses were observed in 13 unique cancer types, highlighting the importance of *BRAF* V600E as a driver. *BRAF* mutations are present in 5–7% of biliary tract cancers (BTC), and *BRAF* V600E-mutant ICC has been associated with worse overall survival.[15,17] Combination therapy with dual BRAF and MEK inhibition (BRAFi + MEKi) has been used to provide greater inhibition of the MAPK pathway and overcome resistance to BRAFi monotherapy.[18,19] Several case reports, and a recent phase II basket trial (NCT02034110), have shown responses with BRAFi + MEKi in patients with *BRAF* V600-mutant BTC.[19–21]

Here, we present a case of a man with *BRAF* V600E-mutant ICC who progressed on chemotherapy. He was then enrolled in the American Society of Clinical Oncology (ASCO) Targeted Agent and Profiling Utilization Registry (TAPUR) trial (ClinicalTrials.gov identifier: NCT02693535) and treated with vemurafenib and cobimetinib. Shortly thereafter, he developed debilitating myositis requiring hospitalization.

CASE PRESENTATION

A 77-year-old man presented with metastatic ICC. Six months prior, he was diagnosed with a 6-cm right liver mass and underwent surgical resection, with pathology revealing CCA with sarcomatoid features (stage T1bN0M0). Relevant past medical history included use of rosuvastatin at 40 mg by mouth (PO) once daily (QD). Genomic testing (Foundation One CDx) revealed a *BRAF* exon 15 p.V600E mutation along with *CDKN2a* loss, *CDKN2b* loss, *PIK3CA* H1047R, *CDKN1A* R48*, and *PIM1* amplification. Subsequently, he received adjuvant capecitabine, which was discontinued after three cycles due to a drug-related rash. Restaging positron emission tomography–computed tomography revealed a 1.2-cm left upper lobe nodule and a biopsy specimen confirmed metastatic disease. He was transitioned to gemcitabine, cisplatin, and abraxane and received five cycles, with a best response of progressive disease. He was then enrolled in the TAPUR trial (ClinicalTrials.gov identifier: NCT02693535) based on his *BRAF* exon 15 p.V600E mutation and started on vemurafenib (960 mg PO twice daily [BID]) and cobimetinib (60 mg PO once daily [QD], 21 days on, 7 days off).

He first reported fatigue (grade 2) and anorexia (grade 1) 6 days after beginning treatment, and his cobimetinib dose was held the next week when his symptoms did not improve. On cycle 1 day 18, he presented with overwhelming fatigue (grade 2) and proximal upper or lower extremity weakness (grade 3), and was directed to the emergency department. Notably, no cutaneous lesions or rashes were observed. Admission labs were notable for elevated creatine kinase (CK) (3041 units/L), creatinine (1.66 mg/dL), transaminases (aspartate transaminase 137 units/L, alanine transaminase 68 units/L), alkaline phosphatase (362 units/L), aldolase (18.9 units/L), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP; 42, 53.6 mg/L), as well as several electrolyte derangements (potassium 2.7 mEq/L, sodium 135 mEq/L, calcium 8 mEq/L, phosphorous 2 mEq/L) and urine myoglobin more than 5000. Antinuclear antibody (ANA) titer was 1:160 with a speckled pattern. Autoantibody myositis panel and rheumatoid factor were within normal limits. Magnetic resonance imaging of the brain and spine were unremarkable. Cobimetinib, vemurafenib, and rosuvastatin therapies were discontinued and methylprednisolone 80 mg PO BID was started given concern for a drug-related inflammatory or immune adverse event.

While his CK and Cr initially improved with intravenous (IV) fluids, he developed worsening muscle weakness with rising CK levels, which prompted initiation of high-dose pulse corticosteroids with methylprednisolone 500 mg intravenously three times daily (TID). He then underwent 5 days of therapeutic plasma exchange (PLEX) given concern for immune-mediated myositis (Figure). A biopsy procedure was performed of his left quadriceps, revealing severely distorted skeletal muscle with rare degenerative and necrotic fibers, macrophages,

Table 1. Frequency of skeletal muscle–related adverse events and elevated creatinine kinase (CK) (all grades) in trials with MEK inhibitors, both in monotherapy and combination[23,24,26,33–38]

Target	Agent	Musculoskeletal symptoms, *n* (%)	Myositis, *n* (%)	Elevated CK, *n* (%)	Total Patients, *N*	ClinicalTrials.gov Identifier
MEK	AZD8330	Myalgia, 5 (6)	—	—	82	NCT00454090
MEK	Cobimetinib	Rhabdomyolysis, 4 (27)	—	—	15	NCT02089724
MEK	Pimasertib	Myalgia, 7 (21.9)	—	18 (53.6)	32	—
MEK	RO4987655 (CH4987655)	—	—	9 (18.4)	49	NCT00817518
MEK	RO4987655 (CH4987655)	Muscular weakness, 4 (13)	—	22 (71.0)	31	—
BRAF + MEK	Vemurafenib + Cobimetinib	Myalgia, 37 (5.0); pain in extremity, 29 (11.7); muscular weakness, 9 (3.6); rhabdomyolysis, 1 (0.4); myopathy, 1 (0.4)	1 (0.4)	87 (35.2)	247	NCT01689519
BRAF + MEK	Dabrafenib + Trametinib	Pain in extremity, 45 (12.9); myalgia, 66 (18.8)	—	10 (2.9)	352	NCT01597908
BRAF + MEK	Encorafenib + Binimetinib	Pain in extremity, 21 (10.9); myalgia, 26 (13.5)	—	44 (22.9)	192	NCT01909453
BRAF + MEK	Dabrafenib + Trametinib	Myalgia (combination arm 150/1), 13 (24); myalgia (combination arm 150/2), 12 (22)	—	—	54, 55	NCT01072175
BRAF + MEK	Dabrafenib + Trametinib	Myalgia, 7 (28)	—	6 (24)	25	NCT02296996

—, not reported.

rare B cells, and scattered T cells. His CK continued to rise, and he was started on a 4-day course of IV immunoglobulin (IVIG), which led to improvement of his CK levels and symptoms. Repeat ANA was 1:40 without ANA detected by immunofluorescence, CRP normalized, and ESR decreased to 25. Corticosteroids were tapered, and he was discharged home with improvement of his myositis (grade 2). Over the next several weeks, he reported worsening weakness requiring a wheelchair although his CK remained within normal limits. He unfortunately was unable to recover enough to receive additional anticancer therapy and died 1 month after discharge, 62 days after the last vemurafenib and cobimetinib treatment.

DISCUSSION

There is increasing awareness of *BRAF* V600E as a driver in several human cancers. A vemurafenib basket trial in *BRAF* V600E-mutant tumors reported an overall response rate of 33%, including two patients with CCA.[16] *BRAF* mutations have been identified in 5% of BTCs and are more common in ICC than in extrahepatic cholangiocarcinoma (ECC).[19,22] A recent phase II basket trial (NCT02034110) evaluated BRAFi + MEKi in BRAF V600E-mutant BTCs; it reported an investigator-assessed overall response in 22 (51%; 95% CI, 36–67) of 43 patients, and an independent reviewer-assessed overall response achieved by 20 (47%; 95% CI, 31–62) of 43 patients.[20] Further, the responses were durable; the median duration of response in 22 patients with an investigator-assessed objective response was 9 months (95% CI, 6–14 months).[20] Taken together, these data suggest that *BRAF* V600E is an important target across histologies and represents a promising target for *BRAF* V600E-mutant CCA. However, even with targeted therapies that presumably hit the "Achilles heel" of the tumor, while relatively sparing the normal tissue, often there are adverse events.

Skeletal muscle–related adverse events have been reported with the use of MEKi monotherapy as well as the combination of BRAFi + MEKi (Table 1).[23–25] Although myalgia is not uncommon with BRAFi + MEKi (14–19%), the diagnosis of myositis is much rarer, and was reported in only 1 of 247 patients enrolled in the coBRIM trial (ClinicalTrials.gov identifier: NCT01689519) evaluating the combination of vemurafenib and cobimetinib in patients with *BRAF* V600-mutant melanoma.[26] Despite initial improvement of our patient's CK and Cr with fluid resuscitation and corticosteroids, his symptoms worsened and CK levels continued to rise, which ultimately reversed only after PLEX and IVIG administration (Fig. 1).

There are several possible etiologies for myositis in this case, including immune-mediated necrotizing myositis, direct inhibitor effects on skeletal muscle, paraneoplastic syndromes, and statin-induced autoimmune myopathy. Oncogenic BRAF mutations have been associated with T cell suppression, and induction of the tumor–host immune response has been proposed as an off-target mechanism of MAPK inhibition.[27] In several cancers, antigens have been identified that are morphologically similar to myoblasts, resulting in cross-reactivity of autoantibodies and resultant tissue damage.[28] Interestingly, modulation of the FoxP3 transcription factor by MEKi has been proposed as a mechanism to reduce the activity of regulatory T cells.[29] An amplified immune response secondary to MAPK pathway inhibition, in combination with cross-reactivity of autoantibodies, may explain the presentation of myositis in our case.

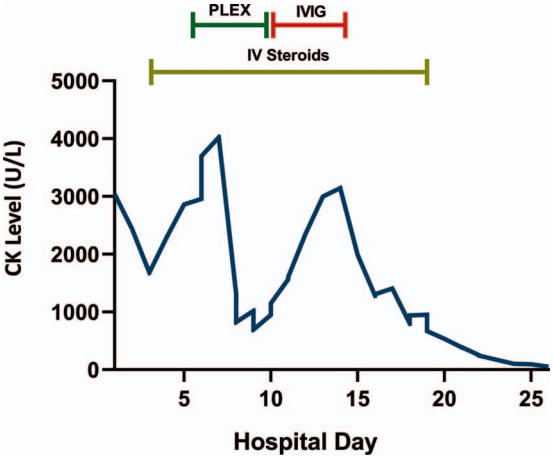

Figure 1. Creatine kinase trend during hospitalization. CK, creatine kinase; IVIG, intravenous immunoglobulin; PLEX, plasma exchange; U, units.

That being said, immune-mediated necrotizing myositis is often associated with antisignal recognition particle (SRP) antibodies and/or anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies, for which the former was normal, and the latter not evaluated.[30] Myositis secondary to direct MEK inhibitor toxicity on skeletal muscle is also a consideration, as it has been seen with cobimetinib and selumetinib.[31] While the effects of MEK inhibition on normal myocytes has not been elucidated, inhibition may have effects on cell survival and homeostasis.[31] A case report from Harrison et al.[28] described a patient with metastatic melanoma on dabrafenib and trametinib who developed dermatomyositis refractory to corticosteroids but responded to IVIG. The absence of skin changes and anti-transcription intermediary factor 1-γ, (TIF1) and/or anti-nuclear matrix protein (NXP) antibodies in our case make this diagnosis unlikely. Statin-induced autoimmune myopathy is also a consideration given our patient's history of rosuvastatin use and necrotic muscle fibers on histopathology, although it is not commonly associated with infiltrating lymphocytes.[32]

To our knowledge, this is the first report of steroid-refractory myositis in a patient receiving the combination of vemurafenib and cobimetinib, requiring PLEX and IVIG. It is essential for clinicians to be aware of skeletal muscle–related adverse events in the setting of dual BRAF and MEK inhibition.

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