Case report

Encorafenib and binimetinib for the treatment of BRAF-mutated metastatic melanoma in the setting of combined hepatic and renal impairment

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SUMMARY

Inhibitors of BRAF, a gene coding a protein called B-raf, with or without inhibitors of MEK (MAPK/extracellular signal-regulated kinase) are often used as palliative treatment in BRAF-mutated metastatic melanoma. Recent data show improved progression-free survival with encorafenib with binimetinib, a newer BRAF/MEK inhibitor combination, compared with older agents, but there have been no reports of this treatment in the setting of renal and liver failure. We report a patient with disease-induced transaminitis and renal failure requiring dialysis who was successfully treated with encorafenib and binimetinib. His transaminitis improved and he was able to stop dialysis without any significant adverse effects during treatment, suggesting encorafenib with binimetinib may be used safely and effectively even in patients with end organ damage.

BACKGROUND

Melanoma is increasing in both men and women with risk factors being fair skin, exposure to ultraviolet (UV) radiation, UV-based artificial tanning, atypical moles or dysplastic nevi, prior history of melanoma and family history of melanoma. There will be an estimated 96 480 new cases of melanoma (22.2 per 100 000 men and women per year) in 2019 with an estimated 7230 deaths from melanoma in 2019.¹ Melanoma treatment has changed over the years with immunotherapy or molecularly targeted agents against the proto-oncogene BRAF and MAPK pathway now replacing chemotherapy as first line. BRAF is a protein kinase component of the RAS–RAF pathway that regulates gene expression by relaying extracellular signals to the nucleus. Inhibiting MEK (MAPK/extracellular signal-regulated kinase) is another way of targeting the MAPK pathway since it is the immediate downstream signal. Inhibitors of BRAF and MEK have a rapid but short-lived response and subsequently are used for palliative treatment in patients unable to be treated with immune checkpoint inhibitors.

Dabrafenib and vemurafenib are both BRAF inhibitors that are approved as monotherapy or in combination with their respective MEK inhibitors, trametinib and cobimetinib. These combinations have a median progression-free survival (PFS) of <12 months. Encorafenib/binimetinib is a newer BRAF/MEK inhibitor combination with improved PFS compared with older combinations. However,

there are no available reports on its use in patients with end organ damage.

CASE PRESENTATION

We present a 60-year-old man originally diagnosed with limited cutaneous melanoma that was resected with local recurrence in 2013. This was again resected followed by adjuvant interferon and observation thereafter until he developed a persistent cough. CT of the chest showed large left upper lobe and right lower lobe masses with biopsy confirmed recurrence of melanoma. Positron emission tomography-CT (PET/CT) redemonstrated the bilateral pulmonary masses along with several liver lesions and bony lesions at C7, L4 and the sacrum, all of which were consistent with metastatic disease.

Genomic testing showed programmed death-ligand 1 (PD-L1) of 0% and BRAF V600E mutation. Treatment with ipilimumab and nivolumab was planned but was delayed twice due to transaminitis that continued to worsen, prompting hospital admission. He reported worsening abdominal pain with lab work showing elevated total bilirubin of 4.0 mg/dL, alkaline phosphatase (AP) 915 units/L, aspartate aminotransferase (AST) 132 units/L, alanine aminotransferase (ALT) 134 units/L and creatinine 1.29 mg/dL. Acute hepatitis panel was negative, and liver ultrasound showed an enlarged liver with numerous metastatic lesions that had progressed compared with the PET/CT findings. His lab abnormalities were thought to be due to progression of disease so he was discharged after symptom control with plans for treatment with immunotherapy.

However, he was unable to receive treatment and was readmitted shortly after with worsening abdominal pain, lower extremity oedema and oliguria. Lab work now showed total bilirubin of 4.9 mg/dL, AP 918 units/L, AST 152 units/L, ALT 108 units/L and creatinine of 4.36 mg/dL.

INVESTIGATIONS

Nephrology was consulted and ordered a renal vein thrombosis ultrasound that was unremarkable. Urinalysis showed eosinophilia and given his reported history of using non-steroidal anti-inflammatory drugs (NSAIDs) for pain, his acute renal failure was presumed to be NSAID-induced acute interstitial nephritis. He was initially started on prednisone 1 mg/kg, but kidney biopsy showed

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Table 1 Hospitalisation lab values

Lab values	Admission	Pretreatment	References
Creatinine	4.36	6.88	0.64–1.27 mg/dL
Total bilirubin	4.9	2.9	0.4–1.3 mg/dL
AP	918	579	34–106 units/L
AST	152	180	10–40 units/L
ALT	108	114	7–56 units/L

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase.

diffuse tubular injury but no other abnormalities so prednisone was stopped. Meanwhile, his renal function continued to worsen with creatinine now at 6.88 mg/dL, ultimately requiring dialysis (table 1).

TREATMENT

Due to the patient's continued decline in liver function and clear progression of melanoma, we decided to start treatment with encorafenib and binimetinib. The package insert for binimetinib allows for a dose adjustment based on total bilirubin to 30 mg two times per day and specifically states there is no clinical effect on binimetinib exposure to patients with severe renal impairment.² However, there is less information available for encorafenib dosing in patients with organ dysfunction. The package insert for encorafenib states a recommended dose has not been established for patients with severe renal or hepatic impairment. Based on plasma protein binding of 86%, dialysis was unlikely to have an effect on the encorafenib levels.² With this information, the patient was consented for treatment with the knowledge that the encorafenib had not been studied in patients with similar organ function and we would continue to monitor for decline in liver and renal function during his hospital stay. After the indicated electrocardiogram (EKG) and echocardiogram were completed, the patient was initiated on encorafenib 450 mg one time per day and binimetinib 30 mg two times per day.

OUTCOME AND FOLLOW-UP

The patient tolerated encorafenib/binimetinib without significant adverse effects. His renal function and transaminitis began to improve, and he was discharged 5 days after starting therapy with creatinine of 4.48 mg/dL, total bilirubin of 4.7 mg/dL, AP 977 units/L, AST 162 units/L and ALT 169 units/L. At follow-up 3 weeks after discharge, lab values had improved with creatinine of 1.66 mg/dL, total bilirubin 0.7 mg/dL, AP 447 units/L, AST 46 units/L and ALT 26 units/L. After 2 months of therapy, the creatinine had normalised (table 2).

The abdominal pain had resolved, and he was able to stop dialysis. At that time, the patient was advanced to full dose binimetinib 45 mg two times per day. CT chest/abdomen/pelvis 3 months after starting therapy showed treatment response with a decrease in size of multiple metastatic lesions.

Table 2 Post-treatment lab values

Lab values	5 days	3 weeks	2 months	References
Creatinine	4.48	1.66	1.00	0.64–1.27 mg/dL
Total bilirubin	4.7	0.7	0.9	0.4–1.3 mg/dL
AP	977	447	225	34–106 units/L
AST	162	46	33	10–40 units/L
ALT	169	26	48	7–56 units/L

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase.

DISCUSSION

Treatment for metastatic melanoma has changed in recent years with immunotherapy and targeted agents replacing traditional chemotherapy. About half of metastatic cutaneous melanomas harbour a mutation of BRAF, which is an intracellular signalling kinase in the MAPK pathway and a target for BRAF inhibitors. Nevertheless, immune checkpoint inhibitors are still preferred as first-line therapy given the short-lived duration with targeted therapies, but the latter can be used when a more rapid clinical response is needed.

BRAF inhibitors can be used as monotherapy or in combination with MEK inhibitors, which act on the signalling molecule downstream of BRAF and in doing so, amplify treatment effects. Vemurafenib and dabrafenib are BRAF inhibitors that have shown improved response rates (RR), PFS and overall survival (OS) as monotherapy agents compared with chemotherapy.^{3 4} Unfortunately, these treatments are soon met with BRAF resistance despite the initial rapid response. The response is slightly more durable, however, when BRAF inhibitors are used in combination with MEK inhibitors. COMBI-v evaluated RR (64% vs 51%), median PFS (11.4 vs 7.3 months) and median OS (not reached vs 17.2 months) for dabrafenib with trametinib compared with vemurafenib alone.⁵ COMBI-d similarly found improved RR (69% vs 53%), median PFS (11 vs 8.8 months) and median OS (25.1 vs 18.7 months) when dabrafenib was combined with trametinib compared with dabrafenib alone.⁶ The Co-BRIM study used a different combination (vemurafenib and cobimetinib) and compared this to vemurafenib alone, again finding better RR (70% vs 50%), median PFS (12.3 vs 7.2 months) and median OS (22.3 vs 17.4 months) for BRAF/MEK inhibitors over BRAF inhibitor monotherapy.⁷

More recently, studies have evaluated a newer BRAF/MEK combination: encorafenib and binimetinib. Encorafenib is a BRAF inhibitor with an impressive dissociation half-life of >30 hours, which is significantly longer than dabrafenib (2 hours) and vemurafenib (0.5 hours) and allows for improved pharmacodynamics.⁸ A large randomised phase III study evaluated encorafenib with binimetinib, encorafenib alone and vemurafenib alone.⁹ Cross-trial comparison shows encorafenib/binimetinib has better median PFS (14.9 months) and median OS (33.6 months) compared with previous combinations of dabrafenib/trametinib and vemurafenib/cobimetinib. As such, encorafenib/binimetinib may be preferable to older BRAF/MEK combinations. However, the patients included in the trial were required to have adequate organ function and laboratory parameters including liver enzymes and creatinine.

To our knowledge, there are no other reports of encorafenib/binimetinib being used in patients with hepatic and renal insufficiencies, which are often present in those with large burden of disease. Not only did our patient tolerate treatment despite his organ damage, but his impairments were also reversible with treatment. He was able to completely come off dialysis and also had resolution of his symptoms. Though more research is needed to evaluate its tolerability, encorafenib/binimetinib appears to be a

Learning points

- ▶ Targeted therapies can be used in BRAF-mutated metastatic melanoma when a rapid response is needed.
- ▶ Encorafenib/binimetinib is a new BRAF/MEK combination with improved progression-free survival and overall survival.
- ▶ Encorafenib/binimetinib can be used in renal and liver failure.

viable option for patients with disease-induced end organ damage. Our case offers a safe and feasible treatment option for patients with hepatic and renal impairment who need rapid response.

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