RESEARCH LETTER

Acute Kidney Injury Following Encorafenib and Binimetinib for Metastatic Melanoma

To the Editor:

Nephrotoxicity is an important adverse effect of BRAF inhibitors, a class of drugs that are a mainstay for the treatment of advanced $BRAF^{V600}$-mutant metastatic melanoma.[1-3] Encorafenib, a new drug in this class, has recently been approved in combination with binimetinib, a MEK inhibitor, for patients with advanced metastatic melanoma.[4,5] In the phase 1 trial of this combination, the maximum tolerated doses of encorafenib were 450 mg daily and 600 mg daily, but 450 mg became the US Food and Drug Administration–approved dose because 3 patients had unexplained acute kidney injury (AKI) at the higher dose.[6] Up to 93% of participants in the phase 3 COLUMBUS trial of the combination in patients with advanced melanoma experienced at least a 0.3-mg/dL increase in creatinine level.[4,5] We aimed to describe the incidence, timing, and clinical features of AKI in patients receiving encorafenib-binimetinib for malignant melanoma.

We retrospectively analyzed data from all patients who received encorafenib-binimetinib at Partners Healthcare between 2013 and 2019. Patients were identified using the Research Patient Data Registry by both medication list and natural language processing of electronic health records searching for "encorafenib," "binimetinib," or "enco-bini." Using chart review, we recorded baseline demographics, comorbid conditions, medications, laboratory studies, and encorafenib-binimetinib dose and start date. Patients were followed up for 1 year. The Kidney Disease: Improving Global Outcomes (KDIGO) criteria were used to diagnose and grade AKI.[7] The cause of AKI was determined by 2 nephrologists (H.S. and M.E.S.). Transient AKI was defined as AKI that resolved with supportive measures in less than 48 hours. Sustained AKI persisted longer than 48 hours despite supportive measures. Univariable logistic regression was used to compare the baseline demographic and clinical characteristics associated with AKI.

This study was approved by the Institutional Review Board at Partners Healthcare (2017P000501), and the need for informed consent was waived.

Fifty-seven patients were included; average age was 60 ± 15 years, 53% were men, 89% were white, 9% had diabetes mellitus, and 53% had hypertension at baseline (Table 1). The majority (81%) of patients received encorafenib, 450 mg, daily and binimetinib, 45 mg, twice daily. Sixty-seven percent had prior immune checkpoint inhibitor exposure. Fifteen (26%) patients experienced AKI. Median time to AKI was 27 (interquartile range, 10-53) days. Among the 15 patients, the KDIGO stages of AKI severity were 53% stage 1, 20% stage 2, and 27% stage 3. Use of diuretics and higher doses of encorafenib were associated with AKI in a univariable logistic regression model.

Ten of 15 (67%) patients with AKI had transient AKI; this resulted from either side effects of BRAF inhibitor (fever, vomiting, and diarrhea) in 8 patients or from a documented infection (pyelonephritis or diverticulitis). Sustained AKI occurred in 5 (33%) patients; 3 experienced tubular toxicity attributed to encorafenib and 2 experienced AKI from tumor lysis syndrome. Sustained AKI lasted a median of 10 (range, 3-37) days. No patient had significant proteinuria (protein excretion > 0.3 g/g). Three (20%) had microscopic hematuria (>10 red blood cells per high-power field) and 2 patients had leukocyturia (>10 white blood cells per high-power field). All 3 patients with tubular toxicity had normal urine sediment without cellular casts. Eleven (73%) patients were hospitalized at the time of AKI. Four (27%) saw a nephrologist. None of the patients underwent kidney biopsy. The majority required dose reduction or treatment discontinuation (66%). Five (33%) patients continued full-dose encorafenib with eventual resolution of AKI with supportive care. Kidney function recovered to within 0.3 mg/dL of pre-AKI baseline in all but 2 patients. The 6-month mortality was 27% for patients with AKI and 14% for patients without AKI.

Nephrotoxicity is a common and important side effect of encorafenib-binimetinib treatment. Twenty-six percent of patients experienced clinically significant AKI, at a median of 27 days after starting therapy. The majority required hospitalization and dose reduction or treatment discontinuation due to AKI. We have determined that the clinical features of AKI in patients receiving encorafenib-binimetinib ranged from transient AKI resolving with hemodynamic support to sustained AKI events likely due to tubular nephrotoxicity or tumor lysis syndrome. This is consistent with kidney biopsy findings from patients receiving other BRAF inhibitors showing acute and chronic tubular injury as the dominant finding, though interstitial nephritis may be concurrently found.[1,2] The incidence of AKI with encorafenib-binimetinib may be lower than in patients receiving other BRAF inhibitors; a retrospective analysis of 74 patients with melanoma receiving vemurafenib demonstrated 60% incidence of at least stage 1 AKI.[2]

Our main limitations were the small sample size with only limited numbers experiencing sustained AKI and lack of biopsy-confirmed diagnosis, relying on retrospective adjudication by 2 nephrologists.

In conclusion, oncologists and nephrologists should be aware of the substantial incidence of clinically significant AKI with encorafenib-binimetinib. It is reassuring that the majority of AKI was transient and almost all patients had recovery to their baseline. However, patients frequently required hospitalization and treatment interruption or

Table 1. Baseline Characteristics of Patients Receiving Encorafenib and Binimetinib by AKI Status

Baseline Characteristic	All (N = 57)	No AKI (n = 42)	AKI (n = 15)	*P*
Age, y	60 (15)	60 (15)	64 (15)	0.31
Male sex	29 (53%)	21 (53%)	8 (53%)	0.45
White race	51 (89%)	37 (88%)	14 (93%)	0.33
Pretreatment serum creatinine, mg/dL	0.9 (0.2)	0.9 (0.2)	0.8 (0.2)	0.35
Estimated glomerular filtration rate, mL/min	96 (26)	95 (25)	98 (29)	0.69
Chronic kidney disease	6 (11%)	5 (12%)	1 (7%)	0.57
Diabetes mellitus	5 (9%)	2 (5%)	3 (20%)	0.07
Hypertension	30 (53%)	23 (55%)	7 (47%)	0.59
Coronary artery disease	7 (12%)	4 (10%)	3 (20%)	0.29
Congestive heart failure	2 (4%)	2 (5%)	0 (0%)	0.39
Prior immune checkpoint inhibitor exposure	38 (67%)	28 (67%)	10 (67%)	1.00
Prior chemotherapy within 6 mo	10 (18%)	9 (21%)	1 (7%)	0.20
ACEi or ARB use	9 (16%)	7 (17%)	2 (13%)	0.76
NSAID use	7 (12%)	4 (10%)	3 (20%)	0.29
Diuretic use	4 (7%)	1 (2%)	3 (20%)	<0.01
Encorafenib dose (daily)				
≥450 mg	46 (81%)	31 (74%)	15 (100%)	<0.01
<450 mg	11 (19%)	11 (26%)	0 (0%)	
Binimetinib dose (daily)				
90 mg	49 (86%)	34 (81%)	15 (100%)	<0.01
<90 mg	8 (14%)	8 (19%)	0 (0%)	

Note: Overall cohort and univariable comparison of baseline characteristics in patients with AKI compared with those without AKI. Chronic kidney disease was defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2. Values expressed as number (percent) or mean (standard deviation). Conversion factors for units: creatinine in mg/dL to μmol/L, ×88.4.
Abbreviations: AKI, acute kidney injury; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drug.

discontinuation; this may lead to higher treatment failure rates and mortality. Future studies are needed to help improve AKI risk stratification for patients receiving BRAF inhibitor therapies for melanoma and other cancers.

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