Nephrotoxicity of the BRAF Inhibitors Vemurafenib and Dabrafenib

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treatment with vemurafenib, a selective BRAF inhibitor, has shown significant improvement in patient survival compared with standard therapy in BRAF V600-mutant metastatic melanoma.1 Similar studies have shown improvement using another BRAF inhibitor, dabrafenib mesylate.2 No cases of acute kidney injury (AKI) have been reported with dabrafenib use. Acute kidney injury has been recently reported in a few case series with vemurafenib use.3,4 One case series included a patient who had a kidney biopsy demonstrating acute tubular necrosis as a potential mechanism of renal injury.4

OBSERVATIONS We reviewed Food and Drug Administration Adverse Event Reporting System (FAERS) data for both agents for renal toxic effects. From July 2011 through June 2014, 132 cases of acute kidney injury in patients receiving vemurafenib therapy were reported. Renal injury was more common in men (85 men vs 47 women; P < .001). From April 2013 through June 2014, 13 cases of renal injury in patients receiving dabrafenib therapy were reported (12 men and 1 woman). Hypokalemia (6 cases in patients receiving vemurafenib and 2 cases in patients receiving dabrafenib) and hyponatremia (8 and 6 cases, respectively) were also reported.

CONCLUSIONS AND RELEVANCE Vemurafenib seems to be more nephrotoxic than dabrafenib. This renal toxicity seems to be more prevalent among male patients with melanoma. On the basis of the few published case reports, the mode of injury seems to be tubular interstitial injury. Our findings suggest a need to monitor renal function and electrolyte levels in all patients who receive these drugs. Dermatologists, oncologists, and nephrologists need to be aware of this potential hazard.

IMPORTANCE The selective BRAF inhibitors vemurafenib and dabrafenib have shown significant improvement in patient survival compared with standard therapy in BRAF V600-mutant metastatic melanoma.
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At a Glance
- Use of the selective BRAF inhibitors vemurafenib and dabrafenib has shown significant improvement in patient survival compared with standard therapy in BRAF V600E-mutant metastatic melanoma.
- A review of Food and Drug Administration Adverse Event Reporting System (FAERS) data for both agents revealed a substantial number of renal toxic effects.
- A total of 132 cases of acute kidney injury in patients receiving vemurafenib therapy and 13 cases in patients receiving dabrafenib therapy were reported; the renal injury was more common in male patients.
- Hypokalemia and hyponatremia were also reported in patients who had received each agent.
- There is a heightened need to monitor renal function and electrolyte levels in all patients who receive these drugs.

Discussion

Although the FAERS reporting system is an unsophisticated database with scant demographic information, the number of AKI cases reported with BRAF inhibitor therapy is still alarming. Vemurafenib appears to be more nephrotoxic than dabrafenib. This renal toxicity seems to be more prevalent among male patients with melanoma. On the basis of the few published case reports, we believe that the mode of injury seems to be tubular interstitial injury. Proteinuria was not reported.

Conclusions

This FAERS reporting system signal of renal injury with BRAF inhibitor therapy is important because this class of drugs confers significant survival benefit in patients with melanoma. On the basis of our findings, there is a heightened need to monitor renal function and electrolyte levels in all patients who receive these drugs. Dermatologists, oncologists, and nephrologists need to be made aware of this potential hazard. Kidney biopsies are needed to elucidate the mechanism behind the toxicity. We urge large cancer centers to look into close follow-up of patients with renal injury from these agents and to determine outcomes.

REFERENCES