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Brief Communications

Cardiogenic Shock and Respiratory Failure in a Patient With Metastatic Melanoma Receiving Trametinib Therapy

Life-threatening heart failure associated with MEK inhibitors has not been previously reported. We present a case of a patient experiencing cardiogenic shock while receiving the oral MEK inhibitor trametinib in the setting of a respiratory syncytial virus (RSV) infection.

A 32-year-old patient with *NRAS*-mutant (Q61E) metastatic melanoma presented with several days of cough and dyspnea. He had been diagnosed with metastatic melanoma 1 year earlier and had received ipilimumab plus granulocyte macrophage colony-stimulating factor, pembrolizumab, and extensive palliative radiation treatment, including to the right chest wall and mediastinum. One month before this presentation, he started taking the oral MEK inhibitor trametinib. He first presented to an outside hospital, where he was found to be tachycardic, hypotensive, and hypoxemic. He was intubated, and vasopressors were started for hemodynamic support. On presentation to our medical intensive care unit, his vital signs were as follows: temperature 100.6°F, pulse 136 beats per minutes, and blood pressure 103/70 mmHg while taking norepinephrine (Levophed), vasopressin, and milrinone. The echocardiogram demonstrated diffuse hypokinesis of both ventricles, with a left ventricular ejection fraction of 11%. He was medically treated for cardiogenic shock with inotropic support and diuresis. Trametinib was discontinued. When his nasopharyngeal swab tested positive for the presence of RSV antigen, he was treated with ribavirin for RSV pneumonitis. A repeat echocardiogram on hospital day 5 demonstrated a persistently depressed ejection fraction of 18%. His course was complicated by methicillin-sensitive *Staphylococcus aureus* and *Klebsiella* pneumonia, requiring intravenous antibiotics. Blood cultures were negative. On hospital day 15, a repeat echocardiogram demonstrated left ventricular systolic function with an ejection fraction of 65% and right ventricular systolic function within normal limits. He was discharged home on hospital day 44. He was subsequently treated with three cycles of ipilimumab. He died 2 months later when he experienced a sudden speech deficit and was found to have a metastatic brain lesion. The autopsy showed widely metastatic melanoma. The pathologic features of the heart were unremarkable, other than mild atherosclerotic disease. Molecular testing for RSV was not performed at autopsy.

The extent to which trametinib versus RSV contributed to the cardiogenic shock in the present patient is unknown. In the phase I trial of trametinib in patients with advanced solid tumors, cardiomyopathy was reported in 16 of 206 patients (8%) [1]. In the phase III trial of trametinib in patients with BRAF-mutant melanoma, decreased ejection fraction or ventricular dysfunction was observed in 14 of 310 patients (7%) [2]. Cardiomyopathy has also been observed with other MEK1/2 inhibitors such as binimetinib and cobimetinib, suggesting a class effect. The use of the MEK1/2 inhibitor PD98059 has been shown to impair organization of the sarcomere in the setting of α_1-adrenergic agonists [3]. MEK1/2 inhibition in cultured rat cardiomyocytes has also been shown to increased ischemia/reoxygenation-induced apoptosis [4]. It is also notable that MEK inhibitors have been associated with skeletal muscle weakness, such as in dropped head syndrome, a focal myopathy of the neck extensor muscles that can develop from the effects of inhibiting MEK1/2 on fatty acid uptake by skeletal muscles [5, 6]. Few reports of RSV leading to decompensated heart failure have been published [7]. Molecular analysis of myocardial tissue in patients with viral myocarditis revealed adenovirus and enterovirus in 95% of cases (227 of 239 cases) but RSV in only 1 of 239 cases [8].

In conclusion, life-threatening heart failure can occur with trametinib therapy and is reversible. It is recommended that patients receiving trametinib be evaluated by echocardiography within 1 month after starting therapy and then at 2- to 3-month intervals [9]. For patients taking trametinib who develop severe cardiomyopathy, we recommend withholding trametinib and searching for other contributing causes, such as a viral infection.

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For Further Reading:

Jason J. Luke, F. Stephen Hodi. Ipilimumab, Vemurafenib, Dabrafenib, and Trametinib: Synergistic Competitors in the Clinical Management of BRAF Mutant Malignant Melanoma. ***The Oncologist*** 2013;18:717–725.

Implications for Practice:

Ipilimumab, vemurafenib, dabrafenib, and trametinib have recently significantly advanced the management of patients with BRAF mutant melanoma. Clinical trials that would guide the use of combinations and/or sequencing of these drugs are currently in progress or being developed. Until those data are available, we suggest that patients with good performance status be treated with immunotherapy prior to consideration of kinase inhibitors such as vemurafenib, dabrafenib, and trametinib. This recommendation is based on the potential time required for induction of an antitumor immune response by ipilimumab, the modest durability of clinical benefit by kinase inhibitors and the observation that a not-insignificant proportion of patients treated initially with kinase inhibitors are unable to later complete ipilimumab induction due to clinical decline.