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Adverse events from new targeted therapies, BRAF and MEK inhibitors, in a patient with metastatic melanoma

*Mary L. Dinh[1], Louis J. Portas[2], Adam J. Albert[1,2]

[1]Penn State College of Medicine, Hershey, PA [2]Lebanon Veterans Affairs Medical Center, Lebanon, PA

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Learning Objectives

1. Recognize manifestations of BRAF/MEK inhibitor toxicity through clinical presentation

2. Describe the use of BRAF/MEK inhibitors in patients with metastatic melanoma

3. Describe the use of the Naranjo Scale

Case Description

An 84-year-old Caucasian man with a past medical history of metastatic melanoma presented with a weeklong history of fevers and rigors. The patient was seen in the Emergency Department 2 days prior with similar complaints. At that time, his oncologist discontinued his targeted therapy, dabrafenib and trametinib (BRAF and MEK inhibitors, respectively). Patient reports he has had previous symptoms of fevers, shortness of breath and rash lesions that have receded after medication dose was decreased in the past.

On physical exam, he was febrile, tachycardic, and dyspneic. No skin lesions or lymphadenopathy were noted. Bilateral crackles were heard on lung auscultation. Initial labs were notable for WBC of 1.8 K/mm³, neutrophils of 1.4 K/mm³, platelets of 89 K/mm³, hemoglobin of 11.5 g/dL, hematocrit of 21%, AST of 1144 U/L, ALT of 638U/L, and ALP of 321 U/L.

Chest X-ray showed bilateral interstitial thickening. Pulmonary embolism was considered due to tachycardia and dyspnea, but was proven negative with CT angiography of the chest. Pneumonia was considered due to neutropenia, crackles on lung auscultation and abnormal chest X-ray findings, so the patient was empirically treated with cefepime and azithromycin. The patient's targeted therapy remained discontinued, and he was treated with 60mg methylprednisolone for presumed drug toxicity causing pancytopenia and liver laboratory abnormalities.

During the patient's 7-day admission, with cessation of dabrafenib/trametinib and antibiotic treatment, all cell lines up-trended with improved clinical symptoms and liver enzyme values, consistent with dabrafenib/trametinib toxicity with a Naranjo score of 9. Oncology was consulted before discharge.

Discussion

Better understanding of the genetic profile of metastatic melanoma has dramatically changed management and improved survival with the use of new targeted therapies, such as the BRAF and MEK inhibitors.[1-2] Approximately 50% of melanomas contain a mutation in the BRAF gene (V600E) that encodes a constitutively active RAF protein, part of the MAPK pathway that leads to cell proliferation.[2] New BRAF and MEK inhibitor drugs, approved by the FDA in 2018, were developed to inhibit proteins that cause cell proliferation in the MAPK pathway.[3] Both inhibitors have been shown through clinical trials to improve overall survival.[4-7]

Adverse events, such as neutropenia (16%), anemia (38%), lymphocytopenia (28%), thrombocytopenia (10%), and elevated serum ALT (28%), ALP (19-25%) and AST (21%) have been documented when using BRAF inhibitors.[7] Analysis using the simple and widely used Naranjo Scale is useful to assess the likelihood a drug has contributed to an adverse event. The scale uses a questionnaire that includes 10 questions based on causal time frame to the drug and response after drug is withheld to assign probability scores.[8] A score of >9 is interpreted as "definite," meaning the drug has a high likelihood of contributing to the adverse event, whereas scores below 9 are interpreted as "probable," "possible," or "doubtful."[8] The case described herein allows clinicians to learn more about these new drug effects on patients and the use of the Naranjo scale in practice.

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Author Information

Corresponding Author

* Mary Dinh, BA
mdinh@pennstatehealth.psu.edu, (408)-677-7315

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