



NATIONAL PBM ALERT

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DEPARTMENT OF VETERANS AFFAIRS - VETERANS HEALTH ADMINISTRATION (VHA)
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), AND
CENTER FOR MEDICATION SAFETY PSCI (VA MEDSAFE)

MICROANGIOPATHIC HEMOLYTIC ANEMIA IN PATIENTS TREATED WITH BEVACIZUMAB PLUS SUNITINIB

I. ISSUE

FDA MedWatch issued a safety alert with details from a “Dear Healthcare Provider” letter issued by Genentech concerning the development of microangiopathic hemolytic anemia (MAHA) in patients treated with bevacizumab plus sunitinib.

II. BACKGROUND

Microangiopathic hemolytic anemia is a type of intravascular fragmentation hemolysis involving microvascular abnormalities. The pathognomonic finding is the presence of schistocytes on the peripheral blood smear, usually in combination with anemia and/or thrombocytopenia. The etiology is highly varied, and has been associated with malignancy as well as with some cytotoxic chemotherapy drugs (cisplatin, cyclophosphamide, carmustine, mitomycin, and bleomycin).

III. DISCUSSION

In a phase I trial investigating a fixed dose of bevacizumab with escalating sunitinib dose cohorts in patients with solid tumors, 5 of 12 patients at the highest sunitinib dose of 50mg per day daily for 4 weeks then off for 2 weeks, developed laboratory findings consistent with MAHA. Two cases were severe with signs of thrombocytopenia, anemia, reticulocytosis, decreased haptoglobin, schistocytes on peripheral smear, reversible leukoencephalopathy syndrome, and proteinuria. In both cases the findings were reversible within 3 weeks of stopping both drugs without any other intervention. This phase 1 trial, was closed as was an additional Genentech sponsored trial using a similar dosing schema. In that trial, 2 of 7 patients developed MAHA. Two additional Genentech sponsored trials of bevacizumab in combination with sunitinib in patients with solid tumors were closed due to poor tolerability, primarily myelosuppression, fatigue, diarrhea, anorexia, dehydration, and stomatitis. There were no episodes of MAHA in these trials.

Bevacizumab is not approved for use in combination with sunitinib.

IV. VA MedSAFE RECOMMENDATIONS *(concurrent by VA Oncology FAC):*

- There is currently no rationale, nor evidence, outside of a clinical trial, to use this combination of drugs to treat any cancer.
- Any active clinical trials in the VA using this combination should be suspended, and local IRB’s will review the trials for any untoward toxicity before determining further actions.
- Providers should document/report all possible adverse events related to bevacizumab plus sunitinib treatment, including microangiopathic hemolytic anemia, as per the usual protocols used at their VA.
- Further information regarding microangiopathic hemolytic anemia in patients treated with bevacizumab plus sunitinib can be accessed via the following link:

<http://www.fda.gov/medwatch/safety/2008/safety08.htm#Avastin>.