CLINICAL VIGNETTE

Bevacizumab Use Beyond Cancer

Evangelia Kirimis, MD

A 48-year old with hereditary hemorrhagic telangiectasia (HHT) was referred to hematology for chronic anemia. She had significant epistaxis for years, particularly worse during allergy season and also noted heavy, irregular menses. In addition to nasal mucosa involvement, she had arteriovenous malformations (AVMs) in the liver and lungs. She presented with a hemoglobin of 7.9 g/dL and mean corpuscular volume of 59 fL, decreased from 10.6 g/dL and 76 fL a year prior. She also reported significant fatigue and dyspnea on exertion. Significant iron deficiency was confirmed and was started on intravenous iron. She could not tolerate sufficient enteral iron supplementation to offset her chronic losses and had great brief responses to treatment. She was busy life, work and children, with poor follow up and would usually return when she was significantly anemic. She was evaluated by head and neck surgery but was hesitant to undergo procedures. Over time she developed worsening shortness of breath limiting her activities of daily living. Her cardiologist noted increasing pulmonary pressures and evidence of worsening high output cardiac failure. Echocardiogram noted a pulmonary artery pressure of 53 mmHg, right atrial pressure of 8 mmHg, and a dilated inferior vena cava with greater than 50% collapse during respiration suggesting elevated right atrial pressures. Two years prior the patient had normal pulmonary artery and right atrial pressures.

HHT is an autosomal dominant disorder also known as Osler-Weber-Rendu.[1-4] The disease is variable but commonly presents with epistaxis.[1-3] However, telangiectasias and AVMs in the gastrointestinal tract, lung, brain, and liver are also common and can lead to bleeding and iron deficiency as the first indication of the underlying disorder.[1-4] Hepatic involvement occurs in about three quarters of patients but less than ten percent develop liver shunting.[3] High output cardiac failure is the most common complication.[3] Clinical diagnosis is based on meeting three or more Curacao criteria or by genetic testing for a pathogenic HHT gene mutation.[1,3] Common mutations appear to encode for proteins involved in endothelial cell regulation with reports of elevated tissue levels of vascular endothelial growth factor (VEGF).[1,3] VEGF acts on vascular endothelium leading to endothelial cell replication and further capillary vessel growth.[1] Although local treatments are often used to control bleeding, benefits are often temporary with limitations in number of times they can be repeated.[4] Some believe HHT is a systemic disorder of angiogenesis related to overexpression of certain receptors including VEGF and improper cell signaling.[1,3] Bevacizumab has been tried on these patients.[1-3]

Bevacizumab is a VEGF inhibitor commonly used in patients with colon cancer and other malignancies.[1] While HHT symptoms are variable, the main complications include excessive bleeding requiring regular blood transfusions and cardiopulmonary compromise in patients with hepatic AVMs.[1,2] Published cases report decreased transfusion requirements with bevacizumab.[1,2] Similarly, small studies also report cardiac failure improvement with treatment.[2,3] In one study, 80% of patients with high output cardiac failure had a benefit three months after starting therapy, 12% with normalization of cardiac output.[3] This study, also reported significantly improved epistaxis in nearly 90% of patients after six months of treatment.[3] These small studies support use of bevacizumab as first-line treatment in patients with refractory bleeding due to HHT.[2] The dosing of the drug varies in different studies, but is commonly 5 milligrams(mg)/kilogram (kg) infusion every two weeks for six treatments followed by potential maintenance therapy.[2,3] Duration of maintenance has not been standardized and varies from only as needed to every one to six months.[2] In general, the medication is well-tolerated with a common side effects of hypertension, which is generally well-controlled with blood pressure medications.[3,4] Bleeding, proteinuria, arterial thrombosis, and peripheral neuropathy are other less often but well-documented complications of therapy.[3,4]

Our patient started bevacizumab 5mg/kg every 2 weeks for 6 doses and then continued every 2 months indefinitely. She noted immediate cessation of epistaxis on treatment. Interestingly as she was premenopausal with heavy menses, she also developed amenorrhea. Her hemoglobin continued to rise without need for iron supplementation and she eventually had stable mild erythrocytosis. Her cardiac markers also dramatically improved. Repeat echocardiogram after four months of treatment noted improved pulmonary arterial pressure, down to 17 mmHg with right atrial pressure of 3 mmHg. Her inferior vena cava was normal in size with greater than 50% respiratory change. She was able to resume her normal daily activities and felt better than she had in years. The patient tolerated treatment well and opted to continue maintenance every two months with no further bleeding. For this young patient, treatment not only benefited her clinically but dramatically improved her quality of life.

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