Blessing for the Bleeder: Bevacizumab in Hereditary Hemorrhagic Telangiectasia

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Hereditary hemorrhagic telangiectasia (HHT) is a genetic disorder characterized by uncontrolled multisystem angiogenesis with epistaxis, gastrointestinal bleeding, iron-deficiency anemia, and arteriovenous malformations, and is often associated with increased levels of vascular endothelial growth factor (VEGF). Bevacizumab, a VEGF inhibitor, reduces epistaxis, telangiectasias, and iron-deficiency anemia. We present the case of a woman with HHT and chronic gastrointestinal bleeding who required iron supplementation and multiple blood transfusions. Bevacizumab resulted in marked symptom improvement and transfusion-independence. Our report describes the dose schedule and calls for a randomized, controlled trial demonstrating the value of bevacizumab therapy.

Keywords: Bevacizumab; Dosing; Epistaxis; Hereditary hemorrhagic telangiectasia (HHT)

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Rendu-Weber disease, is a rare autosomal dominant, vascular disorder occurring in approximately 1 in 8000 individuals.^{1,2} This multisystem angiogenic disorder is genetically and phenotypically variable; however, the most common presenting symptom is severe and recurrent epistaxis.^{1,2} Other clinical characteristics include mucocutaneous telangiectasias, gastrointestinal bleeding, iron-deficiency anemia, and arteriovenous malformations (AVMs), most commonly in the lung, brain, and liver.¹⁻³

Although HHT is often associated with elevated blood levels and tissue expression of vascular endothelial growth factor (VEGF), whether this represents a primary pathophysiologic mechanism or a secondary phenomenon is not clear.^{2,3} Bevacizumab, a VEGF inhibitor, has been shown to reduce epistaxis, telangiectasias, and the need for iron infusions due to stabilized hemoglobin (Hgb).³⁻¹⁰ Additionally, there has been marked improvement in symptoms and transfusion requirements. Other reports demonstrated improvement in symptoms and transfusion requirements without an appreciable change in AVMs.^{4,6} Dupuis-Girod et al showed that bevacizumab administration is associated with improvement in high output cardiac failure, secondary to its effect on liver capillaries and arteriovenous shunting.^{5,7}

In the previously reported cases, the dose of bevacizumab varied from 5 mg per kilogram (mg/kg) body weight^{1,4-10} to 10 mg/kg body weight³ administered every 2 weeks (table 1). The elimination half-life of bevacizumab has been determined to be 18 to 20 days; however, in the study done by Dupuis-Girod et al⁵ it was

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Table 1: Summary of bevacizumab dose and frequency in HHT.

Bevacizumab Dose	Frequency	Citation
5 mg/kg	Every 2 weeks	Flieger D et al ⁸
5 mg/kg	Every 2 weeks	Mitchell A et al ⁷
10 mg/kg first 2 doses followed by 5 mg/kg	Every 2 weeks	Bose P et al ³
5 mg/kg	Every 2 weeks	Retornaz F et al ⁶
5 mg/kg for first 5 months followed by 7.5 mg/kg	Every 2 weeks	Oosting S et al ⁴
5 mg/kg	Every 2 weeks	Brinkerhoff BT et al ⁹
5 mg/kg	Every 3 weeks	Fodstad P et al ¹⁰
5 mg/kg	Every 2 weeks	Dupuis-Girod S et al ⁵

HHT, hereditary hemorrhagic telangiectasia

found to be 21.5 days. The optimal dose and schedule of administration of bevacizumab in the treatment of HHT is unknown.

Case Presentation

A female patient, aged 57 years, was noted to have microcytic hypochromic anemia in 1990 at age 35, when she presented with hematemesis and a history of melena and epistaxis. An esophagogastroduodenoscopy revealed multiple telangiectasias involving the stomach and duodenum. Her father and three of her siblings had been diagnosed with HHT. A clinical diagnosis of HHT was made. She also had recurrent menorrhagia, and in 1995 underwent a laparoscopic right salpingo-oophorectomy and vaginal hysterectomy. Pathology showed no evidence of malignancy. Prothrombin time, activated partial thromboplastin time, von Willebrand factor, von Willebrand factor antigen, and platelet function testing were all normal. The patient also has asymptomatic pulmonary arteriovenous malformations and one required embolization due to its size.

The patient was on oral iron supplementation and maintained a normal Hgb until age 51 when her Hgb declined to <10 g/dL, associated with an increase in melena and epistaxis. Parenteral iron therapy was initially helpful in maintaining her Hgb levels; however, because of persistent melena and symptomatic anemia, a trial of estrogen supplementation (ethinyl estradiol) was started. She required multiple packed red blood cell (PRBC) transfusions, averaging 2 to 4 units per month to maintain Hgb > 8.5 g/dL. Despite iron infusions on a monthly basis, her serum ferritin remained consistently <30 ng/mL. Her estradiol was discontinued in July 2011, since there was no clear clinical benefit.

In September 2011, bevacizumab was initially started at 10 mg/kg body weight at every 2 week intervals. Melena resolved within a week, Hgb rose to 14.2 g/dL within 4 weeks (figure 1), and serum ferritin increased from 28 ng/mL to 246 ng/mL within 6 weeks, with no further parenteral iron supplementation. She also noted a marked decrease in epistaxis and visible oral mucosal telangiectasias. Once the

hematologic picture stabilized, the bevacizumab dose and frequency were gradually reduced (table 2) to lessen the risk of toxicities and cost of therapy with an attempt to determine the minimal effective dose and schedule.

Discussion

Based on the Curacao criteria developed in 1999, a diagnosis of HHT is considered definitive if at least three of four criteria are present.¹¹ The criteria are spontaneous and recurrent epistaxis, telangiectasia, family history, and visceral lesions. Our patient meets all these criteria (four of four).

Genetic linkage studies identified two loci associated with HHT, and the genes involved have been identified: *ENG* coding for endoglin on chromosome 9q33-q34 (HHT type 1)¹² and *ACRLV1* coding for activin receptor-like kinase 1 (ALK1) on chromosome 12q13 (HHT type 2).¹³ Endoglin is a transforming growth factor β (TGF- β) binding protein,¹² while ALK1 is a member of the serine-threonine kinase receptor family.¹³ Each plays a role in the control of blood vessel development and repair. Both endoglin and ALK1 are involved in the TGF- β signaling pathway, and a mutation in either gene appears to be sufficient to cause HHT in most patients.^{2,14}

Angiogenesis is the formation of new capillary vessels from pre-existing blood vessels. The process can occur in both normal and pathological conditions and is regulated by multifunctional cytokines such as TGF- β 1 and VEGF. TGF- β 1 plays a role in cellular proliferation, differentiation, and migration, as well as extracellular matrix production and disposition. It has also been shown to stimulate VEGF production.^{2,3} VEGF is produced by a number of different cell types but acts preferentially on vascular endothelium. Its main function is to induce mitotic activity in endothelial cells which initiates capillary blood vessel sprouting.² It has been hypothesized that HHT is a multisystemic, yet localized, angiogenesis disorder caused by the over-expression of VEGF, TGF- β 1, and ALK1, as well as alterations in other yet to be identified factors.^{2,14}

Table 2. Dose and frequency of administration of bevacizumab and followup parameters.

Bevacizumab dose (mg/kg body wt)	Frequency of administration	Number of bevacizumab doses	Hemoglobin (g/dL)	Urine for protein	Blood pressure (mmHg)	Evidence of bleed
10	Every 2 wks.	3	14.2	Negative	126/63	None
10	Every 3 wks.	3	15.1	Negative	129/68	None
10	Every 4 wks.	3	14.9	Negative	141/63	None
7.5	Every 4 wks.	3	14.6	Negative	129/71	None
5	Every 4 wks	2	11.6	Negative	123/60	Epistaxis, melena
7.5	Every 4 wks	1	13.1	Negative	130/72	Mild epistaxis, melena
7.5	Every 3 wks	3	13.6	Negative	134/72	None

Unregulated VEGF expression can lead to uncontrolled angiogenesis, resulting in formation of disorganized, fragile vessels susceptible to rupture.¹⁵ Thalidomide, with its anti-angiogenic properties involving VEGF inhibition, was studied in the treatment of gastrointestinal vascular malformations such as gastric antral vascular ectasia and angiodysplasia, which can lead to gastrointestinal bleeding and iron-deficiency anemia. These vascular lesions share common developmental mechanisms, such as high expression levels of VEGF or other angiogenic factors. Following thalidomide treatment, there was a reduction in gastrointestinal bleeding, and plasma VEGF levels decreased significantly compared to levels before treatment, with the decrease more significant in responders than non-responders.¹⁶

Bevacizumab is a reasonable agent to consider for the treatment of HHT, based on the molecular mechanisms involved in both angiogenesis and HHT. In our patient, initiation of bevacizumab resulted in rapid resolution of bleeding. The dosing interval of bevacizumab (10 mg/kg) was gradually increased, starting at 2-week intervals. The dose was then gradually reduced to 5 mg/kg every 4 weeks. However, after the second dose of bevacizumab at 5 mg/kg, the patient had three episodes of melena along with a drop in her Hgb to 12.1 g/dL. The administration of 7.5 mg/kg every 2 to 3 weeks has proven effective in controlling her symptoms without significant adverse effects. This dosing schedule has maintained stable Hgb, obviating the need for further blood transfusions and iron infusions and sustaining the improvement in epistaxis, melena, and telangiectases.

Figure 1: Hemoglobin trend before and after initiation of bevacizumab.

Conclusions

This report further supports the potential role of bevacizumab in the management of HHT, with a focus on the appropriate dose and schedule. Our observations suggest that bevacizumab at a dose of 7.5 mg/kg every 2 to 3 weeks is efficacious in controlling bleeding in HHT. We believe that this case adds to a growing body of knowledge demonstrating that there is both a clinical and economic rationale to consider bevacizumab in the management of HHT, and that it may prove superior to conventional therapy in long-term management. A randomized, controlled trial incorporating longer follow-up studies will be necessary to demonstrate the value of this approach.

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