Intravenous Bevacizumab for Refractory Hereditary Hemorrhagic Telangiectasia—Related Epistaxis and Gastrointestinal Bleeding

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Abstract

Objective: To present a multiyear clinical experience with intravenous bevacizumab for the management of severe gastrointestinal bleeding and/or epistaxis in patients with hereditary hemorrhagic telangiectasia (HHT).

Patients and Methods: All patients treated with intravenous bevacizumab for severe hereditary hemorrhagic telangiectasia–related bleeding from June 1, 2013, through January 31, 2017, were included in this report. Severity of epistaxis (determined using the Epistaxis Severity Score questionnaire); hemoglobin, iron, and ferritin levels; and quality of life data were collected serially in all patients.

Results: Intravenous bevacizumab was administered to 34 patients using a standardized treatment protocol. Anemia was primarily related to severe epistaxis (n=15, 44%), severe gastrointestinal bleeding (n=4, 12%), or both (n=15, 44%), with a median baseline hemoglobin level of 9.1 g/dL (range, 8.3-10.5 gm/dL; to convert to mmol/L, multiply by 0.62). Red blood cell (RBC) transfusions had been administered to 28 patients (82%). Of these, 16 patients (47%) were RBC transfusion dependent and had received a median of 75 RBC transfusions (range, 4->500 RBC units) before bevacizumab initiation. The median length of follow-up was 17.6 months from the beginning of bevacizumab treatment (range, 3-42.5 months). There was a significant reduction in epistaxis severity scores (P<.001) and RBC transfusion requirements (P=.007) after completion of the initial bevacizumab treatment cycle. New-onset or worsened hypertension was noted in 4 patients, with 1 patient experiencing hypertensive urgency with a temporary decline in renal function.

Conclusion: Intravenous bevacizumab is an effective treatment option for patients with severe anemia related to epistaxis and/or gastrointestinal bleeding. Further studies are needed to establish a dose-response relationship as well as clinical, genetic, and biomarker predictors of response.

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber disease, is an autosomal dominant disorder affecting vascular beds in multiple organ systems. Pathognomic vascular lesions in HHT include arteriovenous malformations (AVMs) and telangiectasias (angioectasias) that typically involve skin, mucous membranes, and visceral organs including the lung, liver, gastrointestinal (GI) tract, brain, spinal cord, and other organs. Arteriovenous malformations in the nasal cavity and GI tract have a propensity for spontaneous and recurrent bleeding, resulting in chronic recurrent epistaxis and GI bleeding. Epistaxis is a cardinal manifestation of HHT affecting approximately 50% of patients by age 20 and virtually all patients by age 50. The severity of epistaxis varies widely among patients with HHT and even among closely related family members.

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TABLE 1. Criteria for IV Bevacizumab Use for Epistaxis or GI Bleeding"a,b

- Refractory/severe epistaxis (≥2 required)
  - ≥1 RBC transfusion per month on average over the past 6 mo (or ≥6 transfusions over the past 12 mo)
  - ≥1 IV iron infusion per month on average over the past 12 mo for chronic blood loss anemia
  - Epistaxis Severity Score score ≥7
  - Frequent emergency department visits for severe epistaxis
    - ≥4 visits over the past year
  - ≥1 day lost from work per month due to bleeding over the past 12 mo
  - Hemoglobin level <10 g/dL despite oral and IV iron supplementation

- Refractory/severe GI bleeding (≥2 required)
  - ≥1 RBC transfusion per month on average over the past 6 mo (or ≥6 transfusions over the past 12 mo)
  - ≥1 IV iron infusion per month on average over the past 12 mo for chronic blood loss anemia
  - ≥1 endoscopy (EGD and extended/double balloon enteroscopy) unsuccessful at decreasing iron/transfusion frequency
  - Hemoglobin level <10 g/dL despite oral and IV iron supplementation

*aEGD = esophagogastroduodenoscopy; GI = gastrointestinal; IV = intravenous; RBC = red blood cell.
*bSI conversion factor: To convert gm/dL values to mmol/L, multiply by 0.62.

Gastrointestinal bleeding typically occurs from diffuse HHT-related telangiectasias located along the length of the GI tract. Both severe epistaxis and GI bleeding can become life-threatening conditions with severe blood loss anemia and red blood cell (RBC) transfusion dependence. Both problems also appear to worsen with age.1,2

Therapeutic options for both these conditions are limited and rarely result in a durable treatment response. Bevacizumab is a humanized monoclonal immunoglobulin G1 antibody that binds to circulating vascular endothelial growth factor A (VEGF). Binding of VEGF to its receptors (VEGFR-1 and VEGFR-2) normally results in a potent pro-angiogenic cascade with recruitment and proliferation of endothelial cells as well as sprouting and subsequent development of new blood vessels.3 Previous studies have shown increased plasma concentrations and tissue expression of VEGF and other angiogenic cytokines in patients with HHT.4,5 The availability of bevacizumab opened up the therapeutic possibility of inhibiting VEGF-mediated angiogenesis in patients with HHT with an aim to stabilize or even cause regression in visceral angioectasia. A landmark trial of intravenous (IV) bevacizumab primarily for HHT-related high-output cardiac failure found a significant reduction in the severity and duration of epistaxis.6 A few subsequent case reports also documented a beneficial response of IV bevacizumab in patients with refractory GI bleeding; however, there have been no large studies that focused on the use of IV bevacizumab in the treatment of severe epistaxis and/or refractory GI bleeding.7,8 We present our center’s clinical experience with IV bevacizumab in 34 patients with HHT with severe epistaxis and/or GI bleeding over a 3.5-year time frame.

PATIENTS AND METHODS

This retrospective study was approved by our institutional review board. We included all patients with HHT with refractory anemia (due to HHT-related epistaxis and/or GI bleeding) who had been treated with IV bevacizumab at the Mayo Clinic HHT Center of Excellence in Rochester, Minnesota, from June 1, 2013, through January 31, 2017. All patients had definite HHT on the basis of the presence of 3 or more Curacao classification criteria and had initiated treatment with IV bevacizumab at our facility. All patients underwent a comprehensive multidisciplinary evaluation with appropriate consultations including hematology; gastroenterology; ear, nose, and throat; and interventional radiology. Patients who met criteria for severe HHT-related epistaxis and/or GI bleeding (Table 1) received information on the use of IV bevacizumab, including potential risks, benefits, off-label use, and associated out-of-pocket costs (in case of insurance denial). Bevacizumab was dosed according to a standardized treatment algorithm (Figure 1). Patients treated with IV bevacizumab primarily for HHT-related high-output cardiac failure were not included in this analysis.

Routine HHT Management

All patients continued to receive routine HHT care as per our center’s protocol in accordance with the current guidelines.9 All patients completed a panel of screening tests including a magnetic resonance imaging/magnetic resonance angiography of the brain, contrast bubble echocardiography,
contrast-enhanced computed tomography scan of the chest (for positive echocardiography bubble study results), and computed tomography scan of the abdomen and pelvis to assess liver and visceral AVM status. Baseline complete blood count, iron studies, basic metabolic profile, renal function, and urinalysis were also performed in all patients. Genetic counseling along with genetic testing was offered to all patients and appropriate family members. Upper and/or lower GI endoscopy was performed in patients suspected of having ongoing GI bleeding. All patients received education and information about techniques to reduce epistaxis, including ways to enhance nasal humidity and lubrication (eg, petroleum jelly ointment, rose-geranium oil, saline nasal sprays, and environmental humidification). The Epistaxis Severity Score (ESS) questionnaire was used to assess both baseline and after bevacizumab initiation epistaxis severity.

FIGURE 1. Standardized bevacizumab dosing protocol. Hgb = hemoglobin; IV = intravenous; PRN = as needed.
Bevacizumab Dosing Protocol

Initial Dosing. Bevacizumab was dosed in all patients using a standardized outpatient treatment protocol (Figure 1) using a 5 mg/kg dose. The typical initial dosing cycle consisted of 8 doses (4 doses each administered 2 weeks apart followed by 4 doses each administered 1 month apart). Thus, the patient would typically complete the initial dosing protocol around 22 weeks from the initial dose (doses at 0, 2, 4, 6, 10, 14, 18, and 22 weeks). Extra doses as well as dose modifications were allowed in the initial dosing cycle (Figure 1) if the response to 5 mg/kg of bevacizumab was suboptimal.

Maintenance or “Top-Up” Dosing. Further “top up” or maintenance doses after the completion of the initial dosing cycle were individualized in each patient and based on the occurrence of 1 or more of the following: (1) recurrent or worsening epistaxis affecting the patient’s quality of life (QOL) and/or (2) worsening anemia and iron deficiency due to epistaxis and/or GI bleeding. The overall aim was to redose bevacizumab before the bleeding situation had deteriorated significantly. Thus, patients were instructed to maintain close follow-up with monthly laboratory checks so that bevacizumab could be redosed before significant deterioration in epistaxis or GI bleeding. Initially top-up dosing options included 1, 2.5 to 3, 5, and 7.5 mg/kg options, although as experience accumulated, the 5 mg/kg dose became the standard top-up dose amount and the 7.5 mg/kg was used only for nonresponders to the 5 mg/kg dose. “Top-up” bevacizumab doses typically consisted of 1 to 2 infusions (5 mg/kg) 2 weeks apart. Patients who did not achieve an adequate reduction in bleeding could receive 1 to 2 additional doses 2 weeks apart (total of 4 top-up doses each 2 weeks apart). Patients then continued monthly laboratory follow-up and were again redosed as mentioned above if they met the criteria for rebleding.

Statistical Analyses

Unless otherwise specified, data are presented as median (25th, 75th) for continuous variables and as frequency count (percentage) for categorical variables. ESS scores and QOL data collected during and after the initial bevacizumab treatment cycle were compared with data at baseline using the signed-rank test. In patients who completed the initial treatment cycle, the time to retreatment (ie, top-up) was estimated using the Kaplan-Meier method.

RESULTS

Patient Population

Table 2 lists the demographic and baseline characteristics of 34 patients (21 women),
with a median age of 63 years (range, 57-72 years) at the time of IV bevacizumab initiation. The primary source of bleeding was epistaxis in 15 patients (median ESS score, 8.2; range, 4.7-10.0), GI bleeding in 4 patients (median ESS score, 0.7; range, 0.0-0.9), and combined epistaxis and GI bleeding in 15 patients (median ESS score, 5.2; range, 0.7-7.3). All 19 patients with GI bleeding had diffuse GI telangiectasias confirmed and treated (argon plasma coagulation) via upper and/or lower endoscopy on 1 or more occasions before bevacizumab treatment. In all patients, the median ESS score at baseline was 6.0, with 13 patients (38%) having a baseline score greater than 7 (severe epistaxis). All patients were anemic and iron deficient at baseline, with a median hemoglobin level of 9.1 g/dL, a median iron level of 30 mg/dL (to convert to μmol/L, multiply by 0.179), and a median ferritin level of 17 μg/L. All patients were receiving oral iron supplementation and 16 (47%) were receiving regular IV iron infusions. A total of 28 patients (82%) had received 1 or more blood transfusions (median, 9.5 RBC units; range, 1-650 RBC units) preceding bevacizumab initiation. Of these, 16 (47%) were blood transfusion dependent (receiving regular scheduled blood transfusions for refractory anemia). These 16 patients had received a median of 75 RBC units (range, 4-650 RBC units) over their lifetime and a median of 12 RBC units (range, 1-96 RBC units) in the 6 months preceding bevacizumab initiation. Previous therapies for epistaxis are also listed in Table 2.

Genetic mutation analysis was available for 20 patients (ENG, 9; ACVRL1, 10; no mutation detected, 1).

Results After the Completion of the Initial Bevacizumab Dosing Protocol
The median ESS scores (n=30, excluding the 4 patients with isolated GI bleeding) at baseline and up to 12 months after the completion of the initial bevacizumab dosing protocol (∼8 doses) are listed in Table 3. At 1 month after the initiation of bevacizumab treatment, ESS scores were significantly (P<.001) decreased and the improvement was maintained after the completion of the initial bevacizumab treatment cycle. Baseline and follow-up blood transfusion needs are given

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<td>n</td>
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<td>ESS score</td>
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ESS = Epistaxis Severity Score.
in Table 4 for all patients and for patients who were and were not transfusion dependent before bevacizumab treatment. Patients received fewer blood transfusions after initiating bevacizumab. We compared the 6-month time period before the initiation of bevacizumab with the 6-month period after the completion of the initial treatment cycle (7-12 months after the initiation of bevacizumab) (Table 4). McNemar’s test P value for the comparison was .007 in favor of bevacizumab. This was similar for the overall cohort as well as the transfusion-dependent cohort (similar P value of .007). Facial and mucosal telangiectasias improved in most patients and dramatically in 1 patient (Figure 2).

**Maintenance (Top-Up) Dosing of Bevacizumab After the Completion of the Initial Dosing Protocol**

At the time of writing this article, 3 patients were still receiving bevacizumab doses from the initial dosing protocol. Of the remaining 31 patients who had completed the initial dosing cycle, the median duration of follow-up after the initial cycle was 13.6 months. There have been a total of 18 patients who have required at least 1 top-up dosing of IV bevacizumab because of worsening bleeding and/or anemia since the completion of their initial treatment cycle. The number and timing of subsequent “top-up” treatments are presented in Figure 3. Kaplan-Meier analysis revealed that the median time from the end of the initial treatment cycle to the first top-up dosing of IV bevacizumab was 6.4 months (Figure 4).

**Quality of Life After the Initiation of Bevacizumab (N=34)**

Quality of life was assessed at each follow-up appointment using a 7-point self-reported Likert scale with the following question: “How would you rate your overall quality of life since the last appointment?” (1=very poor QOL, 4=fair/average QOL, and 7=excellent QOL). The effect of epistaxis on QOL (epistaxis-related quality of life [E-QOL]) was also assessed using a similar 7-point Likert scale question: “How often has nose bleeding affected or interfered in your day-to-day life since the last appointment?” (1=very seldom, 4=occasionally, and 7=very often). Bevacizumab had a beneficial effect on both QOL and E-QOL (Figures 5 and 6).

**Adverse Effects of IV Bevacizumab**

Intravenous bevacizumab was generally well tolerated. Infusion-related chills and fever were noted in 2 patients. These did not recur on subsequent dosing after premedicating with acetaminophen and diphenhydramine.
Hypertension (HTN) was noted in 4 patients. One patient with preexisting HTN had to double the daily dose of lisinopril from 10 to 20 mg. Two other patients did not have a history of HTN and required initiation of antihypertensive medications. The fourth patient experienced hypertensive urgency with a temporary decline in renal function after the first dose. Bevacizumab dosing was subsequently resumed without any further adverse effect. Renal function remained at baseline in the rest of the patients without an increase in serum creatinine or new proteinuria. No patient experienced abdominal, brain, pulmonary, or other organ-related bleeding or perforation. Three patients (aged 74, 79, and 73 years) died during the follow-up period. Causes of death were stroke in 1 patient (who had previously suffered multiple strokes before bevacizumab initiation), infective endocarditis (methicillin-sensitive Staphylococcus aureus) with multiple cerebral infarcts in the second patient, and postoperative (left atrial appendectomy for paroxysmal atrial fibrillation) respiratory failure in the third patient. No death could be directly linked to bevacizumab treatment.

**DISCUSSION**

Our study found that IV bevacizumab is an effective treatment of severe HHT-related anemia from either epistaxis or GI bleeding. Intravenous bevacizumab dramatically reduced ESS scores and anemia within the first month of treatment, and the efficacy was maintained through follow-up. The ESS scores improved by nearly 1.5 points within 1 month of bevacizumab initiation, twice the minimal clinically important difference of 0.71 described for this instrument. Further ESS score improvements occurred on...
follow-up, with several patients essentially reporting a complete cessation of nose bleeding after bevacizumab treatment. This is notable, given the severe nature of epistaxis in this group that had already failed various medical and interventional therapies before initiating bevacizumab. Gastrointestinal bleeding also similarly improved with resolution or improvement in anemia in all 19 patients with this condition. Remarkably, no patient required further GI endoscopic procedures for bleeding after the initiation of IV bevacizumab treatment. It is also important to note that all patients in the present study were severely anemic and three-fourths had required 1 or more blood transfusions, with nearly half (n=16) being RBC transfusion dependent (requiring regular scheduled RBC transfusions to maintain a stable hemoglobin level). Of these 16 patients, 13 (81%) were completely freed from further RBC transfusions after bevacizumab treatment whereas 1 patient had a 50% reduction in transfusion frequency and the other 2 patients required intermittent (but greatly reduced) RBC transfusion support. There were no patients who were complete nonresponders to IV bevacizumab.

Place of IV Bevacizumab in the Management of Severe Epistaxis
A comprehensive review of all available oral, topical, and interventional therapies for HHT-related epistaxis is beyond the scope of this article. Nonetheless, it is worthwhile to point out that most cases of mild-moderate epistaxis generally respond well to nasal humidification and nasal hygiene precautions in conjunction with other topical, oral, or interventional therapies. The question of whether these patients might benefit from a low dose IV bevacizumab approach remains unanswered and requires further study. In contrast, severe HHT-related epistaxis is a difficult and frustrating entity with few treatment options that provide durable long-term relief from rebleeding. A stepwise approach has been suggested, with various oral and interventional therapies to be attempted in an escalating fashion, including oral aminocaproic acid, danazol, tranexamic acid, selective estrogen receptor modifiers, oral contraceptive pills, sclerotherapy, laser and bipolar cauteration, selective arterial embolization, septodermoplasty, and nasal...
All patients in our study had received and failed 1 or more of these therapies (except nasal closure) on a number of occasions before the initiation of IV bevacizumab. The lack of any head-to-head trials between IV bevacizumab and these other treatment options precludes any firm recommendation regarding the place of IV bevacizumab in the treatment algorithm for severe epistaxis. Nonetheless, the excellent results noted in this study should prompt clinicians to consider IV bevacizumab, especially in transfusion-dependent cases or those with combined epistaxis and GI bleeding. In our clinical practice, IV bevacizumab has worked in a complementary fashion with other therapies. For example, in severe epistaxis, laser cauterization has provided immediate epistaxis relief, which has then been successfully maintained long-term with IV bevacizumab.

Systemic vs Topical Application of Bevacizumab for Epistaxis

A previous study by Dupuis-Girod et al reported the use of IV bevacizumab in 25 patients with HHT-related high-output heart failure. They reported decreased epistaxis duration as well as improved QOL. However, duration of follow-up was limited (total 6 months from the initiation of the treatment) along with lack of ESS scores as well as specific information on efficacy in GI bleeding cases. The role of topical bevacizumab was explored in the North American Study of Epistaxis, which reported on 3 topical agents including bevacizumab 1%, estriol 0.1%, and tranexamic acid 10% as compared with placebo (0.9% saline nasal spray) in 121 patients with moderate epistaxis in a 4-arm multicenter, randomized, double blind, placebo-controlled trial. The study basically found no efficacy for any of the 3 active arms in comparison with the saline nasal spray placebo arm. In contrast, submucosal injections of bevacizumab have been previously reported to be effective, but their durability and precise role in the management of severe, transfusion-dependent HHT epistaxis remain unclear.

One of the biggest drawbacks of nasal-specific interventional approaches discussed above is that they do not address systemic AVM burden. Thus, a patient with concurrent high-output heart failure or GI bleeding may experience epistaxis relief from intranasal procedures but will still require additional therapies for high-output heart failure or GI bleeding. Thus, IV bevacizumab represents a uniquely successful systemic approach to both mucocutaneous and visceral AVMs.

Difficulty in Managing Refractory GI Bleeding

Refractory GI bleeding in patients with HHT is a significant problem, with current treatment options primarily limited to repeated argon
plasma coagulation treatments of GI angioectasia performed via upper or lower endoscopy. In addition, there have been isolated case reports of danazol, aminocaproic acid, and thalidomide being effective in these cases. Although several case reports have established the efficacy of IV bevacizumab in HHT-related GI bleeding, no large studies have been reported to date using a standardized treatment approach. The present study significantly adds to the body of evidence, with all 19 patients with severe GI bleeding in our study exhibiting remarkable improvements in bleeding along with cessation of need for further endoscopic therapies as well as blood transfusions. For refractory GI bleeding in patients with HHT, IV bevacizumab appears to be a safe and extremely effective treatment option.

Effect of Bevacizumab on E-QOL and Overall QOL

Our study found a significantly improved overall QOL after bevacizumab treatment using a simple Likert scale question. In addition, we found that bevacizumab significantly decreased the degree to which epistaxis interfered with day-to-day QOL (E-QOL) and most patients were able to return to normal day-to-day activities they had previously avoided for fear of precipitating a nose bleed. The adverse effect of epistaxis on QOL in patients with HHT has been reported in a number of studies. Geirdal et al. found that epistaxis was associated with higher levels of anxiety, depression, and a sense of hopelessness in patients with HHT and that QOL worsened with increasing severity and duration of epistaxis. A similar study by Pasculli et al. found epistaxis to be the most important factor affecting QOL in patients with HHT.

Safety of Long-Term IV Bevacizumab

Patients were followed for a median of 21.4 months (range, 3-42.5 months) after the initiation of bevacizumab with an excellent safety profile. No patient suffered intracranial hemorrhage or viscus perforation. Of the 14 patients with baseline HTN, 2 experienced worsened HTN after bevacizumab initiation, requiring initiation of additional antihypertensive medications. One of these patients presented as a hypertensive urgency with a transient decline in renal function that resolved subsequently with blood pressure control. Two additional patients developed new-onset HTN requiring initiation of antihypertensive therapy with subsequent normalization of blood pressures. Hypertension occurs because of blockage of normal signaling via VEGFR-2, which mediates the release of nitric oxide and prostaglandin I2, resulting in vasodilation in arterioles and venules.

Limitations and Strengths of the Study

Our study has several limitations including the lack of randomization and blinding of either patients or care providers. Nonetheless, given the dramatic treatment response, it appears less likely that unknown hidden/confounding factors other than bevacizumab could have influenced outcomes. Moreover, the effect of bevacizumab was reproducible with repeat dosing in patients who had relapsed, resulting in a similar rapid improvement, further proving the efficacy of bevacizumab. The lack of a standardized biomarker for measuring or monitoring HHT “disease activity” is a general limitation in this field. Such a biomarker could theoretically help predict response to bevacizumab and/or predict the need for retreatment even before an actual hemoglobin level decline or a significant increase in epistaxis severity.

The strengths of our study include the large number of patients with severe bleeding treated at a single center with a standardized bevacizumab dosing and follow-up protocol. The detailed and comprehensive availability
of follow-up hemoglobin, iron, and ferritin levels along with serial ESS scores, QOL scores, and E-QOL scores in all patients adds greatly to the validity of our study.

CONCLUSION
We present the first large, detailed long-term study of IV bevacizumab used for the treatment of severe epistaxis and/or GI bleeding in patients with HHT. We report excellent short- as well as long-term success with this approach along with an excellent safety profile. Our study suggests that systemic bevacizumab should be considered as a first-line therapy for the treatment of refractory bleeding in patients with HHT.

Abbreviations and Acronyms: AVM = arteriovenous malformation; E-QOL = epistaxis-related quality of life; ESS = Epistaxis Severity Score; GI = gastrointestinal; HHT = hereditary hemorrhagic telangiectasia; HTN = hypertension; IV = intravenous; QOL = quality of life; RBC = red blood cell; VEGF = vascular endothelial growth factor

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Potential Competing Interests: The authors report no competing interests.

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