Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder with a worldwide prevalence rate of approximately 1 case per 5000 persons that results in vascular malformations throughout the body. At least 90% of patients are affected by nosebleeds and up to 81% have gastrointestinal telangiectasias. Both of these can result in severe bleeding and anemia that are refractory to conventional therapy (eg, iron infusions and endoscopic cautery of gastrointestinal and nasal telangiectasias) in perhaps as many as 10% to 15% of patients.

In this issue of Mayo Clinic Proceedings, Iyer et al report the largest experience to date of intravenous bevacizumab to treat HHT-related bleeding (HRB). Although mainly retrospective, the study is prospective in several important aspects. First, before the initiation of the study, Iyer et al developed a detailed algorithm to decide how they would use bevacizumab to treat HRB (Figure 1 in their article). Second, various measures of efficacy (eg, Epistaxis Severity Score [ESS]) were collected prospectively at patient visits. Their algorithm called for infusion of 5 mg/kg bevacizumab every 2 weeks for 4 doses followed by additional infusions every 4 weeks at 2.5 to 10 mg/kg (depending on the response to the first 4 infusions) for 4 more doses. After this “initial treatment cycle” of 8 infusions, patients received additional doses, so-called “top-up” infusions, on the basis of the recurrence of clinically meaningful epistaxis or anemia.

The authors reviewed the course of 34 patients with definite HHT who were treated with bevacizumab infusions for the main indication of severe HRB over a period of 3.5 years. All patients had failed at least 1 previous therapy for HRB, and 53% were transfused blood in the previous 6 months. After treatment, most patients exhibited improvement in transfusion needs, ESS score, mucocutaneous telangiectasias, and quality of life. There was a marked reduction in transfusion need, which occurred as early as 1 month after the initiation of treatment and continued through at least 12 months. At baseline, 16 patients were transfusion dependent and had received a median of 12 units of blood in the previous 6 months. At 9 to 12 months, only 1 of 16 patients had required blood transfusion in the previous 6 months. Epistaxis Severity Score is a composite measure of epistaxis severity based on the answer to 6 questions related to epistaxis frequency and presence of anemia, and the scores range from 0 to 10; the higher the score, the greater the severity. The median ESS score improved from 6.5 at baseline to 3.3 at 1 month after treatment initiation and indicated a durable response with a value of 2.8 at 10 to 12 months after treatment cessation.

The need for “top-up” infusions was highly variable, with some patients requiring infusions every 1 to 3 months and others not at all. Eighteen of 31 patients (58%) required at least 1 infusion at a median of 6.4 months after the completion of the initial treatment cycle. Of those with at least 10 months of follow-up after the initial treatment, 68% required at least 1 infusion beginning at 1.5 to 13 months. However, 7 patients went 11 to 22 months after the initial treatment without needing another infusion. Bevacizumab was generally well tolerated, with 4 patients experiencing hypertension, which was classified as hypertensive urgency in 1 patient. All patients responded to antihypertensive medicines and were able to continue with bevacizumab treatment.

This study has the usual limitations of a retrospective study, with the main limitation being the lack of placebo control. Furthermore, because a traditional prospective protocol was not in place, hemoglobin levels were not measured in a structured manner that would allow for useful analysis and therefore there is no mention of hemoglobin response.
The study by Iyer et al is a semi-prospective study that finds a remarkable improvement in ESS score, quality of life, and transfusion need. Although one can attribute changes in ESS score or quality of life to the placebo effect, it is much harder to attribute so dramatic a change in transfusion need to placebo. It is still desirable to have a randomized placebo controlled trial. However, until we have those data in hand, I agree with Iyer et al that “systemic bevacizumab should be considered as a first-line therapy for the treatment of refractory bleeding in patients with HHT.” At this point, the bulk of the literature suggests that the initial course of treatment should be 4 to 6 infusions of 5 mg/kg bevacizumab every 2 to 3 weeks. Some have reported success with doses as low as 0.125 mg/kg, but most of the literature and informal polling of North American HHT Center Directors (James R. Gossage, MD, oral communication, 2015-2017) favor a dose of 5 mg/kg for most patients. In terms of maintenance therapy, the literature is less clear. Some have advocated a routine infusion every 1 to 6 months, whereas others have based additional infusions on recurrence of symptoms. Finally, although this therapy seems to be well tolerated by patients with HHT, serious adverse effects have been reported in patients with HHT, and therefore careful patient selection along with close monitoring of blood pressure, blood chemistry, and urine protein is advised.

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