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Intravenous and topical intranasal bevacizumab (Avastin) in hereditary hemorrhagic telangiectasia☆,☆☆

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Abstract Current treatment of severe epistaxis in patients with hereditary hemorrhagic telangiectasia is not durable in reducing the frequency and severity of bleeds. Recent reports have demonstrated marked improvement of epistaxis with administration of either intravenous or topical bevacizumab. We present the long-term outcome of a patient who received repeated treatments of intravenous bevacizumab followed by maintenance intranasal bevacizumab. We demonstrate durable control of epistaxis with intranasal bevacizumab. This allows delivery of bevacizumab effectively, reduces cost, and obviates the risk of systemic adverse effects related to bevacizumab.

1. Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as *Osler-Weber-Rendu syndrome*, is an autosomal dominant inherited disease affecting approximately 1 in 5000. Spontaneous and recurrent epistaxis is the most common presenting symptom. Other manifestations include mucocutaneous telangiectases, visceral organ arteriovenous malformations, and affected first-degree relatives [1]. Recurrent epistaxis can result in severe anemia requiring intravenous (IV) iron and blood transfusions. Management of severe HHT can be invasive, and its effects are not durable in reducing the frequency and severity of bleeds.

Elevated plasma levels of vascular endothelial growth factor (VEGF) play a key pathogenic role in HHT [2]. Bevacizumab, an anti-VEGF monoclonal antibody, prevents the binding of VEGF to VEGF receptor on endothelial cells, thus blocking cellular proliferation and angiogenesis. As a result, bevacizumab has been used as a potential treatment of recurrent epistaxis [3,4]. Previous studies have demonstrated marked improvement of epistaxis with administration of bevacizumab. We recently reported the efficacy of IV bevacizumab for long-term treatment of anemia and epistaxis in a separate patient with severe HHT [5].

Intranasal treatment with bevacizumab, by either submucosal injection or topical nasal spray, has recently been reported to be a safe alternative to IV treatment [6]. We describe a patient initially treated with IV bevacizumab who subsequently demonstrated durable control of epistaxis with topical intranasal bevacizumab.

2. Case report

A 55-year-old woman with HHT, chronic epistaxis, and baseline hemoglobin level of 11 g/dL was treated for breast cancer with chemotherapy. In addition to chemotherapy-induced anemia, chemotherapy also resulted in increased epistaxis despite having a normal platelet count. She required multiple red blood cell transfusions during her chemotherapy course. Her epistaxis persisted after chemotherapy, causing her to be transfusion dependent.

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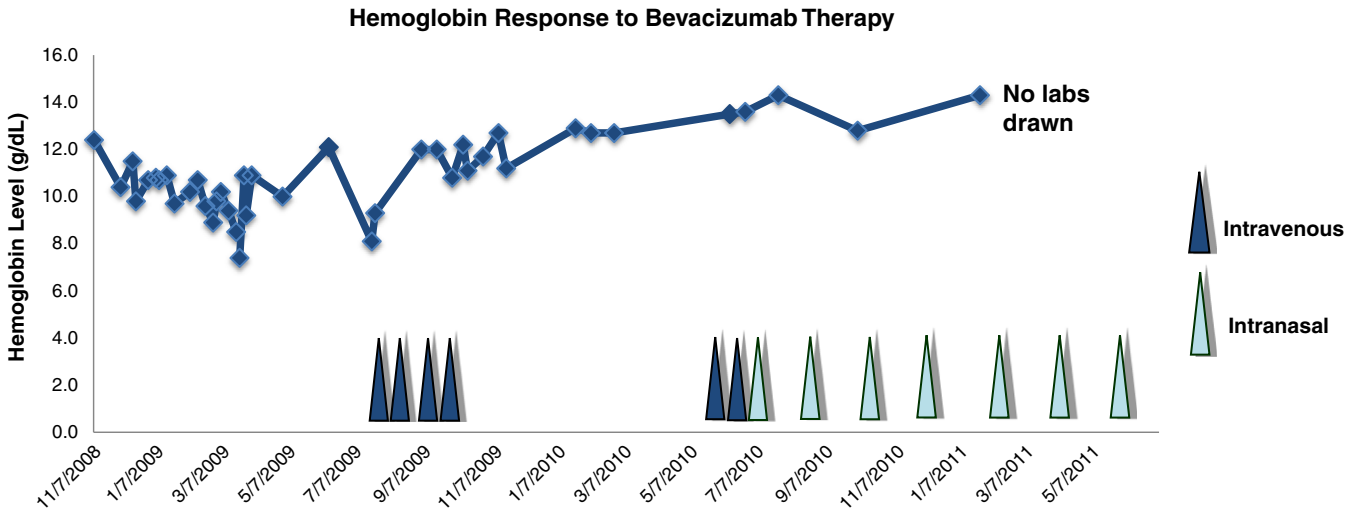

Fig. 1. Hemoglobin response to intravenous and intranasal bevacizumab treatments.

Prior treatments for her HHT-related epistaxis included 2 decades of cauterization, initially with silver nitrate, then neodymium:yttrium-aluminum-garnet laser treatments, followed by potassium-titanyl-phosphate laser treatments. These treatment modalities became less effective the longer she dealt with the disease. Because of chemotherapy-induced anemia and increased epistaxis, a new treatment option was sought.

She received 4 infusions of IV bevacizumab delivered every 2 weeks (10 mg/kg for dose 1 and 2 and 5 mg/kg for doses 3 and 4). Within 1 month, her epistaxis frequency decreased and ceased altogether. She received 2 infusions of IV bevacizumab over the next 9 months whenever her epistaxis recurred. Intravenous bevacizumab therapy resulted in a steady rise in her hemoglobin to 13.6 g/dL. At that point, she began receiving topical intranasal bevacizumab therapy as maintenance treatment of epistaxis. Topical treatment seemed to control her epistaxis for at least 8 weeks at a time. She received 100 mg of scheduled intranasal bevacizumab every 8 to 9 weeks with doses instilled topically in a 4-mL spray with an atomizer. She only had 2 minor episodes of epistaxis throughout her maintenance therapy, which were easily controlled in clinic. Her hemoglobin levels were maintained, and she continues to receive topical therapy to date (Fig. 1). She experienced no systemic adverse effects from intranasal bevacizumab.

3. Discussion

Recurrent epistaxis in patients with HHT causes significant morbidity. Vascular endothelial growth factor is a key pathogenic factor that acts to increase and maintain vascular density. The genetic basis for HHT includes multiple genetic mutations involved in the tumor necrosis factor–β pathway that result in higher levels of serum and tissue VEGF, leading to excessive angiogenesis [2]. Bevacizumab, an anti-VEGF monoclonal antibody, binds to circulating VEGF and thereby decreases the stimulation of VEGF receptor.

In 2006, Flieger et al [3] first reported the efficacy of IV bevacizumab in reducing epistaxis in a patient with HHT. This finding was replicated by Bose et al [4] with the acknowledgment that the results of the treatment were not permanent. Our group also reported the long-term efficacy of repeated dosing of IV bevacizumab. Although efficacy has been demonstrated with IV administration of bevacizumab in HHT patients, bevacizumab delivered intravenously is associated with a significant number of serious adverse effects including anaphylaxis, hypertension, pulmonary hemorrhage, and bowel perforation [7,8].

The efficacy of intranasal bevacizumab therapy has more recently been demonstrated in separate studies by Davidson et al [9] as well as Simonds et al [10]. Chen et al [6] also recently documented the safety of topical treatment for patients with HHT. We report the effective control of epistaxis and anemia with topical nasal spray bevacizumab treatment following IV treatment. This patient's case is unique in that her IV treatment was followed by successful topical treatment. It should be pointed out that our current case consists of a distinctly separate patient than the one previously reported who was also treated with long-term IV bevacizumab.

There are several advantages to using topical intranasal bevacizumab as compared with IV bevacizumab for the treatment of epistaxis in HHT. First, treatment is more local and focused, thereby reducing the potential systemic effects of IV bevacizumab. Local intranasal administration also reduces discomfort to the patient because IV access is not required. In addition, there exists a significant cost savings with topical intranasal application over IV bevacizumab. The price of the topical bevacizumab, at our institution, is approximately $650 compared with several thousand dollars per dose of IV bevacizumab.

Our case has several limitations, the most obvious of which is sample size. Further studies are needed to see if the results of this and previous studies are generalizable. Topical intranasal bevacizumab can also rapidly leak out of the nose especially when blood vessels are hemorrhaging. In contrast, IV bevacizumab allows improved drug delivery and retention. Finally, this patient was treated before the publication of the Epistaxis Severity Score [11]. Thus, we base our claim of improved epistaxis on the patient's report of decreased nasal bleeding.

4. Conclusion

Topical intranasal bevacizumab is a viable and cost-effective long-term maintenance therapy for chronic epistaxis in patients with HHT. The use of topical treatment appears to be both safe and effective and deserves further study.

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