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Case Report

Low-dose bevacizumab did not reduce epistaxis in patient with hereditary hemorrhagic telangiectasia：a case report

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Abstract

A 74-year-old man with refractory epistaxis and melena was diagnosed with hereditary hemorrhagic telangiectasia (HHT). Frequent epistaxis required gauze packing, electrocautery, and blood transfusion. Ileocecal resection did not reduce melena. To control both epistaxis and melena, off-label administration of bevacizumab was planned and approved by the ethical committee at Fukushima Medical University. However, after three courses of low-dose bevacizumab (2 mg/kg, every 3 weeks), the frequency of epistaxis and melena were not reduced. Thus, bevacizumab administration was discontinued.

(Key words：hereditary hemorrhagic telangiectasia, epistaxis, bevacizumab)

Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Rendu-Weber syndrome, is an autosomal dominant inherited disorder characterized by mucocutaneous telangiectasia and visceral arteriovenous malformation. Symptoms of HHT include epistaxis, gastrointestinal bleeding, dyspnea, and cyanosis.

The mechanism of mucocutaneous telangiectasia and arteriovenous malformation has been recently established. Serum concentrations of transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF) are significantly higher in patients with HHT compared to healthy controls (331 ± 335 pg/mL and 20 ± 30 pg/mL, respectively)[1]. Elevated serum levels of TGF-β stimulate the production of VEGF, which leads to abnormal angiogenesis.

Bevacizumab is a recombinant, humanized, monoclonal antibody that binds to and inhibits the biological activity of VEGF, which then prevents angiogenesis. In Japan, bevacizumab is approved for the treatment of colorectal cancer, lung cancer, ovarian cancer, cervical cancer, breast cancer, and glioblastoma.

Following the first report of treatment with bevacizumab (5 mg/kg, every 2 weeks) by Flieger and colleagues[2], there have been many articles describing the efficacy of bevacizumab (5–10 mg/kg, every 2 weeks) in treating patients with HHT[3-6]. However, the appropriate dosage of bevacizumab remains unclear, and a standard regimen has not been established. Although the effectiveness of low-dose (1–2 mg/kg, every 3 weeks) and very low-dose (0.125 mg/kg, every 4 weeks) bevacizumab has been reported in recent years[7-10], there are no case reports describing the treatment failure of low-dose or very low-dose bevacizumab. We herein report the first case of treatment failure with low-dose bevacizumab in a patient with HHT. The aim of this case report is to provide an alert that not every patient with HHT responds to low-dose or very low-dose bevacizumab.

Case report

A 74-year-old man presented with refractory epistaxis and melena. He had a family history of chronic epistaxis in his father. The patient had been treated for myelodysplastic syndrome for a year. He had experienced repeated episodes of epistaxis since he was 20 years old that had worsened for several months prior to presentation. Physical examination revealed multiple telangiectases in his nasal

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cavity (Fig. 1), in his mouth, and on his skin. Colonoscopy revealed multiple telangiectases and a hemorrhagic ulcer in the ileocecum. Laboratory findings showed no signs of coagulopathy (Table 1). Based on these findings, he met three of the four Curaçao criteria (recurrent spontaneous epistaxis, multiple typical mucocutaneous telangiectases in the nose, mouth, and skin, and vascular malformations in the colon)[11], and he was diagnosed with definite HHT. His epistaxis was treated with gauze packing, electrocautery, and blood transfusion. To control the melena, ileocecal resection was performed. Despite these treatments, the frequency of epistaxis and melena was not decreased, and he continued to be transfusion-dependent. Off-label administration of bevacizumab was considered, and approved by our institutional review board. The patient received three courses of intravenous bevacizumab (2 mg/kg, every 3 weeks). After the three courses of bevacizumab, the frequency of epistaxis and melena were not reduced. In addition, the amount of blood transfused was not reduced (Fig. 2). Administration of bevacizumab was discontinued.

Discussion

Bevacizumab is a recombinant human anti-VEGF monoclonal antibody. The first administration of bevacizumab to a patient with HHT was reported by Flieger and colleagues in 2006. In their case report, the patient was a 73-year-old man with HHT and mesothelioma. Due to the progression of mesothelioma, he received four courses of FOLFOX 4 (oxaliplatin, leucovorin, and fluorouracil) and ten courses of doxorubicin. Next, he was treated with pemetrexed (500 mg/m2, every 3 weeks) and bevacizumab (5 mg/kg, every 2 weeks). Immediately after treatment with bevacizumab, the frequency of blood transfusions was dramatically decreased, and his hemoglobin concentration was improved[2]. Following this case report, an oncological bevacizumab dose of 5–10 mg/kg was administered to treat patients with HHT[3-6].

In recent years, trials of low-dose and very low-dose bevacizumab have been reported[7-10]. Suppressa et al. proposed low-dose (1 mg/kg, every 3 weeks) bevacizumab as a safe and cost-effective treatment for HHT[7]. Lazaraki et al. reported successful treatment with bevacizumab using an initial dose of 5 mg/kg, every 2 weeks, followed by a maintenance dose of 1 mg/kg, every 3 weeks[8]. In their report, they mentioned that major problem associated with the cessation of bevacizumab is the relapse of bleeding. They also indicated that continuing the initial dose might cause drug toxicity (gastrointestinal perforation, hemorrhage, arterial thromboembolic events, and hypertensive crisis, etc.). Their regimen was based on the preclinical study by Gordon et al which predicted that a plasma concentration of 10–30 μg/ml bevacizumab would be necessary to achieve maximum tumor growth inhibition[11]. Gordon et al. showed that doses of ≧0.3 mg/kg completely suppressed serum VEGF and doses >1 mg/kg produced serum levels of bevacizumab in the target range of ≧10 μg/ml for at least 14 days[12]. In addition, Lazaraki et al speculated that low-dose bevacizumab (1 mg/kg, every 3 weeks) was adequate to achieve complete suppression of serum VEGF levels. Wee et al. described the efficacy of low-dose (2 mg/kg, every 3 weeks) bevacizumab[9]. They decided upon their protocol based on the patient's financial status. Thompson et al. reported that very low-dose (0.125 mg/kg, every 4 weeks) bevacizumab was effective[10]. They suggested that complete suppression of free serum VEGF is unnecessary in HHT patients because oncological cell kill is not a consideration. We selected the protocol used by Wee et al., as the cost of bevacizumab is very high (41,738 yen/100 mg) and we thought this low-dose regimen could minimize the money the patient would have to pay. Another reason for this low-dose protocol was to control both epistaxis and melena in this patient. Although topical administration (intranasal submucosal injection or topical spray) of bevacizumab was reported to be effective to control epistaxis[13,14], intranasal administration was not thought to be effective to decrease melena. Thus, we decided to administer bevacizumab systemically. Topical administration of bevacizumab can minimize the treatment cost because a lower dose is used (25-100 mg/body). In comparison, the systemic administration (1-10 mg/kg) has a higher treatment cost unless a very low-dose regimen (0.125 mg/kg) is selected. Additionally, topical administration can minimize the risks of systemic adverse effects including venous thrombosis, GI perforation, hypertension, headache, diarrhea, muscle pain and rash. Chen et al reported that of 58 patients treated with intranasal bevacizumab, only five patients had septal perforation as an adverse effect with no other systemic side effects[13].

Although a standard regimen has not been established, Azzoparidi and colleagues proposed a monthly systemic infusion of 5 mg/kg bevacizumab to sustain control of both high-output cardiac failure and epistaxis[15]. Their protocol was based on the simulation of serum bevacizumab concentrations. Kini et al. reviewed the contemporary literature and concluded that submucosal bevacizumab has been effective with a limited risk profile in a number of studies and should now be considered as a treatment option for refractory epistaxis[16]. Further studies are needed to establish a standard protocol.

One question we want to address is why our treatment with bevacizumab did not reduce epistaxis. Parambil et al. reported a 61-year-old-man with HHT and epistaxis was initially responsive to submucosal injection and nasal spray of bevacizumab, but was recalcitrant to six cycles of intravenous bevacizumab (5 mg/kg) administered several months after locally delivered bevacizumab. They

speculated that secondary loss of therapeutic response was likely related to either formation of neutralizing antibodies or due to local adaptive mechanisms[17]. In our case, there was no prior use of locally delivered bevacizumab. We speculated that low-dose bevacizumab (2 mg/kg, every 3 weeks) was not enough to suppress VEGF. We should have tried the oncological dosage (5 mg/kg, every 2 weeks) before we stopped treatment if the patient agreed to the increased cost. In such a case, we should have measured plasma concentration of VEGF and TGF-β before and after the administration of bevacizumab. Recent data from a retrospective evaluation of plasma concentration of VEGF-A predicted progression-free survival and/or overall survival benefit from bevacizumab in phase III clinical trials in breast cancer, pancreatic cancer, and gastric cancer[18]. However, a predictive biomarker (including VEGF and TGF-β) was not identified in HHT patients treated with bevacizumab. In the future, therefore, we should also seek to determine whether plasma concentration of VEGF or TGF-β could be a predictive biomarker in patients with HHT treated with bevacizumab.

Conclusion

We reported a treatment failure of low-dose bevacizumab in a patient with HHT. Not all patients with HHT respond to low-dose bevacizumab and clinicians should be cautious when determining the dosage of bevacizumab.

Conflict of interest

There were no conflicts of interest with regard to this work.

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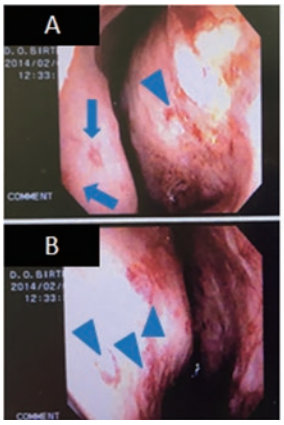

A (right nasal passage), B (left nasal passage): mucosal telangiectases were observed in inferior turbinate (arrows) and septum (arrow heads).

FIGURE 1 : Endoscopic findings of the nose before administration of bevacizumab

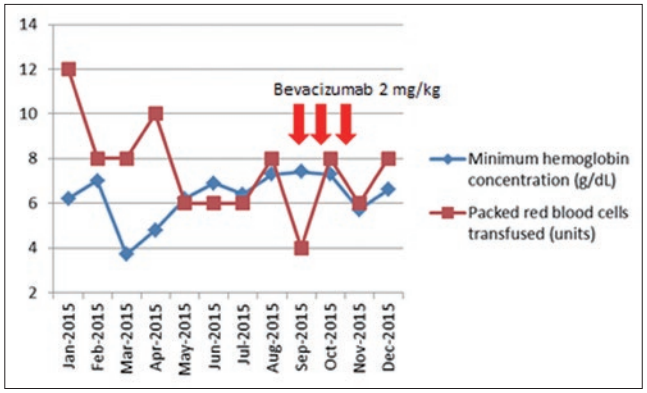

FIGURE 2 : Minimum hemoglobin concentration per month (g/dL) and packed red blood cells transfused per month (units)

TABLE 1 : Laboratory findings before administration of bevacizumab.

CBC	WBC ($/mm^3$)	Band (%)	Seg. (%)	My. (%)	Meta. (%)	Lym. (%)	Atyp. Lym. (%)	Mono. (%)	RBC ($/mm^3$)	Hb (g/dL)	Ht (%)	Plt.
	2,500	7	62	4	7	7	1	10	341×10^4	10.6	31.8	23.1×10^4
Blood Coagulation	PT (%)	APTT (sec)	Fib (mg/dL)	D dimer (μg/mL)		Coagulation Factor XII (%)			Platelet aggregation			
	73.0	28.6	577	1.8		76.0			Normal			
Bone Marrow Aspiration Slightly hypercellular bone marrow												

低用量ベバシズマブで鼻出血の改善が得られなかった遺伝性出血性末梢血管拡張症の一例

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要　　約

74歳男性が，反復する鼻出血と下血を主訴に受診し，遺伝性出血性末梢血管拡張症と診断した。頻回の鼻出血はガーゼパッキング，電気焼灼，輸血を必要とした。下血に対して回盲部切除を施行したが効果は得られなかった。鼻出血と下血の双方を改善させることを目的にベバシズマブを適応外使用する方針とし，福島県立医科大学の倫理員会で承認された。しかしながら，３コースの低用量でのベバシズマブ投与（２mg/kg，３週間毎）を行ったものの効果は認めず，ベバシズマブの投与を終了した。
（キーワード：遺伝性出血性末梢血管拡張症，鼻出血，ベバシズマブ）

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