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Bevacizumab: an option for refractory epistaxis in hereditary haemorrhagic telangiectasia

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Summary
Background Recurrent epistaxis in hereditary haemorrhagic telangiectasia (HHT) patients significantly decreases their quality of life. Treatment in therapy refractory patients is limited although various options have been tested so far.

Case report Herein, one patient is described that was treated for HHT for over 20 years with only intermediate benefits. As epistaxis duration and frequency increased continuously, bevacizumab 5 mg/kg was administered every 2 weeks. During the time of treatment (six doses) and up to 3 month afterwards clinical symptoms, blood pressure, cardiac output, pulmonary arterial hypertension (PAH), bleeding duration and frequency were assessed as criteria for treatment benefit.

Results Duration and frequency of epistaxis decreased immediately after the first application resulting in reduced need of blood transfusions. After completion of six cycles, a further decrease in frequency and duration of bleeding was noted. Cardiac output and PAH decreased or remained stable, respectively, during time and after treatment. No increase in blood pressure could be found but a significant increase in heart rate was experienced after completion of all six applications. Unfortunately, the patient died due to a cerebral abscess.

Conclusion Bevacizumab led to an improvement of HHT related epistaxis, refractory to other treatments.

Keaywords 3D cell culture · Tumour stroma · Microenvironment · Prediciting drug sensitivity · Personalized cancer therapy

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Background

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant hereditary vascular disorder that causes multiple clinical symptoms of different severity. Besides recurrent epistaxis, patients are affected by gastrointestinal telangiectasia, arteriovenous malformations (AVMs), predominantly of the lung and liver, and cerebral vascular malformations [1]. Since the first description of HHT, three genes (ENG, ACVRL1, MADH4) have been identified that are associated with this disease. Mutations in these genes lead to alteration in TGF-b signaling, either by affecting the TGF-b superfamily receptor (endoglin) or the intracellular signaling (Alk 1, smad4) [2]. Genomic mutations in these proteins lead to an impaired function of endothelial driven vascularisation and angiogenesis. Dysfunction leads to thin walled and dilated vessels and thereby to haemorrhage and fibrotic remodelling. So far treatment options are limited for patients suffering from HHT symptoms. Management differs, depending if symptoms are related to local AVMs (e.g. bleeding) or are systemic results thereof.

Besides embolization, treatment includes radiotherapy and the surgical resections of organs (e.g. liver) [3, 4]. In most cases, locally confined bleeding can also be treated by nonsystemic options including laser ablation, surgical resection and embolization [5–7].

The most recent advantages have been made in treating HHT symptoms by the application of drugs that have an effect on endothelial cells. Estrogens continuously administered systemically lead to a transformation from nasal epithelial to squamous epithelial cells resulting in a more robust nasal mucosa [8].

Estrogen receptor blockers inhibit the pulsatile triggered proliferation of endothelial cells and thereby can decrease AVMs [9]. Tranexamic acid decreases bleeding duration by inducing activation of plasminogen to plasmin [10].

Finally, the application of bevacizumab, an angiogenesis inhibitor first administered in age-related macular degeneration (AMD), was further extended from cancer therapy to HHT. This antibody decreases the formation of blood vessels by blocking the vascular endothelial growth factor A (VEGF-A). Treatment options with bevacizumab include, beside local injection and nasal sprays, also a systemic administration. Dupuis-Girod et al. [11] recently published data of 25 patients with HHT related severe liver involvement and a high cardiac index. In most patients a significant reduction of bleeding duration and reduction of mean cardiac index could be achieved after six infusion of bevacizumab. An effect of bevacizumab on bleeding duration was also described in several other case reports [1].

Case presentation

A 66-year-old female was treated over 20 years for HHT dependent symptoms. During this period, she has been in need of multiple therapeutic interventions. In 2001, she was affected by a subacute thrombosis of the mesenterial vein. Before, multiple intestinal AVMs had to be treated by endoscopic sclerotherapy. Surgical treatment included resection of parts of the small intestinal bowel after thrombosis of the mesenterial vein in 2005. Furthermore, multiple hepatic AVMs caused hepatic hypertension and hepatomegaly.

Pulmonary AVMs were treated by coiling in 2008. AVM dependent structural alteration led to pulmonary arterial hypertension (PAH).

However, refractory recurrent epistaxis represented the most affecting symptom concerning her quality of life.

Several therapeutic approaches had been applied to reduce the monthly bleeding duration without a lasting long term effect.

Initially, lenalidomide as a systemic angiogenic drug was given orally at a dose of 10 mg every 2 days in 2010, followed by an episode of bevacizumab application locally by a nasal spray in 2011.

Finally, the longest lasting effect could be achieved by administration of oral tamoxifen 20 mg daily and local nasal estriol crème.

In 2013, as measures started to fail again, the patient became more and more transfusion dependent, requiring 20 units of packed red blood cells in the first half of 2013.

At that time, the bleeding duration had increased up to 950 min per month. The number of heavy bleeding episodes (bleeding duration of up to 6 h) with a simultaneous hospitalization also increased to two episodes per month.

At this time, the patient agreed to the compassionate use of bevacizumab systemically according to the recently published case series of Dupuis Girod et al.

In short, the treatment strategy included the application of 5 mg/kg (250 mg absolute) bevacizumab for six

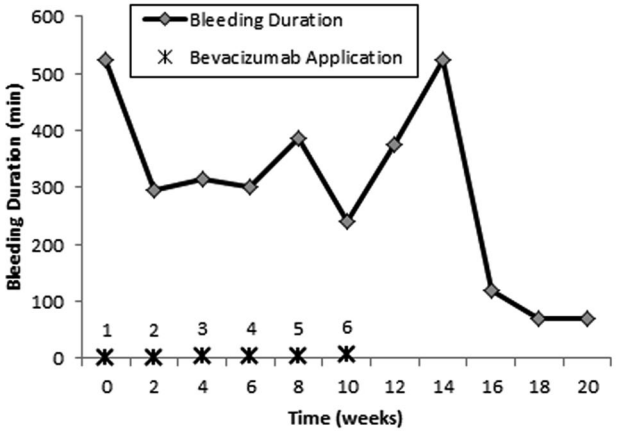

Fig. 1 Bleeding duration from the time before the first application of bevacizumab to the end of the follow-up. Data are shown in minutes/14 days

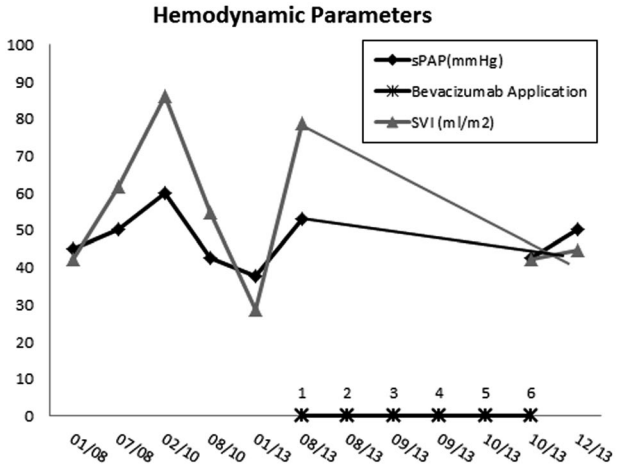

Fig. 2 Systolic pulmonary arterial pressure (*sPAP*) and stroke volume index (*SVI*) were monitored for the last 5 years of patient treatment by regular echocardiography. After six application of bevacizumab both values decreased, associated with an improvement of cardiac output

times every 2 weeks. During the time of treatment and the follow up of 3 months, blood pressure, bleeding duration and intensity were noted closely. Furthermore, the progression of pulmonary hypertension, stroke volume index (SVI), haemoglobin and the need of blood transfusions were monitored.

Duration of bleeding was summarized every 2 weeks according to the application cycle of bevacizumab (Fig. 1). A significant decrease in bleeding duration could be observed immediately after initiating the first application of bevacizumab. The 2 weeks before the first application the patient suffered from severe bleeding for 525 min.

Between the first and the second application, the bleeding duration decreased substantially to only 295 min. This effect could be monitored during all six applications. In the follow-up period, the patient was affected only once with an increased bleeding dura-

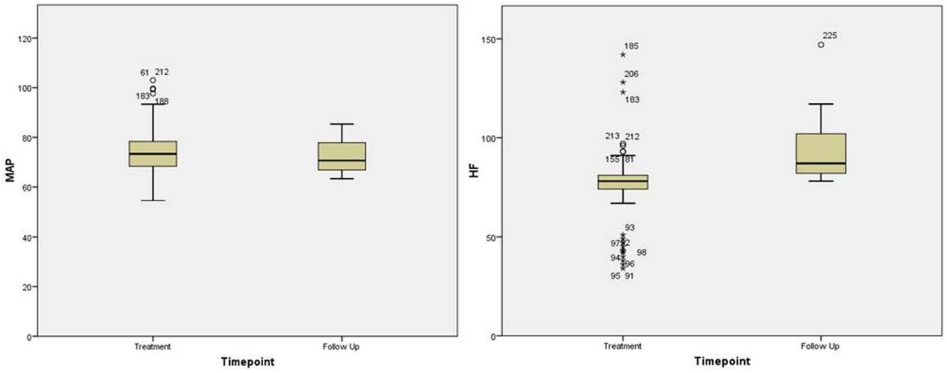

Fig. 3 Mean arterial pressure (*MAP*) and heart rate were closely monitored during phase of treatment and follow up to evaluate bevacizumab induced side effects. There was no increase in MAP and a significant increase in heart rate detected during monitoring

tion episode of up to 525 min simultaneously suffering from an acute infection of the upper respiratory system. Thereby, heavy coughing induced an increased incidence of epistaxis.

Due to AVMs in the lung the patient was monitored closely concerning heart function and pulmonary arterial pressure (sPAP). Because of pulmonary hypertension continuous antihypertensive treatment was needed, consisting of bosentan and spironolactone in combination with furosemide. Additionally, sPAP and the stroke volume index were continuously measured by echocardiography (Fig. 2).

The SVI of the patient varied during the last 5 years concomitant with the sPAP. Before the first application of bevacizumab, both values were increased again above the mean values of healthy controls (sPAP: 53 mmHg, SVI: 78.6 ml). After the sixth application, the sPAP decreased from 53 to 42.5 mmHg and the SVI dropped from 78.6 to 42.2 ml/m^2.

Furthermore, heart rate and blood pressure were monitored closely during all applications of bevacizumab to detect drug induced arterial hypertension as soon as possible (Fig. 3).

There was no increase in blood pressure observed neither during the treatment nor during the follow up period. In contrast, a significant upregulation of the heart rate from 77 in mean to 96 beats per minute was monitored.

Conclusion

Our patient was severely affected by HHT related symptoms, especially by therapy refractory epistaxis. No treatment that was tested during several years of continuous ward visits helped to relieve the patient from epistaxis in a long term setting.

Only after starting with intravenous application of bevacizumab, bleeding duration decreased significantly associated also with a decrease of ward visits.

Similar to the cases that were published by Dupuis-Girod et al. and Chavan et al., bleeding duration decreased approximately the same to only a fifth to sixth of length before treatment started [1, 11].

Cardiac index was also noted to be decreased and stabilized during and after treatment in comparison to the reported data [1].

Dupuis-Girod et al. recently published results where tranexamic acid was evaluated in a placebo-controlled double-blinded trial concerning its efficacy on reducing epistaxis duration and number of bleeding episodes. Herein, a 17.3 % reduction of bleeding duration could be achieved compared to the placebo arm. However, only a minor reduction in bleeding episodes from 23.3 in the placebo arm to 22.1 in the tranexamic acid arm was experienced. In contrast to the data from bevacizumab case series, the reduction in bleeding duration was not that significant [10, 11].

Bevacizumab induced hypertension occurs in 11 % of all patients receiving a dose of 5 mg/kg [1]. Nevertheless on our patient, we could not detect an increase in blood pressure during all time of surveillance.

After the follow up period, the patient was affected by a cerebral abscess (verified by a CT-scan and a cerebral MRI). *Staphylococcus hominis* was grown in blood cultures and antibiotic treatment with rifampicine, cefepime, metronidazole and linezolide was administered. The patient died after several weeks of antibiotic treatment. Although infections can occur during treatment with bevacizumab, no association of this treatment with brain abscesses has been published. However, brain abscesses are a well-known complication of patients with HHT and pulmonary arteriovenous malformations [12, 13].

So far multiple reports and case series display a benefit for systemic application of bevacizumab. Nevertheless, larger trials are needed to further assess the risk-benefit ratio.

Conflict of interest

The authors declare that there are no actual or potential conflicts of interest in relation to this article.

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