

Successful therapy with bevacizumab in a case of hereditary hemorrhagic telangiectasia

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Hereditary hemorrhagic telangiectasia (HHT), genetic disorder manifested by uncontrolled multisystem angiogenesis with epistaxis, gastrointestinal bleeding, iron-deficiency anaemia, and arteriovenous malformations (AVM) is often related with increased levels of vascular endothelial growth factor (VEGF). Bevacizumab, a VEGF inhibitor, reduces epistaxis, telangiectasias, and iron-deficiency anaemia. A case of a female patient with HHT and chronic gastrointestinal bleeding is presented. The patient required iron supplementation and multiple blood transfusions. Bevacizumab brought marked symptomatic improvement and allowed for transfusion-independence. It is intended to apply for approval of the indications for bevacizumab administration in HHT as the 'orphan drug'.

Introduction

A case of favorable therapeutic effect of bevacizumab administration is presented in clinically overt HHT, manifested by chronic nasal and gastric bleeding episodes, as well as by anaemia demanding frequent erythrocyte mass transfusions. Neither nasal nor gastric bleeding episodes explained the intensity of anaemia.

Case description

A 56-year old woman with definite HHT meeting all 4 Curaçao criteria,¹ with family history of HHT, documented in her mother and brother, as well in mother's brother and brother's 2 children, presented telangiectasias located in her nasal mucosa, conjunctiva, and gastrointestinal (GI) mucosa (stomach, duodenum, intestines). Imaging studies performed in the patient revealed no AVM either in brain, lung or liver, and the only AVM were identified in the GI tract and nasal mucosa. In the patient, as for now, no genetic testing has been done.

The patient manifested recurring spontaneous nasal and gastric bleeding episodes of various intensity for 15 years, started since her peri-menopausal period although anaemia had appeared in the younger life-time. Epistaxis was small and never required any surgical laryngological intervention, while the sporadic bleeding from the upper GI tract, originating from the AVM, was periodically of more intense character and required argon beam coagulation – such treatment was performed 4 times within the last 3 years.

Presenting iron deficiency and recurring deep anaemia, the patient has demanded complementary transfusions of packed leukoreduced red blood cells (LRBC). Neither orally nor intravenously iron treatment has brought any major effects. During the

years 2008–2013, she received totally 172 LRBC units (i.e., approximately 51.6 liters - all detailed clinical data such as dates of treatment, blood transfusions and hemoglobin levels are available in the Hospital). It brought about a development of post-transfusion complications, including autoimmune disorders – symptoms of rheumatoid arthritis, pancreas lesion (ultrasound and CT of the abdomen showed the characteristics of chronic pancreatitis), insulin-dependent diabetes mellitus (absence of effects after short-term administration of oral hypoglycaemic medications and a good result of relatively small doses of insulin speaks for T1D), chronic stomatitis. Since 2012, the patient has responded to subsequent transfusions with allergic symptoms, fever, articular and muscular pains and required a glucocorticosteroid cover during transfusion.

Undertaken attempts of hormonal therapy consisting of 1 mg of estradiolum (Estrofen) daily, taken orally, did not bring expected results (symptoms of the condition revealed in a clinically significant way during menopause). Also, endoscopic intervention aimed at elimination of angiomatous lesions in the upper section of the GI tract turned out to be ineffective for anaemia recurrence.

Taking into account some literature reports, describing positive effects of bevacizumab^{2–4} – following the patient's consent and having got a permission of the Bioethical Commission of the District Chamber of Physicians for the use of an "off-label" drug, totally 6 i.v. injections of 200 mg doses of bevacizumab were administered during the period from February to May 2014 in the 3-week intervals. With the patient's weight of 64 kg, it gave a dose of 3.1 mg/kg of body mass per every administration of the drug. Some increase in hemoglobin levels (11 g/dl vs. the baseline 8.6 g/dl) was observed immediately after the first

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administration of the drug. In general, hemoglobin levels were maintained at ≥ 10.6 g/dl during the entire period of the therapy and for one month after the last dose. The patient did not require any LRBC transfusion, while before bevacizumab administration, the frequency of LRBC administration was held at 2–3 units per 2–4 weeks.

–The following observations were made in the course of bevacizumab therapy:

–an increase of reticulocyte numbers as compared to their normal values and of Hb levels to > 11 g/dl levels;

–increased complement's component levels;

–increased numbers of platelets and higher fibrinogen concentrations as a result of VEGF action.

Thus both the expected and the desired clinical effects were achieved – during the last 6 months, the patient did not require any erythrocyte mass transfusion. In the light of the 8-month period of maintained improvement, following an administration of 4 analogous doses of the drug in 2-week intervals, the drug therapy was withdrawn after the 6th dose.

The patient is followed up by the Department of Internal Diseases at the Province Hospital in Opole. It has been agreed that in case of any future LRBC transfusion necessity, it will be followed by bevacizumab administration.

Discussion

HHT is a genetic disorder characterized by uncontrolled multisystem angiogenesis with epistaxis, gastrointestinal bleeding, iron-deficiency anaemia and AVM. HHT is often associated with increased levels of VEGF.^{5,6}

A case of a female patient with HHT and chronic GI bleeding is presented. The patient required iron supplementation and multiple blood transfusions. Because bevacizumab, a VEGF inhibitor, reduces epistaxis, telangiectasias, and iron-deficiency anaemia,^{3,4} we decided to introduce this medicine into the treatment.

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In the presented case, bevacizumab resulted in marked symptom improvement and transfusion-independence. The observed clinical improvement were probably not only caused by remission of nasal and gastric bleedings but also by increased erythropoiesis after bevacizumab administration. Assessing retrospectively, the intensity of bleeding did not explain intensification of anaemia. A significant increase in reticulocytosis after the first administration of the drug might indicate a considerable impact of erythropoiesis suppression in the pathogenesis of the anaemia. It has been demonstrated that VEGF inhibits a synthesis of erythropoietin,⁷ while VEGF suppression at molecule or receptor level increases erythropoietin production.^{8,9} This mechanism, observed in the described patient, may explain the higher reticulocytosis already after the first drug administration to be then maintained at normal level during the entire observation period.

We observed favorable effects of bevacizumab therapy on bleeding episodes and transfusion dependence, and herein we suggest the following possible mechanisms:

–regression of AVM (subjectively observed in our patient on the tongue);

–increased erythropoiesis (higher reticulocytosis and increased erythrocyte and Hb levels in our case);

–regression of coagulability disorders (the observed increased platelets number and higher fibrinogen concentrations – possibly as result of decreasing coagulation in AVM).

The observed increase in the complement's component levels may be associated with the decreased degree of chronic immunisation in the course of repeated LRBC transfusions. Bevacizumab is a well-known drug used for a long time in oncology. However, HHT is a rare disease, thus randomized clinical studies, as proposed by the other authors,^{3,4} may be rather difficult to be carried out. Nevertheless, taking into account the favorable effects of this drug in HHT and clear pathophysiological premises, we should aim at extending the range of indications for the drug, as well as apply for approval of bevacizumab as an 'orphan drug'.¹⁰

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.