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Original Research

Systemic bevacizumab for chronic bleeding and anemia in hereditary hemorrhagic telangiectasia: a retrospective cohort

Bevacizumab in hemorrhagic telangiectasia

Burcu Altındağ Avcı[1] Seval Akpınar[2] Burhan Turgut[2]

[1]1. Department of Hematology, Tekirdağ İsmail Fehmi Cumalıoğlu City Hospital, Tekirdağ, Türkiye.
[2]Department of Hematology, Faculty of Medicine, University of Tekirdağ Namık Kemal, Tekirdağ, Türkiye.

Abstract

Aim: Anti-angiogenic therapy with bevacizumab has shown promise in hereditary hemorrhagic telangiectasia (HHT), although evidence remains limited. This retrospective cohort study evaluated bleeding severity, transfusion and iron requirements, anemia, and quality of life in patients receiving intravenous bevacizumab.

Methods: Eight patients with HHT receiving intravenous bevacizumab were included. Disease severity and health-related quality of life were assessed using the Epistaxis Severity Score (ESS) and SF-36 questionnaire, respectively.

Results: Five patients were female, and three were male, with a median follow-up of 30 months. The mean age was 65 years (range: 44-70). The mean ESS decreased from 7.75 ± 2.7 to 1.4 ± 1.2 after treatment. The median transfusion requirement declined from 5 units before treatment to none during the first 2 years. Median hemoglobin increased from 9.5 g/dL at baseline to 13.1, 14.55, 12.95, and 12.5 g/dL at 3, 6, 12, and 24 months, respectively. Mild headache and increased systolic blood pressure occurred in two patients each. All SF-36 scores improved after treatment.

Conclusion: In this small retrospective cohort, intravenous bevacizumab was associated with improved bleeding control, anemia, and quality-of-life outcomes, with no serious toxicity observed during follow-up

Keywords

bevacizumab, hereditary hemorrhagic telangiectasia, prognosis, quality of life, long-term follow-up

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Corresponding Author: Burcu Altındağ Avcı, Department of Hematology, Tekirdağ İsmail Fehmi Cumalıoğlu City Hospital, Tekirdağ, Türkiye.
E-mail: dravciburcu@gmail.com **P.:** +90 530 207 30 00
Corresponding Author ORCID: https://orcid.org/0000-0002-5265-0940
Other Authors ORCID: Seval Akpınar, https://orcid.org/0000-0002-6961-8971 • Burhan Turgut, https://orcid.org/0000-0001-5729-0043

Introduction

Hereditary hemorrhagic telangiectasia (HHT; Osler-Weber- Rendu disease) is an autosomal dominant inherited genetic disorder characterized by dysregulated angiogenesis with an estimated prevalence of 1 in 5000.[1,2] HHT causes clinically significant malformations of the vasculature. Telangiectasias in the mucous membranes of the nose and gastrointestinal tract cause bleeding, as do arteriovenous malformations (AVMs) in the central nervous system, pulmonary, and hepatic systems. Telangiectasias of the nasal mucosa are present in >68% of HHT patients, and epistaxis is the most common symptom of the disease.[3] Frequent anemia due to repeated nasal or gastrointestinal bleeding is the most common complication and can sometimes be very severe.[4] It may require iron supplementation and sometimes erythrocyte suspension (RBC) transfusions. The impact on quality of life is significant. Sometimes fatal bleeding can develop.[5]

The diagnosis is based on the Curaçao criteria (recurrent epistaxis, telangiectasia, family history, and visceral lesions) and is considered definitive if at least three criteria are met.[6]

It is known that the disease is often caused by mutations in three genes: Endoglin (ENG), Activin A Receptor-Like Type 1 (ACVRL1), and SMAD family member 4 (SMAD4). In addition, rare families may have mutations in Growth Differentiation Factor 2 (GDF2) or RAS Protein Activator 1 (RASA1).[7] The presence of these mutations disrupts the angiogenic balance. Excessive angiogenic proliferation and/or impaired control of maturation are thought to lead to the formation of numerous problematic new vessels.[8]

Vascular endothelial growth factor (VEGF) is a key factor in the activation phase of angiogenesis. Thalidomide, lenalidomide, and pomalidomide, which exhibit immunomodulatory and antiangiogenic properties, have been evaluated in small studies involving HHT patients and shown to be effective.[9,10] Since 2010, bevacizumab, a humanized monoclonal antibody that selectively binds to human VEGF and neutralizes its biological activity, has been tested on HHT patients.[11] A case report, a study, and a case series have been published.[12,13]

In this retrospective cohort analysis, we aimed to evaluate bleeding frequency, severity, the need for blood transfusion, and iron replacement in patients with HHT receiving intravenous bevacizumab compared to the pretreatment period. We also examined the effect of intravenous bevacizumab use on quality of life in patients with severe disease symptoms.

Materials and Methods

The study included 8 patients who were started on bevacizumab for HHT, according to the Curaçao criteria, at Tekirdağ Namık Kemal University Hospital and Tekirdağ Fehmi Cumalioglu City Hospital. Patients resistant to conservative treatments with severe disease symptoms (history of recurrent and severe bleeding, frequent need for transfusions, and frequent visits to the emergency room) were included in the study. Thoracic CT, pulmonary CT angiography, esophagogastroduodenoscopy, colonoscopy, whole abdomen USG, and liver Doppler USG were routinely performed in all patients to detect visceral AVMs. Brain MRI was also performed for symptomatic patients. In addition, all patients were referred for cardiologic examination before treatment.

Patients who were started on bevacizumab continued treatment for at least 18 months from the start of treatment. According to the standard protocol, 5 mg/kg of bevacizumab was administered over 6 cycles at 14-day intervals, followed by 5 mg/kg every 2 months. After one year of treatment, one patient's epistaxis completely resolved, and the patient was continued on observation without maintenance treatment. The 5 patients who responded were switched to maintenance treatment at a dose of 5 mg/kg every 3 months. In 2 patients, the treatment interval was continued at 5 mg/kg every 4 months due to transportation difficulties. Patients were observed for efficacy and side effects. Hemogram, liver function tests, renal function tests, complete urinalysis, ECG, and blood pressure were measured at each visit. Hemogram values and the need for erythrocyte transfusion and iron replacement were recorded. Patients with nosebleeds were advised to use a nasal moisturizer morning and evening. The epistaxis severity score, which is routinely evaluated in HHT practice before treatment, was recalculated at the 3rd, 6th, 12th, and 18th months of bevacizumab treatment.

Epistaxis Severity Score

The Epistaxis Severity Score (ESS) is a standardized, reproducible, and validated patient-reported outcome measure of epistaxis control over the previous 3 months and has been used in many studies of HHT-related epistaxis. It is a weighted model comprising 6 factors, each scored from 0 to 10, that are independent predictors of epistaxis severity. In this study, we used an adapted version to specifically query symptom outcomes before treatment and at 3-month follow-up intervals after treatment. Scoring was done by the physician, who asked the patient questions using the online calculator at CureHHT. org. The minimum clinically important difference (MCID) of ESS was reported as 0.71.[14]

Since HHT severely affects the quality of life of patients with symptoms, SF-36 scales were administered to patients at regular intervals as part of routine practice in both clinics. SF-36 scales administered before treatment and at 6 months of treatment were included in the analysis to assess treatment response among patients receiving bevacizumab.

SF-36

The quality of life of the patients was assessed using the short form of the 36-item (SF-36) scale, one of the most commonly used surveys.[15] It consists of two main subdimensions: a physical component, including physical function, physical role, pain, and general health status, and a mental component, including social functioning, emotional role, and mental health. The scale is a self-assessment tool and is completed by the patient. The Turkish adaptation study of SF-36 was conducted by Koçyiğit et al.[16]

Ethical Approval

This study was approved by the Ethics Committee of Tekirdağ Namık Kemal University, Medical Faculty (Date: 24.09.2024, Decision No: 2024.258.09.08).

Statistical Analysis

Descriptive statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as median (range) or mean ± standard deviation, and categorical variables as number (percentage).

Reporting Guidelines

This study was reported in accordance with the STROBE guideline.

Results

Five patients were female, and three were male. Median follow-up time was 30 months. The mean age was 65 (range, 44-70). Characteristics of patients and response to bevacizumab treatment are given in Table 1.

The median ESS score before treatment was 7.75 ± 2.7 (range,

Table 1: Characteristics of Patients and Response to Bevacizumab

Name	P-1	P-2	P-3	P-4	P-5	P-6	P-7	P-8
Age, sex	69, F	52, F	70, F	65, F	66, M	44, F	65, M	44, M
Age at diagnoses	35	20	22	21	23	20	25	30
Disease involvement	Lung, Gis, Mucosa	Lung, Gis, Mucosa	Lung, Skin, Tongue	Lung, Gis, Mucosa	Bladder, Gis, Mucosa	Mucosa (Nose)	Mucosa (Nose)	Mucosa (Nose)
ESS bt	8	2	8	8	2	8	8	8
ESS at	3	1	1	1	1	1	1	5
Median hemoglobin level, g/dl, bt	7	5	11	10	9	11	10	6
Median hemoglobin level, g/dl, at	11	10.5	14	11.5	13	14	15	14
Transfusion of erythrocytes bt, mo	8	8	4	0	6	0	6	4
Transfusion of erythrocytes at , y	2	3	0	0	2	0	0	0
Treatment duration	28 months, ongoing	28 months, ongoing	31 months, ongoing	26 months, ongoing	30 months, ongoing	18 months	27 months, ongoing	20 months, ongoing

bt: Before treatment at: After treatment

2-8), and after treatment, it was 1.4 ± 1.2 (range, 1-5). The difference was statistically significant (P = .012).

The median transfusion requirement in the last 3 months before bevacizumab use was 5. After treatment, it was 0 in both the first and second 6-month periods. In the second year, the median was 0.

The median baseline hemoglobin value was 9.5 g/dL. The median values at 3, 6, 12, and 24 months after treatment were 13.1 g/dL, 14.55 g/dL, 12.95 g/dL, and 12.5 g/dL, respectively. The change in hemoglobin values in patients is given in Table 2. All SF-36 item scores were significantly increased after treatment, suggesting an improvement in quality of life with bevacizumab. Quality-of-life assessment scores before and after bevacizumab are presented in Table 3.

Two patients reported a headache, and two reported an increase in systolic blood pressure. Each patient tolerated the drug well.

Discussion

In our cohort study, we assessed the effectiveness and side effects of long-term systemic bevacizumab treatment in patients with HHT who experienced severe anemia and epistaxis. These patients frequently required hospitalizations for transfusions, and their work and social lives were significantly affected. Our findings revealed significant improvements in both bleeding and anemia among patients receiving bevacizumab. We found that patients' health-related quality of life also improved with bevacizumab treatment. No serious drug toxicity was observed despite long-term follow-up.

Table 2: Hemoglobin Level, g/dL During Bevacizumab Treatment

Name	Basal level	Months			
		3	6	12	24
P-1, g/dL	7	12	13	10	10
P-2, g/dL	5	9	11	11	10
P-3, g/dL	11	14	15	14	14
P-4, g/dL	10	12	13	11	10
P-5, g/dL	9	14	15	12	12
P-6, g/dL	11	14	15	14	14
P-7, g/dL	10	14	15	15	15
P-8, g/dL	6	13	16	14	14
Median hemoglobin, g/dL levels	9.5	13.1	14.5	12.9	12.5

Although numerous studies in the literature evaluate the efficacy and safety of bevacizumab in the treatment of HHT, data on efficacy and safety after more than 1 year of treatment are limited. Although Inhibit-Bleed is one of the largest clinical trials of HHT,[17] patients were followed for a median of 12 months (range 1-96 months). In our study, the median follow-up period was 30 months (range, 24-36 months), which, to our knowledge, represents a relatively long follow-up period compared with many previously published studies.

Most of our patients had an extensive disease burden, and they had first-degree relatives with bleeding-related deaths. Patients were treated with alternative local and systemic therapies (refractory epistaxis in five patients; hematuria, hematochezia, and bleeding from the tongue and fingertips in one patient each), but none of the methods achieved bleeding control. The longest follow-up with bevacizumab treatment in our study was 100 months, and the shortest was 18 months. Treatment was continued at individualized intervals and doses in all but one patient. The patient with intense nosebleeds, whose nosebleeds were under control as of the 3rd month of treatment and whose iron deficiency never developed during the treatment period, was discontinued at the 18th month, and the patient was followed up without treatment. After six months of treatment- free follow-up, the patient's bleeding did not recur, and the Hgb level remained stable. This suggests that treatment can be discontinued in patients with nasal mucosal bleeding who have a rapid and persistent response after bevacizumab. On the other hand, although good results with bevacizumab for gastrointestinal bleeding were reported in an expert opinion.[18] In which more than 100 patient experiences were presented, the lowest success in our study was observed among patients with gastrointestinal bleeding. We think that this difference may be related to the severity of

Table 3: Quality of Life Assessment Scores Before and After Bevacizumab

SF-36 items	SF-36 scores		P value
	Before treatment	After treatment	
General health	4.5 (0-15)	45 (33-45)	.042
Physical functioning	30 (5-65)	70 (45-85)	.048
Physical role	0 (0-0)	75 (25-100)	.024
Emotional role	0 (0-33.3)	49.9 (33.3-100)	.035
Social functioning	12.5 (0-50)	65 (10-80)	.045
Bodily pain	33.7 (10-67.5)	67.5 (57.5-77.5)	.041
Mental health	44 (20-64)	64 (28-80)	.049
Vitality	17.5 (0-45)	42.5 (20-60)	.037

gastrointestinal involvement. According to the literature, the most common side effects in patients receiving bevacizumab are hypertension (18%), fatigue (10%), proteinuria (9%), myalgia and/or arthralgia (6%), headache (4%), and venous thromboembolism (VTE, 2%).[17] Two of the patients we followed up with complained of headache, and no pathology was detected in neurologic evaluation in either patient. The headache was controlled with paracetamol. In patients with headache, individualized doses were continued at 4 mg/kg every 3 months. Reduced doses resulted in fewer headache complaints, while treatment efficacy was maintained. This may provide a rationale for planning prospective controlled studies to determine whether lower doses of bevacizumab would be effective in treating HHT. In both of the 2 patients with known hypertension, the increase in blood pressure was controlled with the addition of amlodipine 5 mg. On the other hand, in a retrospective study involving 14 centers and 46 patients, infection was reported as the most common side effect in treated patients (22% of patients), and 15 patients died during treatment.[19] In our patient follow-up, no infectious side effects were observed, and no patient died during treatment. The differences between the studies may be related to the patients' comorbidities.

The treatment interval was individualized based on social factors in patients with a good response and good drug tolerance at 1 year after treatment initiation. In six patients, the treatment interval was continued for 3 months. Two patients were able to come to the controls every 4 months because they lived in a rural area, and the treatment continued at 5 mg/kg every 4 months. The frequency and amount of bleeding increased with increasing treatment intervals. This was inconsistent with the data reported in a case report indicating that gastrointestinal bleeding was controlled even after discontinuation of treatment.[18] However, treatment success was regained when the treatment frequency was increased again. This suggests that efficacy may be restored when the treatment interval is prolonged for various reasons and the original dosing regimen is reinstated. In our experience, long-term follow-up with bevacizumab maintained an improvement in the hemogram. Patients did not develop intolerable side effects.

When the maintenance treatment dose was reduced to 3 mg/kg after one year, efficacy was maintained for both epistaxis and bleeding from other sites. In another study involving 6 patients, IV bevacizumab was administered at 0.125 mg/kg every 4 weeks, for a total of 6 treatment cycles. The severity and frequency of epistaxis decreased in all patients.[13] In our study, the lack of efficacy loss with dose reduction suggested that lower treatment doses may also be effective for symptom management in HHT patients.

Patients with long-standing bleeding from tongue and fingertip mucosal lesions, resistant to local and systemic treatments, showed a reduction in bleeding after bevacizumab treatment. In the 3rd month, bleeding from the tongue and fingertips was almost completely controlled. The patients did not require iron or blood transfusions during treatment. This suggests that bevacizumab may be more effective in cases of skin and oral mucosal involvement.

All antiangiogenic therapies carry a theoretical risk of thrombosis that should be discussed with patients during the process of obtaining approval for treatment. However, the published literature suggests that thromboembolic rates in HHT patients are significantly lower than in cancer patients, even among individuals treated with these agents for several years.[20] We did not observe any side effects of neuropathy or thrombosis in our patients treated with bevacizumab. This finding supports the routine and long-term use of bevacizumab in patients with HHT.

Limitations

The most important limitation of our study was the small number of patients, but each patient was followed closely and for a considerably longer period than in the literature, allowing important details to be observed. The lack of a control arm in the study was another limitation. Both limitations were due to the small number of HHT patients in daily practice. Another limitation of our study was that it was not prospective or randomized; however, it should be taken into account that in randomized clinical trials, even when data quality is at the highest level, patients who are not fit enough are excluded, and thus real-life is not adequately represented.

Conclusion

HHT is a little-recognized inherited bleeding disorder for which standard treatment approaches have not yet been developed. In this small retrospective cohort, bevacizumab treatment was associated with improved bleeding control, anemia parameters, and quality-of-life outcomes in patients with HHT. In our long-term follow-up, efficacy was sustained, and no additional toxicity was observed. Bevacizumab treatment positively affected patients' psychological and social lives. However, prospectively designed studies with a larger number of patients are needed to obtain more precise information.

Declarations

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards.

Informed Consent

Written informed consent was obtained from all patients.

Data Availability

The data supporting the findings of this study are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

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None.

Author Contributions (CRediT Taxonomy)

Conceptualization: B.A.A., B.T.
Methodology: B.A.A.
Investigation: B.A.A., S.A.
Data Curation: B.A.A., S.A.
Formal Analysis: B.A.A.
Writing – Original Draft: B.A.A.
Writing – Review & Editing: S.A., B.T.
Supervision: B.T.

AI Usage Disclosure

The authors declare that no AI-assisted technologies were used.

Abbreviations

ESS: Epistaxis severity score
HHT: Hereditary hemorrhagic telangiectasia
HRQOL: Health-related quality of life
MRI: Magnetic resonance imaging
RBC: Red blood cell
SF-36: 36-item short-form health survey
SPSS: Statistical package for the social sciences
USG: Ultrasonography
VEGF: Vascular endothelial growth factor

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