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Thalidomide for the Management of Bleeding Episodes in Patients with Hereditary Hemorrhagic Telangiectasia, Effects on Epistaxis Severity Score and Quality of Life

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Abstract

Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominantly inherited disorder characterized with bleeding episodes. These episodes tend to happen spontaneously and reduce the quality of life. Patients are often unresponsive to local measures. With the pathophysiological role of angiogenesis in HHT, antiangiogenic drugs including thalidomide were used to control bleeding episodes. In our study, we evaluated 6 patients with HHT, evaluated them with epistaxis severity score (ESS) and performed a quality of life assessment with 36 Item Short Form Questionnaire (SF-36) and the alterations of these evaluations with thalidomide treatment. Three patients were male and three were female. Mean age was 60.50 years. No side effects were observed during the treatment period. Improvements of certain SF-36 dimensions including physical functioning, physical component summary and mental component summary and ESS were observed after the treatment. Thalidomide may be effective to control the bleeding episodes and with a reasonable tolerance profile in patients with HHT.

Introduction

Hereditary hemorrhagic telangiectasia (HHT) is a rare, autosomal dominant disorder characterized by telangiectasia and arteriovenous malformations (AVM) of the skin, mucosal tissues and internal organs including gastrointestinal tract, liver and lungs. Its prevalence is estimated to be between 1/5000 and 1/10,000 worldwide. Recurrent epistaxis due to nasal telangiectasia is the most common finding (1-2). There are several mutations linked with the disease and the most frequent mutations are reported as ENG gene encoding endoglin and ACVRL1 gene encoding activin A receptor type II-like kinase 1. (3) . Anemia is a very common symptom in HHT patients, not only due to bleeding from telangiectases located in the nasal mucosa but also to telangiectases located in the gastrointestinal tract, especially active in older ages. Diagnostic criteria for HHT was defined in 2000 and updated in 2011 including epistaxis, telangiectases, vascular malformations and family history. Presence of 3 of these criteria is suggested to be sufficient for diagnosis (4). Since epistaxis is the most common manifestation, patients frequently are admitted and evaluated with ear nose and neck surgeons. Invasive measures and interventions including cauterisation is ineffective and the diagnosis of HHT which is quite rare, comes into consideration. Before the identification of pathogenetical mechanism of bleeding from telangiectases, local or systemically effective antifibrinolytics (tranexamic acid, epsilon aminaproic acid); estrogen or progesteron preparations such as ethinylestradiol, norethisterone, selective estrogen receptor modulators such as mestranol,

norethynodrel, tamoxifen, raloxifene have been used to control recurrent epistaxis and gastrointestinalbleeding episodes(5). Thalidomide was first designed as a sedative, then used for nausea in pregnant women and been responsible for about ten thousand infants born with phocomelia. This disastrous experience has led to further understanding of the mechanism of action of thalidomide. The effects of thalidomide on the innate and adaptive immune system as well as tumor development and angiogenesis have installed thalidomide as a model drug for the development of anti-cancer treatments. Besides the position of anti-angiogenic medications in tumor genesis and cancer treatment, thalidomide and other novel endothelial and vascular growth factor inhibitors including bevacizumab are suggested to be beneficial in patients with HHT since the major pathogenesis of HHT relies on excessive new vessel formation(6-13). This idea has been supported with limited evidence, due to the rare incidence of HHT itself. In our study, we aimed to evaluate our thalidomide experience grounding on a bleeding score developed with a multicenter study and a large cohort of HHT patients (14) as well as their improvement in quality of life assessed with a valid and internationally accepted scale, 36 item Short Form Health Survey Questionnaire (SF-36) (15) (Table 2).

Methods

Data of six patients diagnosed with HHT according to the Curaçao HHT diagnostic criteria were recorded from their files in a retrospective manner. All patients were admitted and treated by ear-nose and throat surgeons with simple epistaxis first, with cauterization and local measures like tampons and compression and as observed to be refractory to such interventions, referred to our department with a consideration of a possible HHT diagnosis. All patients were refractory to local cauterization and local or systemically effective antifibrinolytics. All patients were anemic due to chronic bleeding episodes. Heavy bleeding due to nasal telangiectases were assessed with ESS (14),

the requirement of transfusions based on 2016 American Association of Blood Bank (AABB) clinical guideline on red blood cell transfusion (16). Treatment of bleeding episodes with thalidomide was started as 50 mg daily and dose escalation to 100 mg/daily was scheduled individually according to response. Patients were evaluated every two months for response assessment. Therefore all patients started with 50 mg/daily Patient-1, Patient-2, Patient-3, and Patient-4 escalated to 100 mg/daily after two months. Patient-5 and Patient-6 did not need to escalate 100 mg and continued with 50 mg/daily. Treatment duration was based on controlling of epistaxis episodes, reducing ESS and improvement in anemia. Quality of life of the patients was assessed with Short form 36, the most commonly used survey which consists of two main dimensions as physical component summary including physical function, physical role, pain and general health status and mental component summary including social functioning, emotional role and mental health. The scale is a self-assessment scale and is filled in by the patient in a very short time (15). This study was approved by the Medical Faculty of Trakya University Ethics Committee of non-invasive clinical researches. (2017-334). Written informed consent was obtained from all patients. Statistical calculations were performed using the software program SPSS PC Ver.22 (IBM © SPSS Inc. USA). Wilcoxon signed ranks test was used non parametric data for two related samples.

Results

Three patients were male and three were female. Mean age was 60.50±10,07 years (44-74). The mean ESS score before treatment was 7,40±2,02 (4,31-9,66) and after treatment was 3,10±1,79 (0,92-4,94). This finding was statistically significant (p=0,028 <0,05).The change of hemoglobin level gr/dl was also statistically significant before and after the treatment (p=0,028) (Table 3). One patient reported grade one dizziness and one patient reported nausea which were resolved spontaneously without a need for drug withdrawal. Patients were frequently asked and searched for common side effects of thalidomide which wereneuropathy and constipation. No patient reported these side effects. Besides no patient had neutropenia or hematologic toxicity. Each patient well tolerated the drug. All SF-36 item scores were found to be increased after the treatment which may be regarded as improvement of quality of life with thalidomide treatment. Improvements of certain SF-36 dimensions including physical functioning, physical component summary and mental component summary were statistically significant (p values 0,042, 0,048 and 0,046 respectively). Detailed assessment of each patient was summarized in Table 1 and Table 2. The change in ESS before and end of the treatment demonstrated in Figure 1.

Discussion

As a rare disease, the prevalence of HHT is much higher than inherited bleeding disorders, hemophilia A and B with its autosomal dominant nature. Due to the most common symptoms being associated with bleeding, patients are frequently evaluated by emergency departments, surgical and general practice departments and are simply regarded as simple nose bleeds or gastrointestinal hemorrhage. Whereas, an autosomal dominantly inherited disorder is presented with a prominent family history which is ignored and unappreciated. The development of telangiectasia is related with aging and as the life expectancy is not effected and even reported to be increased in recent studies, the quality of life of these patients should be within the main goal of treatment (17-18). Besides the

irritative nature of mucosal bleeding, the consequence of these chronic bleeding episodes is iron defiency and iron deficiency anemia. Severe recurrent bleeding episodes may surpass a development of iron deficiency and lead to transfusion requirement. As the international guidelines support a restrictive transfusion approach, in our study as well as our daily practice, we followed this approach and limited our transfusion practice as transfusion not indicated until the hemoglobin level is 7-8 g/dL if the patient is hemodynamically stable and asymptomatic and supported the patients with iron supplements. In patients with recurrent severe bleeding episodes, parenteral agents such as iron carboxymaltose may be reasonable to also protect the gastrointestinal tract and irritation of oral iron as well as to limit transfusion. To control the bleeding episodes, once and for all, the pathogenesis of HHT has been researched. Excessive angiogenesis has been the underlying mechanism of telangiectases and vascular malformations and inhibition of angiogenesis was aimed. This idea of anti-angiogenesis has brought back one of the most unfortunate medical hazards in history; thalidomide for morning sickness in pregnancy, causing phocomelia and other malformations. Several case series and a phase two clinical trials with thalidomide reported long term improvements in epistaxis and also hematological parameters (6-10). In our study, though with a limited number of patients, we observed beneficiary effects of thalidomide to control the bleeding episodes, reduce the need to support the patients with transfusions and therefore, increase the life quality of our patients. In a recent study, a systematic analysis on 4 studies involving 43 patients with thalidomide reported beneficial effects of thalidomide to control bleeding episodes though with a comment on the lack of an optimal treatment modality in HHT (6). As an underappreciated inherited disease, HHT should be within the top differential diagnosis of patients with recurrent – refractory and debilitating mucosal bleeding. Family history should not be overlooked as is one solid item of the diagnostic criteria. Besides the short lived supportive measures, patients should be referred to experienced centers for therapeutical modalities.

Ethics: Trakya University Faculty of Medicine Ethical Committee 2017-334

Conflict of Interest: The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

References

1. Kroon S, Snijder RJ, Faughan ME, Mager HJ. Systematic screening in hereditary hemorrhagic telangiectasia: a review. Curr Opin Pulm Med 2018 May;24(3):260-268

2. Faughnan ME, Palda VA, Garcia-Tsao G, Geisthoff UW, McDonald J, Proctor DD, et al. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. Journal of Medical Genetics. 2011;48(2):73-87.

3. Sugden WW, Siekmann AF. Endothelial cell biology of Endoglin in hereditary hemorrhagic telangiectasia. Curr Opin Hematol. 2018 May;25(3):237-244

4. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJJ, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). American Journal of Medical Genetics. 2000;91(1):66-7.

5. Geisthoff UW, Nguyen HL, Roth A, Seyfert U. How to manage patients with hereditary haemorrhagic telangiectasia. Br J Haematol. 2015;171(4):443 PubMed -52.

6. Halderman AA, Ryan MW, Clark C, Sindwani R, Reh DD, Poetker DM, et al. Medical treatment

of epistaxis in hereditary hemorrhagic telangiectasia: an evidence-based review. Int Forum Allergy Rhinol. 2018.

7. Xu M, Hou Y, Sheng L, Peng J. Therapeutic effects of thalidomide in hematologic disorders: a review. Front Med. 2013;7(3):290 PubMed -300.

8. Fang J, Chen X, Zhu B, Ye H, Zhang W, Guan J, et al. Thalidomide for Epistaxis in Patients with Hereditary Hemorrhagic Telangiectasia: A Preliminary Study. Otolaryngol Head Neck Surg. 2017:194599817700573.

9. Hosman et al. Follow-up of Thalidomide treatment in patients with Hereditary Haemorrhagic Telangiectasia. Rhinology. 2015 Dec;53(4):340-4. doi: 10.4193/Rhin14.289.

10. Lebrin et al. Thalidomide stimulates vessel maturation and reduces epistaxis in individuals with hereditary hemorrhagic telangiectasia. Nat Med. 2010 Apr;16(4):420-8. doi: 10.1038/nm.21

11. Invernizzi R, Quaglia F, Klersy C, Pagella F, Ornati F, Chu F, Matti E,Spinozzi G, Plumitallo S, Grignani P, Olivieri C, Bastia R, Bellistri F, Danesino C, Benazzo M, Balduini CL. Efficacy and safety of thalidomide for the treatment of severe recurrent epistaxis in hereditary haemorrhagic telangiectasia: results of a non-randomised, single-centre, phase 2 study. Lancet Haematol. 2015 Nov;2(11):e465-73. doi: 10.1016/S2352-3026(15)00195-7.

12. Steineger J, Osnes T, Heimdal K, Dheyauldeen S. Long-term experience with intranasal bevacizumab therapy. Laryngoscope 2018 Feb 22.

13. Iyer VN, Apala DR, Pannu BS, Kotecha A, Brinjikji W, Leise MD, Kamath PS, Misra S, Begna KH, Cartin-Ceba R, DuBrock HM, Krowka MJ, O'Brien EK, Pruthi RK, Schroeder DR, Swanson KL. Intravenous Bevacizumab for Refractory Hereditary Hemorrhagic Telangiectasia-Related Epistaxis and Gastrointestinal Bleeding. Mayo Clin Proc. 2018 Feb;93(2):155-166

14. Hoag JB, Terry P, Mitchell S, Reh D, Merlo CA. An epistaxis severity score for hereditary hemorrhagic telangiectasia. Laryngoscope. 2010;120(4):838 PubMed -43.

15. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Conceptual framework and item selection. Med Care. 1992;30(6):473 PubMed -82.

16. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA. 2016;316(19):2025 PubMed -35.

17. de Gussem EM, Edwards CP, Hosman AE, Westermann CJ, Snijder RJ, Faughnan ME, et al. Life expectancy of parents with Hereditary Haemorrhagic Telangiectasia. Orphanet J Rare Dis. 2016;11:46.

18. Geerts L, Fantini-Hauwel C, Brugalle E, Boute O, Frenois F, Defrance L, et al. The Subjective Experience of Patients Diagnosed with Hereditary Hemorrhagic Telangiectasia: a Qualitative Study. J Genet Couns. 2017;26(3):612 PubMed -9

Table 1. Characteristics of Patients and Response to Thalidomide

Name		**Patient-1**	**Patient-2**	**Patient-3**	**Patient-4**	**Patient-5**	**Patient-6**
Age and Gender		64-F	44-M	74-F	62-F	56-M	61-M
Age at diagnosis		61	42	70	59	55	60
Heavy menstrual bleeding for female patients		Yes	N/A	Yes	Yes	N/A	N/A
Obstetric Problems		1 abortus	N/A	None	1 abortus	N/A	N/A
Diagnostic Criteria of Curaçao	**Epistaxis**	Yes	Yes	Yes	Yes	Yes	Yes
	Telangiectasia	Yes	Yes	Yes	Yes	Yes	Yes
	AV malformations	Hepatic	None	None	Hepatic	None	None
	Family history	Yes	Yes	None	None	Yes	Yes
ESS before treatment		9,07	9,66	7,31	8,22	4,31	5,86
Hgb Level Gr/dl before treatment		8,7 g/dl	9,2 g/dl	6,7 g/dl	5,9 g/dl	11,6 g/dl	10,8 g/dl
Transfusion of Erythrocytes before treatment		8/month	4/month	6/month	8/month	2/month	2/month
Dose		100 mg	100 mg	100 mg	100 mg	50 mg	50 mg
Treatment duration		1 year, ongoing	1 year, ongoing	1 year, ongoing	6 months, ongoing	3 months, ongoing	3 months, ongoing

ESS after treatment	3,69	3,06	4,94	4,94	0,92	1,05
Hgb Level Gr/dl After treatment	12,3 g/dl	11,8 g/dl	9,1 g/dl	8,8 g/dl	14,0 g/dl	13,1 g/dl
Mean Transfusion of Erythrocyte after treatment	2/month	none	none	3/month	none	none

Table 2. Quality of Life Assessment and Improvement After Thalidomide.

SF-36 Items	**SF-36 Scores before treatment**	**SF-36 scores after treatment**	**P value**
Physical Functioning	**55,83**	**60,00**	**0,042**
Physical Role	45,55	45,58	0,894
Bodily Pain	44,55	50,41	0,103
General Health	58,33	60,00	0,576
Vitality	45,00	55,00	0,272
Social Functioning	54,16	70,83	0,254
Emotional Role	33,33	38,85	0,363
Mental Health	52,66	66,33	0,158
Physical Component Summary	**50,74**	**54,47**	**0,048**
Mental Component Summary	**46,57**	**57,75**	**0,046**

Table 3. Improvement in ESS and Hemoglobin levels before and after treatment

	Before treatment	After treatment	P value
ESS	7,40	3,10	**0,028**
Hemoglobin level gr/dl	8,81	11,51	**0,027**