LetterTJH-2018-0074.R3

Submitted: 19 February 2018

Accepted: 18 June 2018

Successful Treatment of Recurrent Gastrointestinal Bleeding due to Small Intestine Angiodysplasia and Multiple Myeloma with Thalidomide – Two Birds with One Stone

Ida Hude MD[1], Josip Batinić MD, PhD[1,2], Sandra Bašić Kinda MD[1], Dražen Pulanić MD, PhD[1,2,3]

1 Department of Internal Medicine, Division of Hematology, University Hospital Center Zagreb, Zagreb, Croatia

2 University of Zagreb School of Medicine, Zagreb, Croatia

3 Faculty of Medicine Osijek, J. J. Strossmayer University of Osijek, Osijek, Croatia

Correspondence: Dražen Pulanić, MD, PhD, Department of Internal Medicine, Division of Hematology, UHC Zagreb and University of Zagreb School of Medicine, Kišpatićeva 12, 10 000 Zagreb, Croatia; Fax No: +385 1 2376 017; email: dpulanic@yahoo.com

Conflict of Interest Statement: all authors declare no conflict of interest.
Financial Disclosure: authors have nothing to disclose.
Contributor's Statement:
IH and DP contributed to conception and design of the work.
IH, JB, SBK and DP contributed to acquisition, interpretation and data analysis.
IH and DP drafted the manuscript.
All authors revised the work critically for important intellectual content and approved the final version of the manuscript.
This case report has previously been presented as a poster (in Croatian language) on the "7th Croatian Congress of Hematologists" in Šibenik, Croatia, in September 2017. The abstract consisting of <350 words is printed in accompanying congress Abstract book (in Croatian language).

Key words: thalidomide, angiodysplasia, recurrent bleeding, multiple myeloma, antiangiogenic

Running Head: Thalidomide for Angiodysplasia & Myeloma

Gastrointestinal angiodysplasia (GIA) are the most common digestive tract vascular malformations, often causing recurrent gastrointestinal bleeding. Despite association with certain hereditary diseases [1–3], most GIAs are acquired, associated with aortic stenosis, hemodialysis, malignancies, liver cirrhosis or idiopathic, and appear among the elderly (>60years) [4]. Advances in endoscopy brought to management improvements, but due to numerous lesions disseminated over the digestive tract, treatment of GIA remains a clinical challenge. Novel studies suggest that use of thalidomide might be beneficial to these patients due to antiangiogenic properties [5,6]. Nowadays, thalidomide and its modern analogues represent a backbone treatment of another disease: multiple myeloma (MM) [7]. Hereby, we would like to present a case of successful MM and GIA treatment with thalidomide.

Male patient born in 1947, who suffers from arterial hypertension, benign prostate hyperplasia and COPD, was diagnosed with symptomatic iron deficiency anemia in 2012. He underwent extensive gastroenterological workup which revealed multiple small intestine GIA causing recurrent bleeding. Several attempts of endoscopic argon-plasma coagulation during the following years had not been able to control the disease and the patient required regular blood transfusions (every 3-4 weeks) and parenteral iron supplementation. The patient was referred to a hematologist in 2016 for further assessment. Bleeding disorders were excluded (Table 1), but advanced IgG kappa MM was found (ISS 1, with 20-25% clonal plasma cells in bone marrow and multiple osteolytic lesions), with no signs of bone marrow or gastrointestinal amyloidosis. Treatment with cyclophosphamide (500mg/week), thalidomide (100mg/day) and dexamethasone (40mg/week) together with monthly zoledronate was initiated in 3/2016. Cyclophosphamide was discontinued after 3 applications due to development of paroxysmal atrial fibrillation, requiring thromboprophylaxis with enoxaparin. Six months after treatment initiation the patient achieved a very good partial remission (vgPR) of MM. Owing to age, comorbidities and patient's preferences, he has been further considered transplant ineligible so thalidomide (100 mg/day) and dexamethasone (20 mg/week) were continued. The patient has had no apparent bleeding since 3/2016, he is transfusion free since 10/2016, and received last parenteral iron supplementation in 10/2017, so GI endoscopy was not repeated. MM evaluations revealed continuous vgPR after 22 months of treatment, patient is asymptomatic, suffers no side-effects and continues with thalidomide maintenance (Table 1).

Efficacy of thalidomide as first line treatment (in combination regimens) and as maintenance therapy of MM is well established [8]. Despite the irrefutable success of some novel therapeutic agents, such as proteasome inhibitors and the next generations immunomodulatory drugs, thalidomide still presents a valid treatment choice especially in countries with limited health-care resources. Thalidomide has an emerging role in GIA treatment, with shown efficacy in a single, yet quite small, randomized trial [5] and multiple case reports (nicely reviewed in [6]). Certain patients, especially with several susceptible conditions as in case presented, seem to achieve utmost clinical benefit and quality of life improvement. The optimal dosage of thalidomide in GIA is currently not defined, and the side-effect profile might limit its long-term use for disease control. Nevertheless, its efficacy and side-effect manageability make further research worth-while.

References:

[1] M. Makris, A.B. Federici, P.M. Mannucci, P.H.B. Bolton-Maggs, T.T. Yee, T. Abshire, E. Berntorp, The natural history of occult or angiodysplastic gastrointestinal bleeding in von Willebrand disease, Haemophilia 2015;21,338– PubMed ;342. doi:10.1111/hae.12571.

[2] B.K.L. Duarte, S.M. de Souza, C. Costa-Lima, S.S. Medina, M.C. Ozelo, Thalidomide for the Treatment of Gastrointestinal Bleeding Due to Angiodysplasia in a Patient with Glanzmann's Thrombasthenia, Hematol Rep 2017;9,6961. PubMed doi:10.4081/hr.2017.6961.

[3] M.A. Alam, S. Sami, S. Babu, Successful treatment of bleeding gastro-intestinal angiodysplasia in hereditary haemorrhagic telangiectasia with thalidomide, Case Reports 2011;4585. doi:10.1136/bcr.08.2011.4585.

[4] A. Becq, G. Rahmi, G. Perrod, C. Cellier, Hemorrhagic angiodysplasia of the digestive tract: pathogenesis, diagnosis, and management., Gastrointest Endosc 2017;86,792– PubMed ;806. doi:10.1016/j.gie.2017.05.018.

[5] Z. Ge, H. Chen, Y. Gao, W. Liu, C. Xu, H. Tan, H. Chen, W. Wei, J. Fang, S. Xiao, Efficacy of Thalidomide for Refractory Gastrointestinal Bleeding From Vascular Malformation, Gastroenterology 2011;141;1629– PubMed ;1637.e4. doi:10.1053/j.gastro.2011.07.018.

[6] J. Bauditz, Effective treatment of gastrointestinal bleeding with thalidomide - Chances and limitations, World J Gastroenterol 2016;223,158. doi:10.3748/wjg.v22.i11.3158.

[7] S.K. Kumar, R. Vij, S.J. Noga, D. Berg, L. Brent, L. Dollar, A. Chari, Treating Multiple Myeloma Patients With Oral Therapies., Clin Lymphoma Myeloma Leuk 2017;17,243–251. doi:10.1016/j.clml.2017.02.024.

[8] P.M. Aguiar, T. de Mendonça Lima, G.W.B. Colleoni, S. Storpirtis, Efficacy and safety of bortezomib, thalidomide, and lenalidomide in multiple myeloma: An overview of systematic reviews with meta-analyses., Crit Rev Oncol Hematol 2017;113,195–212. doi:10.1016/j.critrevonc.2017.03.014.

Table 1: Relevant laboratory findings at baseline and during thalidomide treatment

Key Laboratory Findings	***Baseline (2/2016)***	***8/2016***	***2/2017***	***11/2017***
Hemoglobin (g/L)	77	95	117	127
MCV (fL)	71	84.1	85.7	90.9
Fe (umol/L)	2	5	5	19
Ferritin (ug/L)	<5	25.1	23.8	184.8
PT	1.13	NA	NA	NA
aPTT (s)	22.7	NA	NA	NA
Fibrinogen (g/L)	4.0	NA	NA	NA
VWF (%)	154	NA	NA	NA
FVIII (kIU/L)	2.80	NA	NA	NA
FXIII (kIU/L)	0.85	NA	NA	NA
Total serum protein (g/L)	72	66	67	68
Total serum IgG (g/L)	18.93 (high)	11.8 (normal)	13.09 (normal)	14.37 (normal)
M potein by immunofixation – serum IgG kappa	present	present	present	present
Serum free light chains (mg/L) kappa	26.3	13.2	19.6	20.5
lambda	21.0	10.2	14.6	17.7
Kappa/lambda ratio serum	1.25 (normal)	1.29 (normal)	1.34 (normal)	1.16 (normal)
M protein - urine	NA	NA	Negative	Negative
Bone marrow plasma cells count (%)	20-25	<5	NA	NA