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Letters to the Editor

Thalidomide Treatment for Thrombocytopenia Secondary to Hypersplenism in Children with Transfusion-Dependent β-Thalassemia: A Case Series

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To the editor.

β-Thalassemia is a genetic hemolytic disorder caused by mutations or deletions in the β-globin gene, leading to abnormal erythropoiesis and varying degrees of anemia.[1] The disease spectrum varies, with clinical manifestations ranging from no symptoms in individuals with the β-thalassemia trait to lifelong transfusion dependence in those with the most severe forms. The severe phenotypes of thalassemia can present with splenomegaly, hypersplenism, and thrombocytopenia.[2] Thrombocytopenia is a common complication of hypersplenism, and treatment options for this condition are currently limited. Conservative management or splenectomy is commonly recommended for hypersplenism, but splenectomy can result in complications and may not be appropriate for all patients. Therefore, alternative treatment strategies are necessary to manage thrombocytopenia caused by hypersplenism in thalassemia.

Thalidomide is an antiangiogenic, anti-inflammatory, and immunomodulatory drug that has shown promise in increasing fetal hemoglobin levels and reducing transfusion requirements in patients with β-thalassemia.[3] Furthermore, thalidomide has been shown to significantly reduce spleen length and increase platelet levels, indicating its potential utility in managing thrombocytopenia in β-thalassemia patients with hypersplenism.[4] However, there are no reported studies on the role of thalidomide in managing thrombocytopenia secondary to hypersplenism in children with β-thalassemia. Herein, we report three cases of transfusion-dependent β-thalassemia (TDT) patients with thrombocytopenia secondary to hypersplenism who experienced a reduction in spleen length and an increase in platelet levels after treatment with thalidomide.

The clinical characteristics of the three patients with TDT are outlined in **Table 1**. Thalidomide was administered daily at an initial dose of 100 mg/day. Patient 1 showed a significant increase in hemoglobin concentration after one month of treatment and was gradually weaned off transfusions. By three months, hemoglobin increased from 8.9 g/dL to 12.5 g/dL. Spleen length was reduced from 7.8 cm to 4.5 cm, and platelet count normalized, rising from 71×10^9/L to 131×10^9/L. The thalidomide dose was then reduced from 100 mg/day to 50 mg/day, and treatment was continued. Beyond hematologic improvements, liver function also showed positive changes. After 12 months, serum ferritin levels declined from 8280.7 ng/mL to 4510.02 ng/mL, indicating reduced iron overload and potential long-term benefits of treatment.

Similarly, patients 2 and 3 experienced significant increases in hemoglobin levels and were weaned off blood transfusions after two months of treatment. At three months, patient 2's hemoglobin increased from 8.6 g/dL to 9.8 g/dL, while patient 3's hemoglobin rose from 8.7 g/dL to 10.5 g/dL. Spleen length in patient 2 decreased from 5.6 cm to 3.1 cm, and platelet count increased from 62×10^9/L to 112×10^9/L. In patient 3, spleen length shrank from 11.5 cm to 8.6 cm, and platelet count increased from 36×10^9/L to 76×10^9/L. Following these improvements, the thalidomide doses for patients 2 and 3 were reduced to 75 mg/day and 50 mg/day, respectively, for maintenance therapy. Both patients also showed low levels of hemolysis markers, including bilirubin and lactate dehydrogenase, alongside significant reductions in iron overload. By 12 months, all three patients exhibited sustained improvements in hemoglobin levels, platelet counts, and spleen size compared to baseline (**Figure 1**).

Massive blood transfusions, along with iron chelation therapy, remain the primary treatment for thalassemia. While early and standardized blood transfusion therapy may help prevent splenomegaly in some patients, hypersplenism can still progress. Hypersplenism due to thalassemia is not uncommon, and in these cases, splenectomy may improve the

Table 1. Clinical characteristics of the three patients with transfusion-dependent β-thalassemia.

Characteristic	Patient 1	Patient 2	Patient 3
Gender	female	female	male
Age (years)	17	14	15
β-Genotype	$\beta^{CD41-42}/\beta^{CD41-42}$	$\beta^{CD17}/\beta^{IVS-II-654}$	$\beta^{CD17}/\beta^{CD17}$
α-Genotype	αα/αα	αα/αα	αα/αα
Age of diagnosis (months)	12	7	6
Age of transfusion (months)	12	7	6
Transfusion interval (weeks)	4	3	4
Alanine aminotransferase (U/L)			
Baseline	61	9	8
3 months	59	13	15
12 months	50	7	13
Aspartate aminotransferase (U/L)			
Baseline	67	14	17
3 months	54	19	16
12 months	31	16	25
Total bilirubin (μmol/L)			
Baseline	38.7	31.4	53.5
3 months	37.7	23.9	45.9
12 months	25.8	20.8	37.6
Indirect bilirubin (μmol/L)			
Baseline	32.4	23.7	46.8
3 months	27.2	14.3	39.3
12 months	14.1	10.8	28.9
Lactate dehydrogenase (U/L)			
Baseline	210	158	290
3 months	187	145	257
12 months	160	171	212
Serum ferritin (ng/ml)			
Baseline	8280.7	2019.54	2010.15
3 months	7985.95	1380.02	508.12
12 months	4510.02	1109.21	390.56
Spleen length (cm below costal margin)			
Baseline	7.8	5.6	11.5
3 months	4.5	3.1	8.6
12 months	4.6	3.5	7.2
Hemoglobin level (g/dL)			
Baseline	8.9	8.6	8.7
3 months	12.5	9.8	10.5
12 months	11.2	9.6	10.9
Platelet count ($\times 10^9$/L)			
Baseline	71	62	36
3 months	131	112	76
12 months	119	132	91

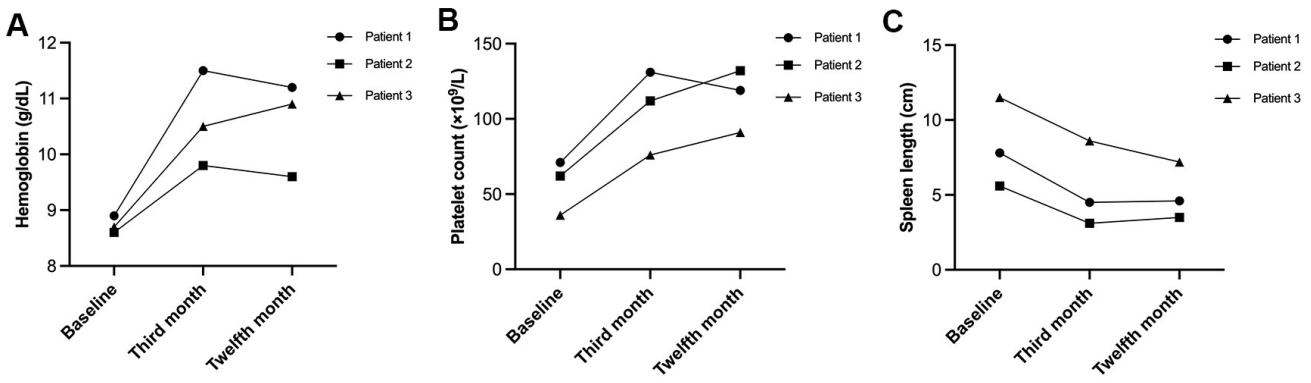

Figure 1. Hemoglobin levels, platelet counts, and spleen size compared to baseline.

pancytopenia associated with splenic enlargement. However, the potential side effects of splenectomy, including thromboembolism and postoperative infections, should not be overlooked. The patients in this study experienced a significant reduction in spleen length and a marked increase in platelet count following thalidomide treatment for thrombocytopenia secondary to hypersplenism. No serious adverse events were observed during the study, and thalidomide was well tolerated. Based on these findings, we suggest that thalidomide may have potential as a new therapeutic option for treating thrombocytopenia associated with hypersplenism in patients with β-thalassemia.

The results of our study indicate that thalidomide improved platelet counts in patients with secondary hypersplenism, which was accompanied by a progressive decrease in spleen length throughout the treatment. We propose that this platelet improvement resulted from a reduction in hypersplenism, leading to less platelet sequestration in the spleen. The spleen typically stores around 30% of the body's platelets, and increased sequestration due to splenomegaly is well-recognized as a cause of thrombocytopenia.[5] In patients with β-thalassemia, extramedullary hematopoiesis increases to compensate for anemia, leading to greater production and clearance of abnormal red blood cells (RBCs), contributing to hypersplenism and spleen enlargement.[6] Thalidomide has been shown to increase RBC production and maturation in patients with TDT, while simultaneously reducing erythropoietin levels and reticulocytes.[7] This improved erythropoiesis likely results in more effective RBC production. Beyond its effects on erythropoiesis, thalidomide may also help manage iron overload, improving organ function in these patients, which may indirectly support platelet production.[7-9] Furthermore, thalidomide has been shown to significantly inhibit the secretion of IFN-γ and IL-17 in immune thrombocytopenia while also preventing antiplatelet antibody-mediated platelet destruction by reducing macrophages, which are central to platelet phagocytosis.[10] In our previous studies, we observed a significant reduction in endothelial activation and stress index in patients with TDT following thalidomide treatment.[8] Thus, thalidomide's effects on hypersplenism and thrombocytopenia in patients with β-thalassemia may also be attributed to its anti-inflammatory, immunomodulatory, and antiangiogenic properties.

In conclusion, thalidomide represents a promising therapeutic option for patients with thrombocytopenia secondary to hypersplenism in β-thalassemia. Our case series indicates that thalidomide effectively improves both splenomegaly and thrombocytopenia associated with hypersplenism in children with TDT. However, further studies are needed to confirm these findings and establish optimal treatment regimens and long-term safety.

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Ethics Statement. The study protocol was approved by the Medical Ethics Committee of the First People's Hospital of Zigong. The participating families provided written informed consent.

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References:

1. Kattamis A, Kwiatkowski JL, Aydinok Y. Thalassaemia. Lancet. 2022;399:2310-24. https://doi.org/10.1016/S0140-6736(22)00536-0 PMid:35691301
2. Pines M, Sheth S. Clinical Classification, Screening, and Diagnosis in Beta-Thalassemia and Hemoglobin E/Beta-Thalassemia. Hematol Oncol Clin North Am. 2023;37:313-25. https://doi.org/10.1016/j.hoc.2022.12.003 PMid:36907605
3. Chen JM, Zhu WJ, Liu J, Wang GZ, Chen XQ, Tan Y, Xu WW, Qu LW, Li JY, Yang HJ, Huang L, Cai N, Wang WD, Huang K, Xu JQ, Li GH, He S, Luo TY, Huang Y, Liu SH, Wu WQ, Lu QY, Zhou MG, Chen SY, Li RL, Hu ML, Huang Y, Wei JH, Li JM, Chen SJ, Zhou GB. Safety and efficacy of thalidomide in patients with transfusion-dependent beta-thalassemia: a randomized clinical trial. Signal Transduct Target Ther. 2021;6:405. https://doi.org/10.1038/s41392-021-00811-0 PMid:34795208 PMCid:PMC8602273
4. Chen Y, Cai N, Lai Y, Xu W, Li J, Huang L, Huang Y, Hu M, Yang H, Chen J. Thalidomide for the Treatment of Thrombocytopenia and Hypersplenism in Patients With Cirrhosis or Thalassemia. Front Pharmacol. 2020;11:1137. https://doi.org/10.3389/fphar.2020.01137 PMid:32792958 PMCid:PMC7394185
5. Smock KJ, Perkins SL. Thrombocytopenia: an update. Int J Lab Hematol. 2014;36:269-78. https://doi.org/10.1111/ijlh.12214 PMid:24750673
6. Kolnagou A, Michaelides Y, Kontoghiorghe CN, Kontoghiorghes GJ. The importance of spleen, spleen iron, and splenectomy for determining total body iron load, ferrikinetics, and iron toxicity in thalassemia major patients. Toxicol Mech Methods. 2013;23:34-41. https://doi.org/10.3109/15376516.2012.735278 PMid:23039902
7. Yang K, Liu X, Peng W, Hua F, Li L, Chen K, Zhang J, Luo S, Li W, Ding Y, Chen J, Xiao J. Effects of Thalidomide on Erythropoiesis and Iron Homeostasis in Transfusion-Dependent beta-Thalassemia. Mediterr J Hematol Infect Dis. 2024;16:e2024001. https://doi.org/10.4084/MJHID.2024.001 PMid:38223482 PMCid:PMC10786143
8. Chen J, Kong W, Xiao J, Liu X, Yang K. Effects of Thalidomide on Endothelial Activation and Stress Index in Children with beta-Thalassemia Major. Mediterr J Hematol Infect Dis. 2024;16:e2024076. https://doi.org/10.4084/MJHID.2024.076 PMid:39534709 PMCid:PMC11556424
9. Chen J, Luo T, Huang L, Lu Q, Yan D, Meng Y, Xie J, Chen W, Chen J, Long L. Magnetic Resonance Imaging Quantification of the Liver Iron Burden and Volume Changes Following Treatment With Thalidomide in Patients With Transfusion-Dependent ss-Thalassemia. Front Pharmacol. 2022;13:810668. https://doi.org/10.3389/fphar.2022.810668 PMid:35250561 PMCid:PMC8894715
10. Xu M, Wang X, Xu X, Wei G, Lu W, Luo Q, Li X, Liu Y, Ju W, Li Z, Xu K, Zeng L, Qiao J. Thalidomide prevents antibody-mediated immune thrombocytopenia in mice. Thromb Res. 2019;183:69-75. https://doi.org/10.1016/j.thromres.2019.09.035 PMid:31670229