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Letter to the Editor

Effects of Thalidomide on Endothelial Activation and Stress Index in Children with β-Thalassemia Major

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To the editor.

β-thalassemia major (TM) is a congenital hemolytic disease characterized by reduced or absent β-globin production, hemolysis from resulting unstable β-globin tetramers, ineffective erythropoiesis, and severe anemia that is fatal in the absence of life-long red cell transfusions.[1] Hematopoietic stem cell transplantation (HSCT) remains the only curative option, achieving thalassemia-free survival rates as high as 97%.[2] However, HSCT presents various risks, particularly in older children and those without a fully matched donor, limiting its widespread use. The Endothelial Activation and Stress Index (EASIX) is a biomarker calculated using lactate dehydrogenase (LDH), creatinine, and platelet counts and is significantly associated with complications and mortality after transplantation.[3-6] Thalidomide, known for inducing fetal hemoglobin production, can effectively increase hemoglobin levels in TM patients, often serving as a bridging treatment. However, the impact of pre-transplant thalidomide treatment on transplant outcomes remains uncertain. This study evaluates the changes in EASIX following thalidomide treatment in children with TM.

We retrospectively assessed children with TM who received thalidomide for more than three months between May 2021 and June 2024. The study included 25 patients (15 males and 10 females) aged 14-18 years. The EASIX score was calculated using LDH (U/L) × creatinine (mg/dL) / platelet count ($\times 10^9$/L) from laboratory data recorded after approximately three months of thalidomide treatment. A significant reduction in EASIX was observed in TM patients post-treatment (p=0.002) (**Figure 1**). We investigated the correlations between EASIX and baseline indicators. In addition to platelets (r=-0.601, p=0.001), LDH (r=0.536, p=0.006), and creatinine (r=0.595, p=0.002), EASIX was inversely correlated with white blood cell count (r=-0.450, p=0.024) and positively correlated with total bilirubin (r=0.615, p=0.001) and indirect bilirubin (r=0.561, p=0.004). No other significant correlations were found between EASIX and other parameters.

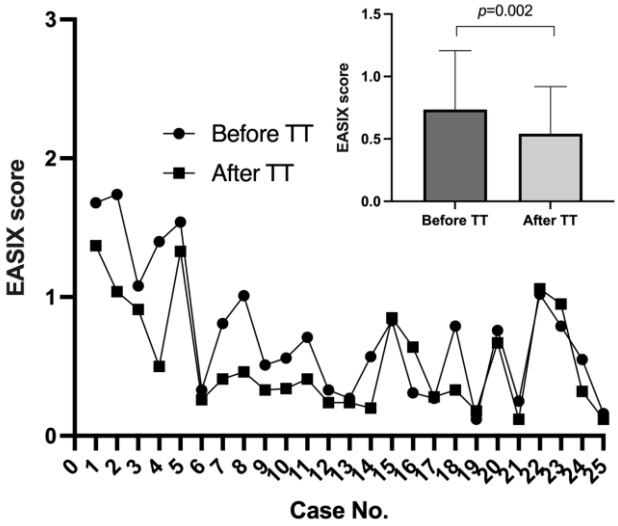

Figure 1. 25 children with β-thalassemia major were detected Endothelial Activation and Stress Index (EASIX) before and after thalidomide treatment (TT).

Patients with thalassemia undergoing transplantation suffer a unique spectrum of complications, particularly those related to vascular endothelial injury, such as hepatic venular occlusive disease/sinusoidal obstruction syndrome (VOD/SOS), transplant-associated thrombotic microangiopathy, and graft-versus-host disease.[7] VOD/SOS incidence in thalassemia transplants can reach 10.4%.[8] Increased markers of endothelial cell damage in thalassemia patients are closely linked to post-transplantation thrombotic microangiopathy.[9,10] Therefore, understanding and addressing endothelial injury in these patients is crucial for improving transplant outcomes.

Although endothelial dysfunction is associated with various transplant complications, clear biomarkers are limited. EASIX, first reported in 2017 by Luft et al.,[3] is strongly correlated with transplant outcomes. In patients with SOS/VOD, EASIX was significantly higher on the day of transplantation than in those without SOS/VOD.[4] Elevated EASIX at different time points during

transplantation is associated with higher mortality and poorer overall survival.[5] In TM patients, median EASIX is significantly higher in those with day +100 transplant-related mortality.[6] Consequently, EASIX can serve as a valuable indicator of vascular endothelial injury during transplantation, guiding early interventions to reduce complications and improve prognosis.

Thalidomide has emerged as a treatment option for β-thalassemia, with demonstrated benefits in reactivating fetal hemoglobin production and reducing transfusion needs.[11] Additionally, it has been shown to ameliorate erythropoiesis and iron homeostasis, reduce spleen size, and treat thrombocytopenia in hypersplenism.[12,13] In this study, we evaluated the effects of thalidomide on EASIX and analyzed the correlations between baseline indicators and EASIX to explore the support of the effectiveness of this drug. After thalidomide treatment, a significant reduction in EASIX was found in patients with TM, which may affect transplant outcomes and provide supporting evidence for pre-transplant use. In these 25 TM patients, treatment with thalidomide resulted in a significant reduction in LDH levels (291.0±97.7 vs. 236.4±51.7 U/L, p=0.003). In contrast, no significant changes were observed in creatinine (0.50±0.15 vs. 0.48±0.16 mg/dL, p=0.451) or platelet count (257±150 vs. 271±138 ×10^9/L, p=0.376). Thus, we believe that the improvement in EASIX is attributable to the alleviation of anemia and hemolysis, reducing iron overload, which is the main risk factor for thalassemia transplants.[14]

In summary, this study is the first to assess thalidomide's impact on EASIX in children with TM, offering new insights into its potential role as a pretransplantation therapy. Thalidomide treatment is a potential way to bridge patients to transplantation.

Ethics Statement. The study protocol was approved by the Medical Ethics Committee of the First People's Hospital of Zigong.

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