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Two Cases of Veno-occlusive Disease/Sinusoidal Obstruction Syndrome After Thioguanine Treatment for Acute Lymphoblastic Leukemia

Bernd Gruhn, MD, Grit Brodt, MD,* Hans-Joachim Mentzel, MD,† and Jana Ernst, MD**

Summary: Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of hematopoietic cell transplantation conditioning or high-dose chemotherapy. The underlying pathogenesis involves toxic injury to hepatocytes and sinusoidal endothelial cells. Presenting symptoms include ascites, weight gain, hepatomegaly, and hyperbilirubinemia. Severe VOD/SOS with multiorgan failure has a mortality rate of >80% if left untreated. Thioguanine, a chemotherapy drug used to treat acute lymphoblastic leukemia, has been shown to cause VOD/SOS. Here, we describe cases of 2 patients who developed very severe VOD/SOS after starting thioguanine for acute lymphoblastic leukemia; both achieved complete remission with defibrotide and experienced no defibrotide-related adverse events.

Key Words: pediatric, acute lymphoblastic leukemia, veno-occlusive disease/sinusoidal obstruction syndrome, thioguanine, defibrotide

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Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of hematopoietic cell transplantation (HCT) conditioning or high-dose chemotherapy. The underlying pathogenesis of VOD/SOS involves toxic injury to hepatocytes and sinusoidal endothelial cells, causing a release of inflammatory cytokines and chemokines, which create gaps in the endothelial lining. These gaps allow debris, which gradually sloughs off the endothelial lining, to enter the space of Disse. The sinusoidal lining cells eventually embolize downstream, blocking sinusoidal flow and causing sinusoidal narrowing.[1–3] VOD/SOS typically presents with clinical symptoms such as ascites, weight gain, hepatomegaly, and hyperbilirubinemia. Notably, the most severe form of VOD/SOS is associated with multiorgan failure and has a reported mortality rate of >80% when treated with supportive care alone.[1,3]

Thioguanine is an antimetabolite chemotherapy drug that is commonly used to treat acute lymphoblastic leukemia (ALL). It has cytotoxic activity against ALL cell lines and leukemic blasts,[4] but has been shown to cause VOD/SOS and is acknowledged as a potential cause of chronic VOD/SOS in the National Comprehensive Cancer Network (NCCN) guidelines for pediatric ALL.[5] Thioguanine was first associated with VOD/SOS in 1976 in 2 adult male patients with acute leukemia.[6] In the Children's Cancer Group 1952 study (N = 2027), 1017 pediatric patients with ALL were randomized to receive thioguanine, of whom 257 (25%) subsequently developed VOD/SOS or disproportionate thrombocytopenia attributed to thioguanine and were switched to 6-mercaptopurine.[4] In the United Kingdom Medical Research Council trial ALL97, 95 (13%) of the 748 children randomized to thioguanine developed VOD/SOS, which was assumed to be caused by thioguanine.[7] Lastly, in a case report of 99 children with ALL who received either thioguanine or 6-mercaptopurine, 12% of those on thioguanine developed VOD/SOS.[8]

Over the years, VOD/SOS has been diagnosed using various diagnostic criteria, including Baltimore, modified Seattle, and EBMT criteria, which have been regularly used in the clinic. In contrast to the Baltimore and modified Seattle criteria, the pediatric EBMT criteria recognize anicteric VOD/SOS (bilirubin < 2 mg/dL), thus allowing for earlier diagnosis of VOD/SOS by not requiring hyperbilirubinemia for diagnosis, and consider refractory thrombocytopenia as a VOD/SOS diagnosis criterion.[9–12]

Currently, defibrotide is the only approved drug for the treatment of severe VOD/SOS;[13] a number of studies have demonstrated the safety and efficacy of defibrotide in the VOD/SOS setting.[14–16] In a historically controlled, multicenter, open-label, phase 3 study (N = 102), patients with hepatic VOD/SOS with multiorgan failure post-HCT were treated with defibrotide. Complete response (CR) was achieved by day 100 post-HCT in 25.5% of defibrotide-treated patients compared with 12.5% of historical controls ($P = 0.016$), and defibrotide was well tolerated with manageable toxicity.[14] In an expanded-access program (T-IND), the Kaplan-Meier (KM)–estimated day 100 survival post-HCT for the 1000 patients with VOD/SOS treated with defibrotide was 58.9%;[16] among the 82 patients with VOD/SOS following nontransplant-associated chemotherapy, KM-estimated day 70 survival was 74.1%.[17] Lastly, in an open-label, international compassionate-use program, 272 patients with VOD/SOS (that primarily developed post-HCT) received defibrotide at the recommended dose of 25 mg/kg/day and had a KM-estimated day 100 survival of

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From the *Department of Pediatrics; and †Section of Pediatric Radiology, Institute of Diagnostic and Interventional Radiology, Jena University Hospital, Jena, Germany.
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Reprints: Bernd Gruhn, MD, Head of the Unit for Hematology, Oncology and Stem Cell Transplantation, Department of Pediatrics, Jena University Hospital, Am Klinikum 1, Jena D-07747, Germany (e-mail: bernd.gruhn@med.uni-jena.de).
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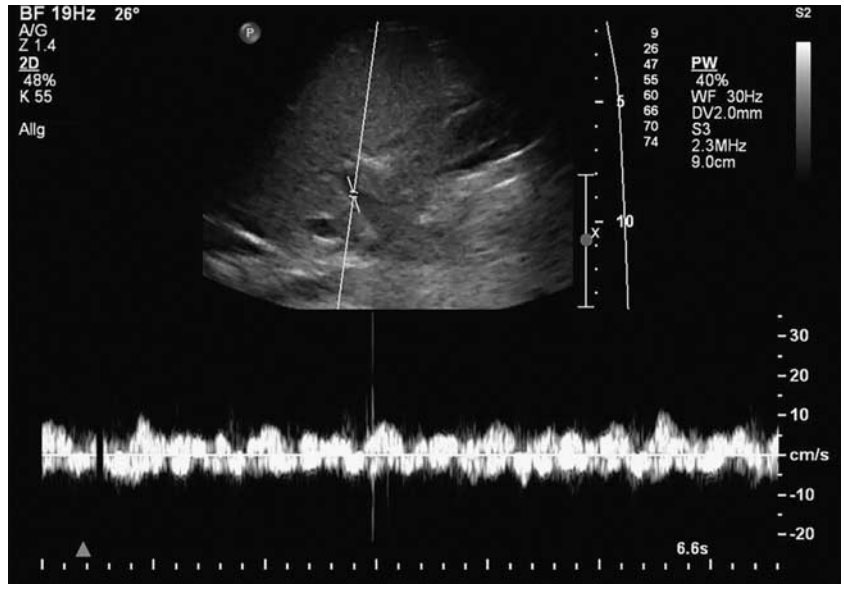

FIGURE 1. Ultrasound of reduced portal vein flow in patient 1. Lateral intercostal view of the region of the portal vein (C9-3 MHz, iU22, Philips, Eindhoven). Doppler mode showed reduced flow velocity and undulant curve.

58%.[15] These studies demonstrate the utility of defibrotide in treating VOD/SOS post-HCT. Here, we describe cases of 2 patients who did not undergo HCT and developed very severe VOD/SOS after starting thioguanine treatment for ALL but were successfully treated with defibrotide.

CASE STUDY 1

In 2017, a 7-year-old boy who presented with low thrombocyte count and increasing abdominal pain was admitted for the administration of platelets. He had previously been diagnosed with standard-risk B-cell precursor ALL and was undergoing reinduction (protocol IIB) using the AIEOP-BFM ALL 2009 protocol,[18] which consisted of oral thioguanine, intravenous cyclophosphamide, intravenous cytarabine, and intrathecal methotrexate. The patient received a 14-day course of thioguanine, which was his first exposure to thioguanine. However, on the day of admission, he suddenly exhibited slurred speech, reduced left arm strength, and numbness in his left hand. The patient had received his last dose of intrathecal methotrexate 5 days before the presentation of neurologic symptoms. Magnetic resonance imaging did not reveal thromboses, bleeding, or suspicious foci. It is possible that the neurologic symptoms could be attributed to methotrexate leukoencephalopathy. No treatment was given specifically to address neurologic symptoms. Over the course of 3 days, the patient experienced weight gain $>5\%$, ascites, refractory thrombocytopenia, hepatomegaly,

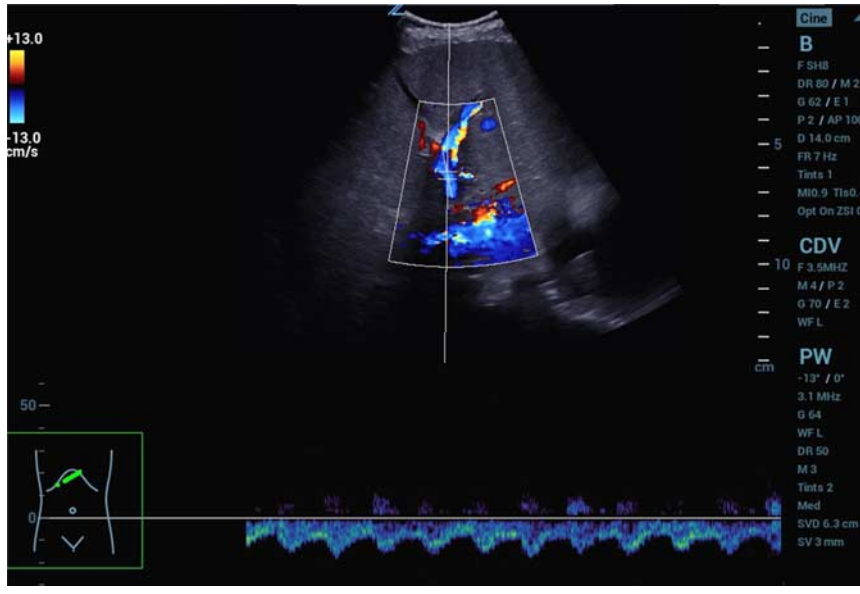

FIGURE 2. Ultrasound of reversal of portal vein flow in patient 2. Lateral intercostal view of the portal vein (C9-3 MHz, ZS3, Zonare Med Syst., Mountain View). Color Doppler revealed a red signal in the hepatic artery and a blue signal in the portal vein, corresponding to a reversal flow direction in the portal vein. The duplex curve showed negative values according to this finding.

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and reduced portal vein flow observed through ultrasound (Fig. 1). These findings led to the diagnosis of very severe VOD/SOS, 4 days after the last dose of thioguanine, using the pediatric EBMT severity grading criteria based on persistent refractory thrombocytopenia lasting more than 7 days and liver function tests more than 5× normal.[12] Thioguanine was therefore discontinued based on the assumption that it was the causative factor for VOD/SOS. As a result, defibrotide 25 mg/kg/day was initiated, which was considered off-label use for VOD/SOS since the patient had not undergone HCT. The patient received defibrotide for 21 days and achieved CR on day 18. He experienced no defibrotide-related adverse events (AEs). The patient was alive at the time of this report.

CASE STUDY 2

In 2019, a 4-year-old girl with standard-risk B-cell precursor ALL and no prior thioguanine exposure was admitted for planned chemotherapy under the AIEOP-BFM ALL 2017 protocol.[19] Reinduction (protocol IIB) was initiated, which included oral thioguanine, intravenous cyclophosphamide, intravenous cytarabine, and intrathecal methotrexate. The patient received a 14-day course of thioguanine. On the last week of reinduction, she presented with an increasingly distended abdomen; on examination, she was discovered to have ascites, hepatomegaly, and reversal of portal vein flow observed through ultrasound (Fig. 2). Using the pediatric EBMT diagnostic criteria, these findings suggested a diagnosis of very severe VOD/SOS on the last day of thioguanine administration, because of persistent refractory thrombocytopenia lasting more than 7 days and a bilirubin level $>34\ \mu mol/L$.[12] Thus, defibrotide 25 mg/kg/day was administered for 21 days. The patient showed significant improvement within 10 days and achieved CR on day 17. Similar to patient 1, she experienced no defibrotide-related AEs and was alive at the time of this report.

DISCUSSION

Physicians need to be aware of the potential for VOD/SOS when using thioguanine to treat patients with ALL, with or without HCT. Here, we reviewed 2 cases in which patients who did not undergo HCT developed very severe VOD/SOS after treatment that included thioguanine. The present cases add to previously published reports of VOD/SOS in patients with newly diagnosed ALL who had received short courses of thioguanine.[20,21] In the case series of 10 patients reported by McAtee et al,[21] patients developed moderate to severe VOD/SOS within 6 to 42 days of initiating thioguanine therapy, with the vast majority demonstrating isolated thrombocytopenia and reversal of flow by ultrasound. Similar to the patients in McAtee et al, the patients described in the present series had refractory thrombocytopenia and ultrasound findings indicative of abnormal portal vein flow.

Treatment for VOD/SOS consists of defibrotide, in addition to intensive supportive care, which can include maintenance of electrolyte balance and measures to relieve symptoms arising from ascites, hypoxia, pleural effusion, and renal dysfunction.[3,9] Both patients described here achieved CR after defibrotide treatment, with no defibrotide-related AEs.

Thioguanine is a purine analog of guanine that has been specifically associated with VOD/SOS.[22] The mechanism behind development of VOD/SOS in patients receiving thioguanine is unclear. Current hypotheses include acute inflammation of the hepatic sinusoidal vasculature and accumulation of hepatotoxic thioguanine metabolites.[8,20–22] Toxic exposure of hepatocytes to thioguanine metabolites likely leads to an imbalance between coagulation and fibrinolysis, accumulation of fibrin, and occlusion of the hepatic sinusoid.[20,23]

Refractory thrombocytopenia was the earliest sign of VOD/SOS in both patients in this case series. Both patients were diagnosed using the pediatric EBMT diagnostic criteria, which acknowledge thrombocytopenia as a criterion for VOD/SOS and, thus, allowed for earlier diagnosis and treatment compared with the Baltimore or modified Seattle criteria, which do not consider refractory thrombocytopenia for diagnosis of VOD/SOS.[9] Further, patient 1 did not present with hyperbilirubinemia and did not exhibit weight gain until 3 days after the initial symptom presentation. Elevated bilirubin and weight gain are key criteria for VOD/SOS diagnosis using Baltimore or modified Seattle criteria. In both patients, use of EBMT criteria facilitated prompt diagnosis; later diagnosis may have resulted in delayed treatment and led to different outcomes.

In this case report, prompt diagnosis and initiation of defibrotide treatment was associated with positive outcomes in both pediatric patients with very severe VOD/SOS. Following the patients' diagnosis using EBMT criteria, early initiation of the recommended defibrotide treatment for at least 21 days and until full resolution of VOD/SOS[23] resulted in a CR and no defibrotide-related AEs. In conclusion, the very severe VOD/SOS, which we believe resulted from thioguanine use, was successfully treated with defibrotide in these patients.

REFERENCES

1. Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. *Biol Blood Marrow Transplant*. 2010;16:157–168.
2. Carreras E, Diaz-Ricart M. The role of the endothelium in the short-term complications of hematopoietic SCT. *Bone Marrow Transplant*. 2011;46:1495–1502.
3. Richardson PG, Grupp SA, Pagliuca A, et al. Defibrotide for the treatment of hepatic veno-occlusive disease/sinusoidal obstruction syndrome with multiorgan failure. *Int J Hematol Oncol*. 2017;6:75–93.
4. Stork LC, Matloub Y, Broxson E, et al. Oral 6-mercaptopurine versus oral 6-thioguanine and veno-occlusive disease in children with standard-risk acute lymphoblastic leukemia: report of the Children's Oncology Group CCG-1952 clinical trial. *Blood*. 2010;115:2740–2748.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Pediatric Acute Lymphoblastic Leukemia Version 2. 2020.
6. Griner PF, Elbadawi A, Packman CH. Veno-occlusive disease of the liver after chemotherapy of acute leukemia. Report of two cases. *Ann Intern Med*. 1976;85:578–582.
7. Lennard L, Richards S, Cartwright CS, et al. The thiopurine methyltransferase genetic polymorphism is associated with thioguanine-related veno-occlusive disease of the liver in children with acute lymphoblastic leukemia. *Clin Pharmacol Ther*. 2006;80:375–383.
8. Stoneham S, Lennard L, Coen P, et al. Veno-occlusive disease in patients receiving thiopurines during maintenance therapy for childhood acute lymphoblastic leukaemia. *Br J Haematol*. 2003;123:100–102.
9. Bonifazi F, Barbato F, Ravaioli F, et al. Diagnosis and treatment of VOD/SOS after allogeneic hematopoietic stem cell transplantation. *Front Immunol*. 2020;11:489.
10. Jones RJ, Lee KS, Beschorner WE, et al. Venoocclusive disease of the liver following bone marrow transplantation. *Transplantation*. 1987;44:778–783.
11. McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Ann Intern Med*. 1993;118:255–267.

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12. Corbacioglu S, Carreras E, Ansari M, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in pediatric patients: a new classification from the European society for blood and marrow transplantation. *Bone Marrow Transplant*. 2018;53:138–145.
13. DEDefitelio (defibrotide sodium). Summary of product characteristics. Villa Guardia, Italy: Gentium SpA; 2018. Avalable at: https://www.ema.europa.eu/documents/product-information/defitelio-epar-product-information_en.pdf. Accessed March 3, 2021.
14. Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood*. 2016;127:1656–1665.
15. Corbacioglu S, Carreras E, Mohty M, et al. Defibrotide for the treatment of hepatic veno-occlusive disease: final results from the international compassionate-use program. *Biol Blood Marrow Transplant*. 2016;22:1874–1882.
16. Kernan NA, Grupp S, Smith AR, et al. Final results from a defibrotide treatment-IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome. *Br J Haematol*. 2018;181:816–827.
17. Kernan NA, Richardson PG, Smith AR, et al. Defibrotide for the treatment of hepatic veno-occlusive disease/sinusoidal obstruction syndrome following nontransplant-associated chemotherapy: final results from a post hoc analysis of data from an expanded-access program. *Pediatr Blood Cancer*. 2018;65:e27269.
18. ClinicalTrials.gov. International collaborative treatment protocol for children and adolescents with acute lymphoblastic leukemia. Available at: https://clinicaltrials.gov/ct2/show/study/NCT01117441. Accessed September 8, 2020.
19. ClinicalTrials.gov. Treatment protocol for children and adolescents with acute lymphoblastic leukemia—AIEOP-BFM ALL 2017. Available at: https://clinicaltrials.gov/ct2/show/study/NCT03643276. Accessed September 8, 2020.
20. Pawlik-Gwozdecka D, Irga-Jaworska N, Tomaszewski M, et al. Sinusoidal obstruction syndrome in a paediatric patient with acute lymphoblastic leukaemia after completion of reinduction therapy according to ALL Intercontinental Berlin-Frankfurt-Münster 2009. *Contemp Oncol (Pozn)*. 2018;22:266–269.
21. McAtee CL, Schneller N, Brackett J, et al. Treatment-related sinusoidal obstruction syndrome in children with de novo acute lymphoblastic leukemia during intensification. *Cancer Chemother Pharmacol*. 2017;80:1261–1264.
22. Oancea I, Png CW, Das I, et al. A novel mouse model of veno-occlusive disease provides strategies to prevent thioguanine-induced hepatic toxicity. *Gut*. 2013;62:594–605.
23. Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives—a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant*. 2015;50:781–789.

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