Sinusoidal obstruction syndrome (SOS), also termed veno-occlusive disease (VOD) of the liver, is a well-known complication of haematopoietic stem cell transplantation (HSCT) both in children and adults. In the medical literature there are occasional reports of SOS in patients receiving conventional chemotherapy. In children with solid tumours this entity occurs during treatment of nephroblastoma, rhabdomyosarcoma, and medulloblastoma. In the late 1990s SOS was quite often observed as the complication of oral 6-thioguanine (6-TG) in patients suffering from acute lymphoblastic leukaemia (ALL), who received 6-TG throughout maintenance. In current protocols, the syndrome has become uncommon because treatment with 6-TG is limited to two weeks of oral therapy. Here, we report a case of a nine-year-old boy with ALL, who developed sinusoidal obstruction syndrome shortly after completing the reinduction block of chemotherapy (cyclophosphamide, cytarabine, thioguanine) according to the ALL Intercontinental Berlin-Frankfurt-Münster 2009 (ALL IC BFM 2009) treatment protocol.

**Key words:** acute lymphoblastic leukaemia, veno-occlusive disease, sinusoidal obstruction syndrome, children.

# Sinusoidal obstruction syndrome in a paediatric patient with acute lymphoblastic leukaemia after completion of reinduction therapy according to ALL Intercontinental Berlin-Frankfurt-Münster 2009

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## Introduction

Veno-occlusive disease (VOD) of the liver, more correctly described as sinusoidal obstruction syndrome (SOS), is a well-known complication of high-dose chemotherapy given before haematopoietic stem cell transplantation (HSCT), whereas it is rather rare during treatment with conventional chemotherapy. SOS is the consequence of toxic injury to sinusoidal endothelial cells, followed by a series of biologic processes at the molecular level, which leads to an imbalance between coagulation and fibrinolysis, aggregation of platelets, deposition of fibrin in subepithelial space, and obstruction of the hepatic sinusoids [1]. Two groups: Seattle in 1984 and Baltimore in 1987, created clinical criteria for the diagnosis of SOS for adults and children undergoing HSCT. The Baltimore criteria include total bilirubin > 2 mg/dl and additionally at least two of the following signs: hepatomegaly, ascites, and > 5% weight gain. According to the Seattle criteria, two of the three signs (bilirubin > 2 mg/dl, hepatomegaly with right upper quadrant pain, and > 2% weight gain from baseline due to fluid retention) must be observed. Over the last few years, we have gained a better understanding of the difference in frequency, predisposition, and symptomatology of SOS between children and adults. Therefore, the European Society for Blood and Marrow Transplantation proposed new diagnostic criteria for SOS in children [2, 3]. Additionally, along diagnostic criteria the Ponte di Legno group established grading of SOS severity specific to children with acute lymphoblastic leukaemia (ALL). Criteria of both groups are summarised in Table 1 [4]. Liver biopsies of patients with SOS most often present nodular regenerative hyperplasia (NRH) characterised by diffuse transformation of normal hepatic parenchyma into small, regenerative nodules with little to no fibrosis [3]. Treatment of SOS requires aggressive supportive care; defibrotide has been approved to treat SOS in the HSCT setting [5, 6].

In children with haematopoietic malignancies, receiving conventional chemotherapy, SOS was most often observed as the complication of oral 6-thioguanine (6-TG) during maintenance therapy in ALL. SOS following short (14-days) courses of thioguanine is an extremely rare, clinically different, and poorly understood syndrome [7]. Here, we report an uncommon case of sinusoidal obstruction syndrome in a paediatric patient with ALL shortly after completing block of reinduction therapy according to the ALL Intercontinental Berlin-Frankfurt-Münster 2009 (ALL IC BFM 2009) treatment protocol.

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**Table 1.** Diagnostic criteria for hepatic SOS/VOD in children

| EBTM diagnostic criteria for hepatic SOS/VOD in children | Ponte di Legno diagnostic criteria for SOS in children with ALL |
|---|---|
| The presence of two or more of the following: <br>• unexplained consumptive and transfusion-refractory thrombocytopaenia, <br>• otherwise unexplained weight gain on three consecutive days despite the use of diuretics or a weight gain > 5%, <br>• hepatomegaly above baseline value, <br>• ascites above baseline value, <br>• rising bilirubin from a baseline value on 3 consecutive days or bilirubin >2 mg/dl within 72 h. <br><br>No limitation for time of onset of SOS/VOD | Fulfilment of at least three of five, otherwise unexplained, criteria: <br>• hepatomegaly, <br>• hyperbilirubinaemia more than upper normal limit, <br>• ascites, <br>• weight gain of at least 5%, <br>• thrombocytopaenia (transfusion-resistant and/or otherwise unexplained by treatment). <br><br>Doppler ultrasound could document changes in hepatic portal venous flow and rule out alternative causes, but normal findings do not exclude sinusoidal obstruction syndrome. <br><br>Grading: <br>• mild: bilirubin less than 103 µmol/l and weight gain less than 5%, <br>• moderate: bilirubin 103–342 µmol/l and/or weight gain more than 5% or ascites, <br>• severe: bilirubin more than 342 µmol/l and/or respiratory or renal failure or hepatic encephalopathy, <br>• death due to sinusoidal syndrome |

*SOS – sinusoidal obstruction syndrome; VOD – veno-occlusive disease; ALL – acute lymphoblastic leukaemia*

## Case report

A nine-year-old boy diagnosed with B-cell ALL had been treated in our clinic according to ALL IC BFM 2009 – chemotherapy for intermediate-risk group. The patient started to complain of pain localised to the right upper quadrant of the abdomen on the second day after completing the second part of reinduction block of chemotherapy (cyclophosphamide 1000 mg/m$^2$/d once, cytarabine 75 mg/m$^2$/d eight times during the protocol, and oral thioguanine at a daily dose of 60 mg/m$^2$ for 14 days). On physical examination, his liver was palpable and tender. Routine laboratory tests revealed pancytopaenia (WBC 1.04 × 10$^3$/µl; Hb 10.4 g/dl; platelet 3 × 10$^3$/µl); in biochemistry C-reactive protein (CRP) increased to 42 mg/l (two days earlier 8 mg/l); liver enzymes were above the laboratory norms (aspartate transaminase [AST] 151 U/l, alanine transaminase [ALT] 218 U/l), and total level of bilirubin was 1.5 mg/dl. Coagulation status was normal. Abdominal ultrasound (US) showed hepatomegaly, acute acalculous cholecystitis, and ascites. Broad-spectrum of intravenous antibiotics (tazobactam + piperacillin) were immediately added for the suspicion of abdominal infection. Despite numerous platelet transfusions, refractory thrombocytopaenia was observed. Suspecting immunisation processes anti-platelets antibodies were checked and came back negative. Within a few hours his clinical status deteriorated drastically. The patient developed fever; subsequent lab results revealed CRP elevated at 161 mg/l and procalcitonin (PCT) at 6.89 ng/ml. His body weight increased 4% above baseline value. The antibiotics were modified to meropenem. Therapy with caspofungin and granulocyte colony-stimulating factor was also initiated. In spite of the negative result of the anti-platelets antibodies test, the patient received high-dose pulses of methylprednisolone. We carefully monitored water management as well. Laboratory tests revealed impaired liver function: total serum bilirubin level 2.32 mg/dl, AST 366 U/l, and gamma-glutamyl transpeptidase (GGTP) 146 U/l. The serologic tests for cytomegalovirus, Epstein-Barr virus, and hepatitis B virus were negative. We repeated abdominal US. Imaging showed hepatomegaly, acute acalculous cholecystitis, and ascites as in the previous examination. Additionally, Doppler US showed reversed blood flow in the proximal part of the left branch of the portal vein. Furthermore, fluid in both lungs was noted. On the second day of meropenem infusion the patient's body temperature normalised. Inflammatory parameters (CRP, PCT) stopped rising and gradually began to fall. Body weight and laboratory results including Hb and WBC started to improve within a few weeks. Laboratory abnormalities normalised and US improved two months after onset.

## Discussion

Over the last few years we have gained a better understanding of the pathomechanism, frequency, and genetic predisposition of SOS, but the recognition of patients at the highest risk still remains a challenge [2]. In children with solid tumours, SOS has been most often reported in patients with Wilms tumour and rhabdomyosarcoma after therapy including vincristine, actinomycin D, and cyclophosphamide (VAC) [8]. At the turn of the 1980s and 1990s there were many speculations about which of the drugs is the causative agent of SOS.

SOS was observed in patients with rhabdomyosarcoma along with increasing doses of cyclophosphamide. Thus, some researchers hypothesised that the syndrome was associated with the side effect of escalated doses of cyclophosphamide [8]. Actinomycin was also suspected as the causative agent because the complication was reported in patients receiving vincristine and actinomycin only. In many studies the hepatotoxic action of actinomycin has been proven; however, the pathomechanism of actinomycin-induced SOS is incompletely understood [9, 10]. In medical literature there is also one case report about SOS in a child with a brain tumour after therapy with carboplatin, vincristine, and lomustine; Thus, that patient did not receive either actinomycin or cyclophosphamide [11]. Some authors noticed that the only common dominator
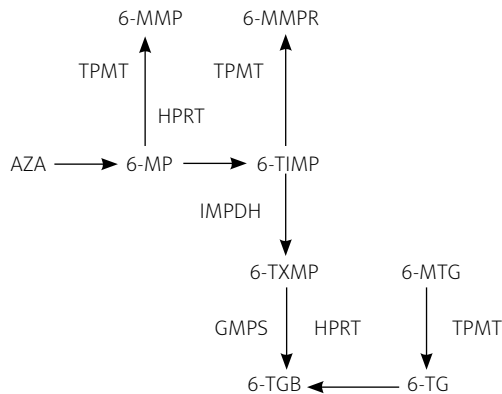
**Fig. 1.** Thiopurine metabolic pathway

to all these chemotherapy regimens was vincristine. Consequently, they came to the conclusion that this drug may play a potentiating role in the development of SOS [12].

In the group of children with haematopoietic malignancies, SOS is a well-known complication of oral 6-thioguanine. In comparison to SOS following HSCT, the symptoms are reported as much less severe and often reversible, and with extremely rare mortality. However, there was still concern about the incidence of SOS during maintenance therapy [7].

Based on Mc Atee et al.'s report, we suppose that SOS following short courses of 6-TG is a rather rare, clinically different, and probably distinct syndrome. For over eight years of their study, only 10 of 680 newly diagnosed patients with ALL were identified with SOS after short courses (14 days) of 6-TG. Eight of them had moderate disease; they achieved full recovery. Two out of ten had severe disease, and they died during hospitalisation [7]. This rate is comparable to the outcome of SOS related to HSCT [13].

6-Thioguanine is a purine analogue of guanine classified as antimetabolite. It works by incorporation of metabolites into the DNA, which is disruptive to its normal synthesis. 6-TG may stimulate apoptosis of WBCs as well [14, 15]. Due to promising results of in vitro studies, thioguanine was evaluated in the late 1990s in a few clinical trials as a component of ALL therapy. The results confirmed that oral 6-thioguanine, more often than 6-mercaptopurine (6-MP), was an SOS-triggering factor [16, 17].

Some researchers tried to connect the syndrome with the activity of thiopurine methyltransferase (TPMT) or with polymorphism of the gene encoding the enzyme. TPMT is responsible for inactivation of thiopurines by a process of methylation. Overproduction of methylated derivatives in turn causes liver toxicity (Fig. 1). Unfortunately, the results of the studies were contradictory and there was no compatibility in this topic, because SOS does not seem to be the consequence of accumulation of hepatotoxic metabolites and direct damage of hepatocytes. The culprit of the injury is sinusoidal endothelial cell ischaemia followed by central venous occlusion, whereas hepatotoxicity is probably just simply the epiphenomenon [3]. Liver biopsies of patients with SOS present nodular regenerative hyperplasia (NRH) characterised by diffuse transformation of normal hepatic parenchyma into small, regenerative nodules with little

to no fibrosis. There is neither inflammation nor cholestasis [18]. The mechanism by which thiopurines induce NRH is poorly understood. DeLeve et al. in 1996 suggested that the syndrome was related to sinusoidal endothelial damage associated with glutathione depletion [19]. The hypothesis was confirmed in another report, but the study was only carried out on rats [20]. It remains unclear why 6-TG causes NRH more frequently than 6-mercaptopurine (6-MP) or azathioprine (AZA). There is one main difference in the metabolism of 6-TG compared to 6-MP or AZA: its conversion is less multistage and results in an almost five-fold higher concentration of 6-TG in RBC and its active metabolites in the portal vein (first pass metabolism), leading to accumulation in zone 1 of the liver [3]. Subsequently, this initiates biologic processes leading to an imbalance between coagulation and fibrinolysis processes, deposit of fibrin in subepithelial space, and obstruction of the hepatic sinusoids [1]. In 2003 Stoneham et al. revealed that high concentrations of 6-thioguanine nucleotides (6-TGNs) in RBC in children with ALL did not correlate with more frequent incidence of SOS [21]. Nevertheless, Oancea demonstrated in his study that hypoxanthine-phosphoribosyl transferase-deficient (HPRT) mice, lacking thioguanine nucleotides, did not develop SOS, suggesting that the problem may lie in the intrinsic pathway of transforming thioguanine metabolites [22].

## Conclusions

Summing up, despite of extremely low incidence of the syndrome in current protocols of ALL treatment, patients receiving even short courses of oral 6-TG are at risk of this complication. Unlike in SOS during maintenance therapy, it is clinically different due to the severity and outcome [7]. Thus, further study is needed to find the risk factors in order to avoid the serious consequences of the disease.

*The authors declare no conflict of interest.*

## References

1. 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.
2. 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.
3. Al Hadithy, AF, de Boer, NK, Derijks, LJ, et al. Thiopurines in inflammatory bowel disease: Pharmacogenetics, therapeutic drug monitoring and clinical recommendations. Dig Liver Dis 2005; 37: 282-297.
4. Schmiegelow K, Attarbaschi A, Barzilai S, et al. Consensus definitions of 14 severe acute toxic effects for childhood lymphoblastic leukaemia treatment: a Delphi consensus. Lancet Oncol 2016; 17: e231-e239.
5. Strouse C, Richardson P, Prentice G, et al. Defibrotide for treatment of severe veno-occlusive disease in pediatrics and adults: an exploratory analysis using data from the center for international blood and marrow transplant research. Biol Blood Marrow Transplant 2016; 22: 1306-1312.

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6. Deleve LD. Sinusoidal obstruction syndrome. Gastroenterol Hepatol (N Y) 2008; 4: 101-110.

7. McAtee CL, Schneller N, Brackett J, Bernhardt MB, Schafer ES. Treatment-related sinusoidal obstruction syndrome in children with de novo acute lymphoblastic leukemia during intensification. Cancer Chemother Pharmacol 2017; 80: 1261-1264.

8. Cecen E, Uysal KM, Ozguven A, Gunes D, Irken G, Olgun N. Veno-occlusive disease in a child with rhabdomyosarcoma after conventional chemotherapy: report of a case and review of the literature. Pediatr Hematol Oncol 2007; 24: 615-621.

9. Sulis ML, Bessmertny O, Granowetter L, Weiner M, Kelly KM. Veno-occlusive disease in pediatric patients receiving actinomycin D and vincristine only for the treatment of rhabdomyosarcoma. J Pediatr Hematol Oncol 2004; 26: 843-846.

10. D'Antiga L, Baker A, Pritchard J, et al. Veno-occlusive disease with multi-organ involvement following actinomycin-D. Eur J Cancer 2001; 37: 1141-1148.

11. Elli M, Pinarli FG, Dagdemir A, et al. Veno-occlusive disease of the liver in a child after chemotherapy for brain tumor. Pediatr Blood Cancer 2006; 46: 521-523.

12. Kotecha RS, Buckland A, Phillips MB, Cole CH, Gottardo NG. Hepatic sinusoidal obstruction syndrome during chemotherapy for childhood medulloblastoma: report of a case and review of the literature. J Pediatr Hematol Oncol 2014; 36: 76-80.

13. Cesaro S, Pillon M, Talenti E, et al. A prospective survey on incidence, risk factors and therapy of hepatic veno-occlusive disease in children after hematopoietic stem cell transplantation. Haematologica 2005, 90: 1396-1404.

14. Evans WE. Pharmacogenetics of thiopurine S-methyltransferase and thiopurine therapy. Ther Drug Monit 2004; 26: 186-191.

15. de Boer NK, van Bodegraven AA, Jharap B, et al. Drug Insight: pharmacology and toxicity of thiopurine therapy in patients with IBD. Nat Clin Pract Gastroenterol Hepatol 2007; 4: 686-694.

16. Vora A, Mitchell CD, Lennard L, et al. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. Lancet 2006; 368: 1339-1348.

17. 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.

18. Calabrese E, Hanauer SB. Assessment of non-cirrhotic portal hypertension associated with thiopurine therapy in inflammatory bowel disease. J Crohns Colitis 2011; 5: 48-53.

19. DeLeve LD, Wang X, Kuhlenkamp JF, Kaplowitz N. Toxicity of azathioprine and monocrotaline in murine sinusoidal endothelial cells and hepatocytes: the role of glutathione and relevance to hepatic venoocclusive disease. Hepatology 1996; 23: 589-599.

20. Wang X, Kanel GC, DeLeve LD. Support of sinusoidal endothelial cell glutathione prevents hepatic veno-occlusive disease in the rat. Hepatology 2000; 31: 428-434.

21. Stoneham S, Lennard L, Coen P, Lilleyman J, Saha V. Veno-occlusive disease in patients receiving thiopurines during maintenance therapy for childhood acute lymphoblastic leukemia. Brit J Haematol 2003; 123: 100-102.

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.

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