REVIEW ARTICLE

How to prevent sinusoidal obstruction syndrome/ /veno-occlusive disease?

Patrycja Mensah-Glanowska[1], Paulina Pyrcak[1], Anna Czyż[2]

[1]Department and Clinic of Hematology, Collegium Medicum, Jagiellonian University in Krakow, Kraków, Poland
[2]Department of Hematology, Blood Neoplasms, and Bone Marrow Transplantation, The Silesian Piasts Medical University of Wroclaw, Wrocław, Poland

Address for correspondence:
Patrycja Mensah-Glanowska
Katedra i Klinika Hematologii
Collegium Medicum
Uniwersytet Jagielloński
Kopernika 17
31–501 Kraków
e-mail: patrycja.mensah-glanowska@uj.edu.pl

Hematology in Clinical Practice
2023, vol. 14, 55–63
DOI: 10.5603/HCP.2023.0007

ISSN: 2720–1015
e-ISSN: 2720–2690

Received: June 02, 2023
Accepted: June 25, 2023

ABSTRACT

Sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) is a life-threatening complication following hematopoietic stem cell transplantation (HSCT). It clinically manifests as a syndrome of symptoms, with the most important ones being jaundice, weight gain, ascites, and painful hepatomegaly. In patients with severe SOS/VOD, serious complications such as respiratory failure, renal dysfunction, and cardiovascular insufficiency occur, ultimately leading to multi-organ failure, associated with a mortality rate exceeding 80%. The incidence of SOS/VOD after HSCT is estimated to be around 5–15%, but it significantly depends on the patient population, including age, indications for transplantation, conditioning regimen intensity, and diagnostic criteria. The highest frequency of this complication occurred during decades when myeloablative conditioning based on oral busulfan was dominant in HSCT. The introduction of monoclonal antibody-drug conjugates with ozogamicin in the treatment of acute leukemias has renewed interest in the prevention and treatment of SOS/ /VOD due to the increased incidence of this complication in patients undergoing transplantation preceded by the new drugs. This paper provides an overview of contemporary knowledge regarding diagnostic criteria, risk factors, biomarkers, diagnostic techniques, pharmacological and non-pharmacological prophylaxis of SOS/VOD.

Keywords: sinusoidal obstruction syndrome/veno-occlusive disease, diagnosis criteria, risk factors, prophylaxis

INTRODUCTION

Sinusoidal obstruction syndrome (SOS)/veno--occlusive disease (VOD) is a potentially fatal form of liver injury that occurs primarily, if not exclusively, after exposure to drugs or other toxic compounds and is most commonly diagnosed in patients after hematopoietic stem cell transplantation (HSCT). It manifests clinically with at least two of the following: fluid retention, ascites, jaundice, weight gain, painful hepatomegaly, and transfusion-resistant thrombocytopenia, in the absence of other recognizable causes of liver disease. The incidence of SOS/VOD after HSCT is estimated at 5–15%, but the frequency reported in the literature varies depending on the presence of risk factors and the intensity of conditioning, type of transplantation, and diagnostic criteria used. The range of reported rates of this complication in patients after HSCT is very wide and ranges from 0% to 77% [1–5]. The understanding of the pathomechanisms, risk factors, and clinical course of SOS/VOD has evolved over many years. Historically, the highest incidence of this complication occurred in the decades when myeloablative conditioning based on oral busulfan dominated in patients undergoing bone marrow transplantation. In recent years, there has been renewed interest in the prevention and treatment of SOS/VOD, as new effective drugs consisting of conjugates of monoclonal antibodies with ozogamicin have been introduced for the treatment of acute leukemias. In patients treated with these drugs, i.e., inotuzumuab

ozogamicin (InO) and gemtuzumab ozogamicin (GO), an increased incidence of SOS/VOD is observed compared to patients undergoing standard chemotherapy, which was confirmed based on randomized trials and real-world data (RWD) [6–10]. In patients with developing severe SOS/VOD, serious complications occur, such as respiratory failure, kidney injury, and cardiovascular failure, which constitute the picture of multiple organ failure (MOF). The appearance of MOF is generally considered an indicator of severe SOS/VOD. The mortality rate in such situations is very high and exceeds 80% [2, 11].

PATHOPHYSIOLOGY

Sinus obstruction syndrome/hepatic veno-occlusive disease is an important, life-threatening complication induced by the toxicity of chemotherapy and radiotherapy used primarily for high-intensity conditioning in patients undergoing HSCT [12]. High concentrations of busulfan and its metabolites generated during conditioning have a toxic effect on endothelium functioning, especially when the enzymatic mechanism of their removal is not sufficient, i.e., in poorly oxygenated areas of the liver with low intensity of glutathione synthesis. The damaged cells are primarily the endothelial cells of the liver sinuses and hepatocytes in acinar zone 3 [13–16]. Activated sinusoidal endothelial cells (ECs) release heparinases that degrade the extracellular matrix and disrupt cytoskeletal architecture. As a result of these processes, endothelial cells become rounded, and the change in their shape and loss of tight intercellular connections lead to the creation of gaps between them, through which erythrocytes, leukocytes, and cell fragments penetrate the perisinusoidal space (or space of Disse) located under the endothelium. The lumen of the vessels gradually narrows, resulting in a gradual decrease of the flow through the sinus vessels, leading to portal hypertension caused by extra sinusoidal block [17–20]. This process leads to the appearance of clinically overt SOS/VOD, which consists of a set of symptoms such as weight gain, fluid retention with ascites, painful hepatomegaly, and jaundice. In severe cases, renal and pulmonary dysfunction also occur, and ultimately MOF with encephalopathy. The main role in the pathogenesis of SOS/VOD is played by endothelial activation and damage. However, this disease is a complex phenomenon, resulting from the overlap of many different disorders, such as the release of pro-inflammatory cytokines by cells and tissues damaged during conditioning, the release of endotoxins by microorganisms penetrating through damaged mucous barriers of the gastrointestinal tract, or the toxic effects of other drugs used during transplantation. for example, granulocyte growth factors, calcineurin inhibitors, or azoles [17–21]. Finally, the process of engraftment itself, with its accompanying release of pro-inflammatory cytokines, contributes to the development of SOS/VOD. Damage and activation of the endothelium of sinus vessels, in turn, initiate secondary effects, such as changes in proteins involved in the coagulation cascade and activation of cytokines [21]. The release of individual factors initiates the activation of various stages of coagulation and fibrinolysis, for example, von Willebrand factor (vWF) stimulates platelet aggregation, and tissue factor (TF) stimulates the activation of other coagulation proteins, while plasminogen activator inhibitor 1 (PAI-1) inhibits fibrinolysis [17, 22–24]. As a result, prothrombotic and hypofibrinolytic states develop inside the hepatic sinuses. Fibrin deposition and platelet aggregation occur there, which, combined with the progressive narrowing of the sinus vessels, ultimately leads to their closure. Tissue damage resulting from radiotherapy and chemotherapy used in conditioning, both before autologous HSCT (auto-HSCT) and allogeneic HSCT (allo-HSCT), increases the release of inflammatory cytokines [25]. While in patients after auto-HSCT pro-inflammatory and pro-apoptotic changes on epithelial cells decrease after completion of the implantation period, after allotransplantation, they may continue to increase as a result of immune reactions, which contributes to further damage to the endothelium [20, 25–27]. Experimental models have also shown that vascular endothelial cells can be directly attacked by donor T-lymphocytes, which recognize incompatible antigens on their surface in terms of the human leukocyte antigen (HLA) system [28–30].

DIAGNOSTIC CRITERIA SOS/VOD

For over three decades, the diagnosis of SOS/VOD has been based on one of two systems: the more restrictive Baltimore criteria [31] or the broader Seattle criteria/modified Seattle criteria [32]. In both systems, the key criterion was the time of symptom onset, which was 20–21 days after transplantation. However, this criterion has been revised in the last decade because observational studies have shown that up to 20% of SOS/VOD cases may occur later, after day +21. In 2016, experts from the European Society for Blood and Marrow Transplantation (EBMT) updated the diagnostic criteria for SOS/VOD in such a way that it is possible to diagnose late SOS/VOD [33]. Additionally, in 2023, the same group divided SOS/VOD into three categories: probable, clinical, and confirmed. Clinical SOS/VOD is diagnosed when, in addition to elevated bilirubin levels (≥ 2 mg/dL), two other clinical SOS/VOD criteria are met (Table 1); it is probable based on less restrictive clinical criteria if the results of ultrasonography (US) and/or elastography confirm the diagnosis, and confirmed if the diagnosis is supported by histopathological or hemodynamic examination (Table 1) [34]. Patients meeting the criteria for probable SOS/VOD should be monitored very closely in order to initiate therapeutic intervention as soon as possible, before the occurrence of MOF, which is expected to improve treatment outcomes. EBMT experts also precisely defined the criteria for MOF, introducing an assessment using the Sequential Organ Failure Assessment (SOFA) scale (Table 2) [34].

Table 1. Diagnostic criteria of sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) in adults proposed by the expert panel of the European Society for Blood and Marrow Transplantation in 2023 (source [34])

Probably	Clinical	Confirmed
At least 2 of the following criteria need to be met: • bilirubin concentration ≥ 2 mg/dL • painful hepatomegaly • weight gain > 5% • ascites • ultrasound or elastography result suggesting the diagnosis of SOS/VOD	Bilirubin concentration ≥ 2 mg/dL and two of the following criteria need to be met: • painful hepatomegaly • weight gain > 5% • ascites	SOS/VOD confirmed histologically or hemodynamically (HVPG ≥ 10 mm Hg)
Symptoms onset		
In the first 21 days after HSCT: classic SOS/VOD	> 21 days after HSCT: late SOS/VOD	

Note: in each patient, the symptoms should have no other known cause; HSCT — hematopoietic stem cell transplantation; HVPG — hepatic venous-portal gradient; US — ultrasonography

Table 2. Sequential Organ Failure Assessment scale adapted for the needs of sinusoidal obstruction syndrome/hepatic veno-occlusive disease (source [34])

Organ or system	0	1	2	3
Respiratory system: PaO_2/FiO_2 [mm Hg]	Normal	< 400	< 300	< 200 with respiratory support
Coagulation: platelet count [$10^3/mm^3$]	Normal	< 150	< 100	< 50
Liver: bilirubin concentration [mg/dL (μmol/L)]	Normal	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)
Circulatory system: arterial hypotension	Normal	MAP < 70 mm Hg	Dopamine < 5 or dobutamine (regardless of dose)*	Dopamine > 5 or adrenaline ≥ 0.1; norepinephrine ≥ 0.1*
CNS: GCS score	Normal	13–14	10–12	6–9
Kidney: creatinine concentration [mg/dL (μmol/L)]; diuresis	Normal	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–5.0 (300–400) or < 500 mL/day

*Catecholamine doses expressed in μg/kg body weight/min and administered for ≥ 1 h; CNS — central nervous system; GCS — Glasgow Coma Scale; MAP — mean arterial pressure; PaO_2/FiO_2 — oxygenation index

RISK FACTORS

Risk factors for SOS/VOD can be divided into several groups: transplant-, patient-, disease- and liver-dependent [33, 34]. The first category includes transplantation from an unrelated donor, from an HLA-incompatible donor, transplantation without lymphodepletion, myeloablative conditioning, the use of oral busulfan or high doses of this drug in conditioning, the use of high doses in total body irradiation (TBI), or a second allo-HSCT. Patient-dependent factors include older age, suboptimal general condition (according to the Karnofsky scale, < 90% of functional capacity), metabolic syndrome, use of norethisterone derivatives, advanced cancer (3rd and subsequent remissions, recurrent and resistant forms), thalassemia as an indication for transplantation and the presence of genetic factors, such as genetic polymorphism of glutathione S-transferase M1 (GSTM1) with the presence of C282Y alleles and mutations of the methylenetetrahydrofolate reductase gene (*MTHFR*) 677CC/1298CC. The third category includes liver-related factors, i.e., elevation of transaminase levels above 2.5 times the upper limit of normal (ULN) or bilirubin levels above 1.5 times ULN. This category also includes cirrhosis, active viral hepatitis or abdominal irradiation, iron overload, use of hepatotoxic drugs, and GO or InO. The use of antibody-ozogamicin conjugates, increased bilirubin concentration before HSCT or the use of norethisterone derivatives are factors that increase the risk of SOS/VOD more than 10-fold. For practical reasons, SOS/VOD risk factors can also be divided into those occurring before or after transplantation, and modifiable and non-modifiable factors [34–37]. The most obvious modifiable risk factor is the choice of conditioning or method of SOS/VOD prevention. The use of myeloablative conditioning with busulfan and a second alkylating agent will significantly increase the risk of SOS/VOD, as will the use of tacrolimus and sirolimus in the prevention of graft-versus-host disease (GvHD).

Based on data from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry, covering 13,000 patients undergoing HSCT in 2008–2013, a predictive model of SOS/VOD risk was developed and verified, based on which it is possible to identify patients at high risk of SOS/VOD even before transplantation. Independent prognostic factors in this analysis include the patient's age, Karnofsky score, use of sirolimus in immunosuppressive therapy, presence of hepatitis B and C, type of conditioning, primary diagnosis, and stage of underlying disease immediately before HSCT [36]. Due to the period in which the CIBMTR study was conducted, these data do not include patients treated with antibody-ozogamicin conjugates before transplantation.

SOS/VOD BIOMARKERS

Many different predictive and diagnostic biomarkers of SOS/VOD have been identified so far [32]. The best-studied one is increased PAI-1 levels [38–41]. Other biomarkers identified by various research groups include increased concentrations of vWF, thrombomodulin, soluble intercellular adhesion molecule 1 (sICAM-1), as well as decreased concentrations of vascular cell adhesion molecule 1 (VCAM-1), angiotensin 2 and L-ficolin [42–44]. Han et al. [45]

recently published the results of a study in which on day +3 after HSCT, they measured the concentrations of three proteins: L-ficolin, hyaluronic acid, and stimulation 2 (ST-2) protein belonging to the interleukin (IL) 1 receptor family. The use of a panel of these three biomarkers showed 80% [95% confidence interval (CI): 55–100%] sensitivity and 73% (95% CI: 62–83%) specificity in predicting the occurrence of SOS/VOD. Patients with low L-ficolin concentrations had a 9-fold higher risk of developing SOS/VOD, while patients with high hyaluronic acid and ST-2 concentrations had a 6.5-fold (95% CI: 1.9–22.0) and a 5.5-fold (95% CI: 2.3–13.1) higher risk of developing SOS/VOD, respectively. These three markers also had prognostic significance for poorer survival in the period up to day +100 after HSCT [45]. Another study demonstrated that increased levels of IL-6 and tumor necrosis factor-alpha (TNF-α) after HSCT were associated with an increased risk of SOS/VOD [46, 47]. Recently, the usefulness of assessing the Endothelial Activation and Stress Index (EASIX) on the day of transplantation in predicting the occurrence of SOS/VOD after HSCT was also confirmed. The EASIX is based on routinely assessed parameters: serum lactate dehydrogenase and creatinine levels and platelets count [48]. Jiang et al. [48] showed in two independent large cohorts (n = 446 and n = 380) that the use of the EASIX allows precise prediction of SOS/VOD occurrence ($p < 0.0001$), as well as overall survival and mortality from other causes [48]. It should be noted, however, that the use of biomarkers or their panels has not yet been used in daily clinical practice.

DIAGNOSTIC TECHNIQUES

Since the criteria for the diagnosis of SOS/VOD were established over three decades ago, many new diagnostic techniques have been introduced that may serve to increase the precision of diagnosing this complication. Measurement of the hepatic venous pressure gradient (HVPG) through the jugular vein is the most accurate method to confirm the diagnosis of SOS/VOD. The finding of HVPG equal to or higher than 10 mm Hg is characterized by high diagnostic sensitivity and specificity [49–52]. The limitations to the widespread use of this method are its invasive nature and the need for the test to be performed by experienced staff, which is why it is not routinely available in most centers. Abdominal ultrasound is most often used to diagnose SOS/VOD because it is a relatively easy, non-invasive and widely available method. Gray-scale ultrasound can detect non-specific abnormalities such as hepatomegaly, splenomegaly, thickening of the gallbladder wall, ascites, and impaired portal venous flow. In color Doppler ultrasound, a reduction in the velocity or reversal of portal venous flow can be observed, which is a more specific SOS/VOD symptom, but these disorders usually occur late in the course of the disease [53–55]. The use of a highly sensitive and specific assessment of SOS/VOD with ultrasound is possible thanks to the use of a new assessment scale called HokUS-10 [56]. Recently, liver stiffness measurement as an indirect measure of portal hypertension and its complications has become a new and accurate diagnostic tool. The test is performed using the elastography method, which involves measuring the propagation speed of the ultrasound wave emitted by the head during liver ultrasound. The speed of wave propagation depends on the stiffness of the organ, i.e., the degree of fibrosis. This method is called non-invasive liver biopsy. It can be used at various time points: at the initial stage to assess the risk of SOS/VOD, after HSCT to diagnose SOS/VOD and later to monitor the treatment course [57, 58]. Other imaging techniques are also used in the diagnosis of SOS/VOD, such as computed tomography (CT), which is useful in confirming the diagnosis of SOS/VOD, or magnetic resonance imaging (MRI), which is used to assess the risk based on the iron load in the patient's body [57].

PHARMACOLOGICAL PREVENTION

The effectiveness of many drugs has been evaluated in the prevention of SOS/VOD, including heparin, antithrombin, prostaglandin E1, pentoxifylline, thrombomodulin, and ursodeoxycholic acid (UDCA). The drug that has been used for the longest time in the prevention of SOS/VOD is heparin. The effectiveness of unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) was assessed in prospective randomized studies, as well as in observational and retrospective studies [59–64]. In the 1990s, several studies in patients undergoing allo-HSCT after myeloablative conditioning demonstrated the effectiveness of heparin used as monotherapy or in combination with lipo prostaglandin E1 or UDCA [59–62, 65, 66]. Already in 1992, Attal et al. [62] showed in a prospective randomized study that UFH used in continuous intravenous infusion at a dose of 100 μg/kg body weight/day effectively prevents VOD in patients undergoing myeloablative allo-HSCT. However, a meta-analysis published in 2006 that included 12 studies on the prophylactic use of LMWH or UFH did not demonstrate a significant reduction in the risk of VOD/SOS [relative risk (RR) 0.90; 95% CI: 0.62–1.29], although it is worth noting that two of three randomized studies included in the meta-analysis documented the effectiveness of heparin in preventing this complication [67]. In 2015, another Cochrane meta-analysis was published, which brought similar negative results for both UFH and LMWH: RR 0.47 (95% CI: 0.18–1.26) and RR 0.27 (95% CI: 0.06–1.18), respectively, but the quality of evidence was low [68]. Due to the discrepancy in study results regarding the effectiveness of heparin and bleeding complications related to its use, the British Committee for Standards in Hematology (BCSH) and the British Society for Hematology and Marrow Transplantation (BSBMT) in a position paper published in 2013 do not recommend heparin for use in the prevention of SOS/VOD [69]. It should be emphasized, however, that some centers with extensive experience

have been using this method of prevention, introduced in the 1990s based on the results of the randomized trials cited earlier, for years. This controversial subject remains an area of research. In 2022, further studies were published presenting the results of two large analyses on the use of low-dose UFH in the prevention of SOS/VOD. One study additionally compared the incidence of SOS/VOD in the study group with historical data. In both analyses, SOS/VOD was rare in patients receiving heparin prophylaxis. Moreover, both studies showed that heparin prophylaxis was safe and associated with a low incidence of bleeding complications [70, 71].

The basis for the use of UDCA, also known as ursodiol, i.e., synthetic bile salt (first identified in bears), is the observation that hydrophilic bile acids, unlike hydrophobic forms, are not toxic to hepatocytes. UDCA has been shown to have a hepatoprotective effect by regulating the release and expression of inflammatory cytokines and its immunomodulatory effects [18, 72, 73]. Various daily doses were evaluated, from a total dose of 600 mg to 12 mg/kg body weight. In controlled studies, including randomized ones, the use of UDCA resulted in a reduced incidence of SOS/VOD and mortality after HSCT [74–76]. These results were further confirmed in a meta-analysis that included 612 patients who participated in four randomized clinical trials [68]. Based on these data, prevention with UDCA up to day +90 after HSCT is recommended by both EBMT and BCSH/BSBMT experts [69, 77]. It is worth adding that recently a research group from Basel published a single-center experience on the use of dual prophylaxis based on UDCA and low doses of UFH in a very large cohort of patients (n = 1016), suggesting the high effectiveness of such treatment, as the cumulative incidence of SOS/VOD was only 2.3% (95% CI: 1.3–3.3) [71]. Among other studies on the pharmacological prevention of SOS/VOD, it is worth mentioning a recently published meta-analysis, the results of which indicate the effectiveness and safety of recombinant thrombomodulin in this indication [78]. The results of a randomized trial on the use of defibrotide in the prevention of SOS/VOD in children, published over 10 years ago, suggested a benefit from such treatment [79]. However, recently published results of a large prospective randomized phase III trial in children and adults (n = 372) at high risk of SOS/VOD, comparing defibrotide for SOS/VOD prophylaxis with best supportive care, did not confirm these historical results. Survival without SOS/VOD on day +30 after HSCT was 67% in the defibrotide-treated group and 73% in the SOC group (p = 0.85) [80, 81].

SOS/VOD PREVENTION IN SPECIAL GROUPS OF PATIENTS AT HIGH RISK OF SOS/VOD ASSOCIATED WITH TREATMENT WITH ANTIBODY-OZOGAMICIN CONJUGATES

Hepatic sinusoidal obstruction syndrome/hepatic veno-occlusive disease is a well-known and documented complication of InO and GO treatment, the risk of which increases in patients subsequently undergoing HSCT. Therefore, it has become an important issue to develop principles of treatment in this group of patients [82, 83]. Ladha et al. [82] analyzed the risk factors and incidence of SOS/VOD in patients treated with InO or GO in controlled clinical studies and formulated recommendations for management before HSCT and after transplantation in this clinical situation.

The most important expert recommendations are summarized in Table 3 [82, 83].

Table 3. Principles of management before and after hematopoietic cell transplantation in patients previously treated with inotuzumab ozogamicin (InO) or gemtuzumab ozogamicin (GO) (based on [82, 83])

Patients treated with In	• Limiting the number of InO cycles to 2 in patients qualified for allo-HSCT • Close monitoring of the patient's weight and fluid balance during InO treatment and allo-HSCT • Monitoring of laboratory parameters of liver function before and after administration of each dose of InO, with modification of this dose based on test results • Possibly a long time interval between the last InO cycle and HSCT (the time range has not been precisely defined; the decision should be made based on the assessment of the patient's clinical situation)
Patients treated with GO	It is recommended that the interval between the last GO administration and HSCT should not be shorter than 3.5 months
Both groups of patients	• Avoiding the use of 2 alkylating agents in conditioning before HSCT • Pharmacological prevention of SOS/VOD during HSCT — ursodeoxycholic acid • Avoiding azoles for antifungal prophylaxis after HSCT • Very frequent monitoring of laboratory parameters of liver function in the first month after transplantation, then according to standard procedures

allo — allogeneic; HSCT — hematopoietic stem cell transplantation; SOS/VOD — sinusoidal obstruction syndrome/veno-occlusive disease

PREVENTION STRATEGY AND SUPPORTIVE CARE MEASURES

Another noteworthy document is the Australian SOS/VOD Management Guidelines [84]. According to them, in the first stage, it is necessary to identify individual risk factors for SOS/VOD in each patient. Particular attention is paid to modifiable risk factors that must be properly managed. Examples include normalizing transaminase activity before starting conditioning, refraining from using potentially hepatotoxic drugs, extending the interval between the administration of antibody-ozogamicin conjugates and starting conditioning, and, finally, replacing myeloablative conditioning with conditioning of reduced intensity and/or toxicity. The last element of preventing the occurrence of SOS/VOD is pharmacological prophylaxis [84].

Fluid retention and weight gain are necessary phenomena for the diagnosis of SOS/VOD but are not unique to this syndrome. The results of studies in various diseases and different patient populations prove the negative impact of overhydration on the outcomes. In patients

undergoing HSCT, it was shown that the risk of non-relapse mortality (NRM) was significantly higher in patients with fluid overload [85]. Moreover, poorer overall survival was observed in patients whose body weight increased by more than 10%. Given the above-mentioned results, it was postulated to consider fluid overload as an independent risk factor for death after allo-HSCT. Attention should be paid to the frequent practice of excessive hydration of the patient in the early peritransplantation period to reduce toxicity. However, paradoxically, in conditions of a highly pro-inflammatory environment and endothelial damage resulting from conditioning toxicity, overhydration enhances endothelial activation, leading to fluid leakage through the vessel walls and retention of fluids outside the lumen, which in turn promotes the occurrence of acute kidney injury (AKI). In patients with fluid overload, an increase in blood creatinine is a late indicator of kidney damage. Additionally, in patients with symptoms of severe intestinal toxicity during conditioning, endotoxins released in the intestinal lumen stimulate non-specific immune mechanisms, the activation of which adversely affects the function of the heart and kidneys [86]. In clinical practice, in the peritransplantation period, it is recommended to be particularly careful in administering fluid therapy, monitoring body weight and daily diuresis, avoiding excessive hydration, and early therapeutic intervention in patients with fluid retention. Strict control of fluid balance is a key preventive measure in SOS/VOD [87]. Observational studies in children have shown that early implementation of renal replacement therapy in overhydrated patients, before an increase in serum creatinine concentration or a decrease in diuresis, improved treatment outcomes [88, 89].

Considering the complex pathogenesis of SOS/VOD, avoiding excess medications during conditioning is an important element in preventing the occurrence of this dangerous complication. It is strongly recommended to discontinue the use of hepatotoxic drugs. If antifungal treatment is necessary, azoles should be replaced with other drugs — echinocandins or liposomal amphotericin B. The hepatic toxicity rate of azoles in the population of patients undergoing HSCT is very high and in the case of voriconazole, it is as high as 34% [90]. In the prevention of seizures that may be the result of busulfan neurotoxicity, it is preferable to replace phenytoin with levetiracetam or benzodiazepines. Caution is also recommended when using paracetamol due to its hepatotoxic potential [87]. Moreover, the use of tyrosine kinase inhibitors before transplantation may be associated with a higher risk of liver toxicity [91]. However, the recommendation to discontinue treatment with tyrosine kinase inhibitors even 2–3 weeks before starting conditioning may be controversial [87].

Particular caution in the antimicrobial strategies used should be recommended in patients who are candidates for HSCT. Initially, it was suggested that the use of prophylactic antibiotic therapy translates into reduced mortality and a lower risk of SOS/VOD. However, it is now known that microbiome diversity plays an important role in protecting against liver damage and inflammation, both associated with the risk of developing SOS/VOD. Moreover, it has been shown that the presence of specific bacterial species has a protective effect on the proper gastrointestinal system functioning, improving the tightness of the intestinal barrier, reducing the intensity of inflammation in the intestine, and regulating the immune response. Knowledge about the immunomodulatory properties of the intestinal microbiome should lead to the development of antibiotic therapy strategies. A key problem is also the prevention of infections and colonization with multi-resistant bacteria in candidates for HSCT. Avoidance of pathological colonization and caution in the use of broad-spectrum antibiotic therapy in order to preserve particularly valuable components of the commensal flora should serve to protect the integrity of the intestinal mucosa, indirectly reducing the risk of SOS/VOD.

For patients with confirmed liver disease, reduced intensity conditioning (especially without busulfan) should be considered. However, in patients with cirrhosis or transitional fibrosis, allo-HSCT should be considered with particular caution due to the high mortality rate — both related to the high risk of severe SOS/VOD, and hepatic GvHD, which is particularly difficult to treat.

SUMMARY/CONCLUDING REMARKS

EBMT experts emphasize the priority of reducing modifiable SOS/VOD risk factors. The introduction of intravenous forms of busulfan into clinical practice and the replacement of cyclophosphamide with fludarabine allowed to reduce the incidence of SOS/VOD. However, the introduction of new anticancer therapies, primarily antibody-ozogamicin conjugates, has resulted in a renewed increase in the incidence of SOS/VOD, despite the introduction of safer conditioning methods in the last decade. In terms of pharmacological agents for the prevention of SOS/VOD in adults, only UDCA is recommended, administered from the beginning of conditioning up to day +90 after transplantation [77]. However, despite the documented effectiveness of this drug, this serious complication is observed after HSCT [68, 71, 74–77]. In addition to UDCA, LMWH or UFH are still used for the prevention of SOS/VOD, despite the negative results of meta-analyses on the effectiveness of heparin and the lack of clear recommendations regarding its use in this indication [67–71]. Early treatment with defibrotide offers a chance to save some patients, but the very high cost of such treatment remains a significant problem. The introduction of the probable SOS/VOD category in the latest version of the EBMT expert statement may improve the care of high-risk patients and speed up the diagnosis of SOS/VOD [34]. The search for and validation of new methods of prognosis and early diagnosis of this dangerous complication is an important research direction because it is still not possible to precisely determine the degree

of damage to the endothelium of the liver sinuses, which occurs several weeks before the onset of SOS/VOD clinical symptoms. It can be assumed that starting treatment at such an early stage of liver damage would reduce mortality associated with severe SOS/VOD and thus contribute to further improvement of HSCT results.

Article Information and Declarations

Acknowledgments: Not applicable.

Conflict od interest: The authors declare no conflict of interest.

Funding: None.

Supplementary material: None.

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