Iran Red Crescent Med J. 2023 September; 25(9):e2885 doi: 10.32592/ircmj.2023.25.9.2885

Published online 2023 September 20 **Original Article**

Four-drug Combination Therapy for Venous Occlusive Disease Prophylaxis after Allogeneic Hematopoietic Stem Cell Transplantation

Meilin Tian[1,2], Le Ma[2], Lan Yang[3], Qiang Gong[2*], Jieping Chen[2*]

[1]Zunyi Medical University, Zunyi 563000, China
[2]Department of Hematology, Southwest Hospital, First Affiliated Hospital of the Army Medical University, Chongqing 400038, China
[3]Medical College of Guizhou University, Guiyang 550025, China

*** *Corresponding author:*** Qiang Gong, Department of Hematology, Southwest Hospital, Third Military Medical University, Gaotanyan Road Street, Shapingba district 400038, China. Email: gongqiang_cool@163.com; Jieping Chen, Department of Hematology, Southwest Hospital, Third Military Medical University, Gaotanyan Road Street, Shapingba district 400038, China. Email: CJPXNYY@163.com

Received 2023 May 23; **Revised** 2023 June 15; **Accepted** 2023 September 04.

Abstract

Hepatic sinusoidal occlusion syndrome (SOS) or venous occlusive disease (VOD) is a frequent complication of allogeneic Hematopoietic stem cell transplantation (allo-HSCT). The mortality rate of patients with severe VOD is extremely high. It is of utmost importance to explore practical ways to reduce the incidence of VOD. The present study aimed to evaluate the efficacy and safety of a prophylaxis strategy involving the combined use of prostaglandin E1 (PGE1), dalteparin, low molecular weight glucan dextran (LMWD), and ursodeoxycholic acid (UDCA). We conducted a single-center retrospective clinical observation of 225 patients who received allo-HSCT for hematological disorders between 2008 and 2022, all of whom received these four medicines for VOD. These 225 patients were within the age range of 6-58 years, and their donors were classified as related donors (75.5%) and unrelated donors (24.5%). All patients underwent a myeloablative conditioning regimen prior to transplantation. Each patient possessed at least one risk factor for VOD, and 167 (74.2%) cases were deemed to be at high risk. Ultimately, only two patients developed VOD, with an incidence of only 0.89%, of whom one was late-onset VOD. The bleeding rate was 32.9%, with predominantly grade 1-2 (93.2%). The incidence of bleeding aligns with findings reported in other literature. Remarkably, the mortality rate associated with bleeding during transplantation was a mere 1.8%, significantly lower than the average. The results of the study demonstrated the effectiveness and safety of the four PGE1-based medications in the prevention of VOD after allo-HSCT.

Keywords: Allogeneic hematopoietic stem cell transplantation, Dalteparin, Dextran, PGE1, Ursodeoxycholic acid, Venous occlusive disease

1. Background

Hepatic sinusoidal obstruction syndrome (SOS)/venous occlusive disease (VOD) is a serious early complication after hematopoietic stem cell transplantation (HSCT), typically developing within three weeks following the procedure (1). This condition is characterized by the significant narrowing or complete occlusion of hepatic veins, resulting from endothelial cell damage in the venous sinusoids of the hepatic lobules. The clinical manifestations of SOS/VOD include right upper abdominal pain, jaundice, ascites, weight gain, and in severe cases, systemic multiple organ failure or even death (2,3). Several major risk factors have been identified for the development of VOD, including those associated with the transplant process, patient's characteristics, underlying disease, and hepatic-related factors (4). Studies indicated that the incidence of VOD post-HSCT ranges from 3%-13% (5,6), with a mortality rate of up to 80% observed in patients with severe VOD (6). Given these alarming statistics, the prevention of VOD holds paramount importance in ensuring favorable patient outcomes.

Defibrotide, although recognized as an effective treatment for VOD, has limitations due to its high cost and unavailability in China. As a result, it is essential to explore safe, effective, and cost-effective preventive regimens for VOD. At present, several prevention regimens have been studied, including single-agent and multi-drug combination regimens. A prospective study conducted in Korea Children's Hospital used prostaglandin E1 (PGE1) alone to prevent VOD after allo-HSCT(allogeneic hematopoietic stem cell transplantation) and demonstrated a VOD incidence of 6.7% (7). Another study using PGE1 to prevent VOD after allo-HSCT found no statistical difference in the incidence of VOD between the PGE1 group (n=50) and the control group (n=59) (12.2% vs. 25.5%; P=0.05). Nonetheless, in a subgroup analysis, the incidence of VOD was significantly lower in patients with acute leukemia (AL) using PGE1 prophylactically in the course of transplantation than in the control group (12.8% vs. 39.1%; P=0.02) (8).

Ursodeoxycholic acid (UDCA) has also been studied for VOD prophylaxis in patients undergoing HSCT. A systematic review demonstrated that UDCA appears to be effective in the prevention of VOD and should be considered a prevention strategy (RR,0.36; 95%CI,0.15-0.90) (9). Imran H et al. reported that prophylactic anticoagulant use has shown promise in the prevention of VOD after HSCT in some randomized controlled trials (10). Heparin has been studied both in its ordinary form and low molecular weight heparin (LMWH) for VOD prophylaxis. One study administering ordinary heparin found it to be

effective in preventing VOD without increasing the risk of bleeding (11).

Another study suggested that prophylactic use of LMWH may reduce VOD-related parameters; nonetheless, a larger randomized controlled trial is needed for confirmation (12). A large cohort study combined UDCA with low-dose heparin for VOD prophylaxis and found a lower incidence of VOD. Nevertheless, patients who developed VOD had a higher rate of moderate to severe VOD (74%)(13). A retrospective study in China used a combination of heparin, PGE1, and compound salvia miltiorrhiza to prevent VOD after HSCT, with an incidence of 2.7% (2/72); however, the risk of bleeding was not assessed in this study (14).

Compound salvia miltiorrhiza is an extract of salvia miltiorrhiza, and main component is salvia magnesium acetate, which promotes blood circulation and anticoagulation. There is also a study exploring the use of antithrombin III to prevent VOD after transplantation in children suggested no significant difference in the incidence of VOD compared to controls (15). Currently, there are such limitations as small sample sizes and uncertain efficacy in the clinical studies of VOD prevention. The usage and dosage of these drugs, as well as whether they should be used alone or in combination with multiple medications, are also controversial. There is currently no standardized program for the prevention and treatment of VOD.

We report our single-center retrospective clinical observation and analyze the outcome of 225 consecutive patients who received PGE1, dalteparin sodium, low molecular weight dextran (LMWD), and UDCA as VOD prophylaxis in the course of allo-HSCT for various hematological malignancies and severe aplastic anemia (AA), as well as the incidence of VOD and adverse drug reactions.

2. Objectives

The present study aimed to evaluate the four-drug combination therapy for VOD after allo-HSCT.

3. Methods

Study population

We conducted a single-center retrospective clinical observation of consecutive patients who underwent allo-HSCT between 2008 and 2022 at the Southwest Hospital in China. Patients who deceased from causes unrelated to VOD or bleeding within three months after transplantation (n=2), were excluded. One of the two patients died due to a relapse of the hemophagocytic 60-kg patient syndrome (HLH), and the other patient's cause of death was septicopyemia. Both patients died within 20 days after transplantation. A total of 225 patients were included in our analysis. The included patients encompassed various disease types, including AL, advanced chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), AA, non-Hodgkin lymphoma (NHL), and HLH. All patients underwent evaluation and were deemed suitable candidates for allo-HSCT. Analyses were performed following the Declaration of Helsinki and this study was approved by the Ethics Committee of Southwest Hospital.

Transplantation Procedures

Conditioning regimen

The conditioning regimen used in the study was based on the "Chinese Expert Consensus on allo-HSCT in the treatment of hematological diseases (Ⅰ) -- Indications, preconditioning protocol and Donor Selection (2014 edition)"(16). All transplant patients were treated with a myeloablative preparative regimen. Patients with AL, CML, or MDS were treated with the mBuCy or TBI/CY myeloablative regimen. Patients with AA were treated with the BuCyFluATG or FluCy-ATG myeloablative regimen. The mBuCy protocol included the administration of cytarabine (Ara-c) at a dose of 4-8g/m2 on day -10 to -9, busulfan (Bu) at a dose of 9.6mg/kg on day -8 to -6, cyclophosphamide (Cy) at a dose of 3.6g/m2 on day -5 to -4, MeCCNU at a dose of 250mg/m2 on day -3, and anti-thymocyte globulin (ATG) at a dose of 10mg/kg on day -5 to -2. The TBI/CY protocol included the administration of Cy at a dose of 120mg/kg on day -6 to -5 and total body irradiation (TBI) at a dose of 12-14Gy on day -3 to -1. The BuCyFluATG protocol included the administration of Bu at a dose of 8mg/kg on day -7 to -6, fludarabine (Flu) at a dose of 120mg/m2 on day -10 to -7, Cy at a dose of 200mg/kg on day -6 to -3, and ATG at a dose of 10mg/kg on day -4 to -1. The FluCy-ATG protocol included the administration of Flu at a dose of 120mg/m2 on day -5 to -2, Cy at a dose of 90mg/kg on day -3 to -2, and ATG at a dose of 10mg/kg on day -5 to -2. None of the patients had ever received gentuzumab or inotuzumab with the AML and ALL. These protocols were specifically designed to ensure the complete destruction of the patient's existing bone marrow (BM) and immune system, allowing for the successful engraftment of the transplanted hematopoietic stem cells.

Infusion of hematopoietic stem cells

The bone marrow (BM) and peripheral blood hematopoietic stem cells (PBSC) were used for the allo-HSCT stem cell source. Umbilical cord blood (UCB), whose source was Shandong Provincial Cord Blood Bank, was used to assist hematopoietic reconstruction in the study. The number of mononuclear cells infused was required to be $\geq 5\times10^8$/kg, and the number of CD34+ cells infused was required to be $\geq 2\times10^6$/kg.

Prevention of GVHD

The prophylactic drugs for GVHD (graft versus

host disease) included CsA, ATG, mycophenolate mofetil(MMF), methotrexate (MTX), and anti-CD25 monoclonal antibody. In addition, some patients at high risk of GVHD were also administered the anti-CD25 monoclonal antibody on -1 and +4 days (17). For patients with HLA (human leukocyte antigen)-matched sibling donors, a combination of CsA, MTX, and ATG was used as a prophylactic strategy. If the donors were haploidentical or unrelated, MMF would be added to the existing prophylactic strategy.

Prevention and Treatment of Infection

Before transplantation, all patients were transferred to the sterile laminar flow ward. Ganciclovir/acyclovir and human immunoglobulin were applied for patients with CMV/EB (cytomegalovirus/epstein-barr virus) IgM positive or virus polymerase chain reaction (PCR) positive before transplantation until IgM or virus PCR turned negative. CMV/EB PCR was monitored at least once a week starting from three weeks after transplantation. In the case of CMV/EB infection post-transplantation, immunosuppressant doses were reduced alongside antiviral drug usage when GVHD was under control. Patients with hepatitis B virus (HBV) surface antigen positive or HBV-DNA copy number greater than 10^5 IU/ml were treated with entecavir against HBV before transplantation until the viral copy number turned negative. Patients who were hepatitis B core antibody positive but hepatitis B surface antigen negative and had normal liver function were treated prophylactically with entecavir during trans-plantation. Furthermore, all patients received oral berberine/norfloxacin for pretransplant bowel preparation, oral co-trimoxazole to prevent Pneumocystis carinii infection, and caspofungin/ micafungin to prevent fungal infections during transplantation.

Prophylaxis and diagnosis of venous occlusive disease

Preventive medication was administered from the start of conditioning until 21 days after transplantation, and some patients with high-risk factors of VOD were administered until 28 days after transplantation. Medication usage and dosages: PGE1 10ug intravenously (iv) every 12 hours, dalteparin sodium 2500iu iv every 12 hours, LMWD 500ml iv once daily, and UDCA 250mg orally twice daily. Hemostatic measures were implemented when patients experienced grade 1-2 bleeding, and a transfusion of blood products was given if the patient's platelet count dropped below 20,000/μL. In the event of grade 3 hemorrhage in patients with severe dysphagia, fasting, or a platelet count lower than 20,000/μL, the treatment involved blood transfusion, and the prophylactic use of dalteparin sodium and LMWD was discontinued. The VOD prophylaxis was discontinued, and transfusions were administered when patients experienced grade 4 bleeding or when their platelet count decreased below 10,000/μL. The diagnosis of VOD and its severity grading of VOD were based on the European Society for Blood and Marrow Transplantation (EBMT) criteria(18).

Supportive care

(i) Body weight and abdominal circumference were daily monitored from preconditioning. Coagulation function, liver and kidney function, and blood routine were monitored closely. (ii) The balance of intake and output was controlled, and appropriate diuresis was given when the patient had ascites. (iii) Corresponding analgesic treatment was given when pain caused by abdominal distension occurred. (iv) In case of Grade 1-2 bleeding occurred, local or systemic hemostatic drugs and blood products were administered. In case of Grade 3-4 bleeding occurred, a part of or all VOD preventive drugs were discontinued as appropriate, blood products were transfused, and hemostatic treatment was performed until there was no active bleeding.

4. Results

Patients' characteristics

Patients' characteristics are displayed in Table 1. A total of 225 patients were enrolled in this study, including 132 males and 93 females with a median age of 34 years (range: 6-58). Allo-HSCT was performed mainly in ALL (n=56; 24.9%), AML (n=93; 41.4%), MAL (n=1; 0.4%), advanced CML (n=37; 16.5%), MDS (n=23; 10.2%), AA (n=11; 4.9%), NHL (n=3; 1.3%), and HLH (n=1; 0.4%). Donor types included HLA-haplo identical donors (n=66; 29.3%), HLA-matched sibling donors (n=104; 46.2%), and unrelated donors (n=55; 24.5%). The incidence rates of matched and mismatched were 64.9% and 35.1%, respectively. The pre-transplant disease status included complete response (CR) (n = 135; 60 %), partial response (PR) (n=79; 35.1%), and no response (NR) (n=11; 4.9%).

Infusion of hematopoietic stem cells

The median number of mononuclear cells transfused was 8.7×10^8/kg, and the median number of CD34+ cells transfused was 6×10^6/kg.

Incidence of aGVHD

The overall incidence of aGVHD (acute graft versus host disease) was 31.6%(n=71), and aGVHD (grade≥II) was 10.2% (n=23).

Risk factors for venous occlusive disease

We counted the risk factors for VOD according to the EBMT International Working Group guidelines for VOD prevention and treatment(19) (Figure 1). There are three main different SOS/VOD risk factors: factors directly related to transplantation, factors related to the patient's characteristics and underlying disease, and hepatic-related risk factors. For transplant-

Table1. Basic characteristics and therapeutic intervention of patients（n=225）

Variable	Value（%）
Age（year）	
＜18	34（15.1%）
18-40	129（57.3%）
＞40	62（27.6%）
Gender	
Male	132（58.7%）
Female	93（41.3%）
Diagnoisis	
Acute lymphoblastic leukemia	56（24.9%）
Acute myeloid leukemia	93（41.4%）
Mixed lineage acute leukemia	1（0.4%）
Chronic myeloid leukemia	37（16.5%）
Myelodysplastic syndrome	23（10.2%）
Aplastic anemia	11（4.9%）
Non-Hodgkin lymphoma	3（1.3%）
Hemophagocytic lymphohistiocytosis	1（0.4%）
Viral infection*	
HBV	4（1.8%）
CMV	13（5.8%）
EB	3（1.3%）
Liver damage**	
Yes	53（23.6%）
No	172（76.4%）
Karnofsky scores	
≥90	136（60.4%）
＜90	89（39.6%）
SC source	
PBSC	103（45.8%）
PBSC+BM	56（24.9%）
PBSC+BM+UCB***	66（29.3%）
Donor	
HLA matched related donor	104（46.2%）
HLA haploidentical-related donor	66（29.3%）
HLA unrelated donor****	55（24.5%）
Second transplantation	0
Pretransplant disease status	
CR	111（49.3%）
PR	65（28.9%）
NR	1（0.4%）
PD	48（21.4%）
Conditioning regimen	
mBU/ CY	195（86.7%）
TBI/CY	19（8.4%）
BuCyFluATG	4（1.8%）
FluCy-ATG	7（3.1%）
GVHD prophylaxis	
CsA+MTX+ATG	107（47.6%）
CsA+MTX+MMF+ATG	80（35.6%）
CsA+MTX+MMF+ATG+anti-CD25 McAb	38（16.8%）
Outcome	
2-years OS	165（73.5%）

2-years DFS	157（69.8%）
2-years NRM	21（9.7%）
2-years RR	36（16.0%）

HBV hepatitis B virus, CMV cytomegalovirus, EB epstein-barr virus, SC stem cell, PBSC peripheral blood hematopoietic stem cell, BM bone marrow, UCB umbilical cord blood, HLA human leukocyte antigen, CR complete response, PR partial response, NR not reached, PD progressive disease, BU busulfan, CY cytoxan, TBI total body irradiation, Flu fludarabine, ATG anti-thymocyte globulin, GVHD graft versus host disease, CsA cyclosporin A, MTX methotrexate, MMF mycophenolate mofetil, McAb monoclonal antibody, OS overall survival, DFS disease-free survival, NRM non-relapse mortality, RR relapse rate.
* HBV infection is diagnosed if HBsAg, HBeAg, and HBcAb test positive or HBsAg, HBeAb, and HBcAb test positive or only HBcAb test positive. CMV/EB infection is diagnosed if CMV/EB IgM(+) or CMV/EB PCR(+).
** Liver damage is diagnosed if transaminase >2.5, upper limit of normal, or serum bilirubin>1.5, upper limit of normal.
*** UCB played a role in hematopoietic reconstruction rather than major graft in our study.
**** Unrelated donor donors only choose the one who was high-resolution HLA identical or incompatible with only one locus.

related factors, 55 (24.4%), 80 (35.6%), 255 (100%), 198 (88%), and 19 (8.4%) patients were with unrelated donors, HLA-mismatched donors, myeloablative conditioning regimen, an oral or high-dose Bu-based regimen, and high-dose TBI-based regimen. For patient and disease-related factors, 11 (49%), 89 (39.6), and 5 (2.2%) patients were older, had Karnofsky score below 90, and had advanced disease, respectively. The proportion of patients with active viral hepatitis was 1.8%(n=4), and that of those who used hepatotoxic drugs was 10.2%(n=23) in hepatic-related factors. High-risk factors were defined as two or more risk factors. Each patient has at least one risk factor for the development of VOD in our study, and 74.2%(n=167) of patients were at high risk of VOD.

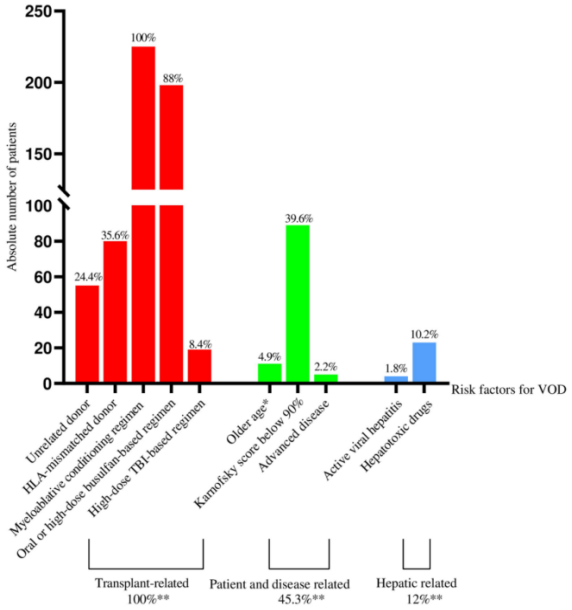

Figure 1. Number and incidence of risk factors for venous occlusive disease (n=225)
*Older age: older than 50 years old.
**The percentage of each type of risk factors, 100% of the patients had risk factors related to transplantation (n=225). Patients with patient and disease-related factors accounted for 45.3% (n=102) of cases. Patients with hepatic-related factors accounted for 12% (n=27) of subjects. 74.2% of patients were at high risk of VOD (n=167). *Older age: older than 50 years old. **The percentage of each type of risk factors, including transplant-related, patient and disease-related, and hepatic-related, which was calculated as the number of people with the corresponding type of risk factor divided by the total number of people.

Incidence of venous occlusive disease

Among 225 allo-HSCT patients, 2 (0.89%) cases developed VOD. One patient was a 48-year-old woman diagnosed with ALL who had achieved CR before transplantation. She had no liver damage before transplantation and tested negative for CMV, EBV, and HBV. She underwent HLA-mismatched allo-HSCT with TBI/CY conditioning regimen. During the conditioning, she experienced Grade 3 gastrointestinal bleeding and discontinued such medications as dalteparin dextran, LMWD, and UDCA. She continued receiving alprostadil infusion and supportive therapy. Nonetheless, she developed abdominal distension one day after transplantation, which rapidly worsened four days later. Ultrasound showed hepatomegaly, massive ascites, and bilirubin increased rapidly, meeting the diagnostic criteria for severe VOD. Unfortunately, the patient discontinued treatment due to financial constraints and died on the fifth day after transplantation.

The other VOD patient was a 38-year-old man who was diagnosed with AML and achieved CR1 before transplantation. He had a history of drug-induced liver injury, but had normal liver function before transplantation. His tests were negative for CMV, EBV, or HBV infection. He underwent HLA-matched 10/10 allo-HSCT with mBU/CY conditioning regimen. The patient with a high risk of VOD began to develop abdominal distension and abdominal pain at +34 days after transplantation, and the symptoms were progressively aggravated. At +36 days, the patient's abdominal circumference increased by six centimeters, and his body weight increased by three kilograms. Abdominal ultrasound demonstrated hepatomegaly and ascites. Combining clinical manifestations and relevant examination, the patient met the diagnostic criteria for mild late-onset VOD and was immediately treated with PGE1, dalteparin sodium, LMWD, UDCA, and hepato-protective drugs. At +57 days, the symptoms were relieved, and all VOD-related indicators returned to normal. There was no significant difference between these two VOD/SOS cases and the rest of the population (Table 2).

Table 2. Number and incidence of risk factors for patients (n=225)

Variable	Total(n=225)	VOD (n=2) (%)	No VOD (n=223) (%)
Transplant-related factors			
Unrelated donor	55 (24.4%)	0	55 (24.4%)
HLA-mismatched donor	80 (35.6%)	1 (0.4%)	79 (35.1%)
Myeloablative conditioning regimen	225 (100%)	2 (0.9%)	223 (99.1%)
Oral or high-dose busulfan-based regimen	198 (88%)	1 (0.4%)	197 (87.6%)
High-dose TBI-based regimen	19 (8.4%)	1 (0.4%)	18 (8.0%)
Patient and disease-related factors			
Older age*	11(4.9%)	0	11 (4.9%)
Karnofsky score below 90%	89 (39.6%)	0	89 (39.6%)
Advanced disease	5 (2.2%)	0	5 (2.2%)
Hepatic related			
Active viral hepatitis	4 (1.8%)	0	4 (1.8%)
Hepatotoxic drugs	23 (10.2%)	1 (0.4%)	22 (9.8%)

HLA, human leukocyte antigen.
*Older age: means older than 50 years old.

Adverse reactions

The primary adverse reaction involved in this prevention regimen was bleeding. According to CTCAE 3.0(20), we counted the occurrence of bleeding during treatment in all patients (Figure 2). The bleeding rate during treatment was 32.9%(n=74). Grade 1-2 bleeding events accounted for the majority (n=69; 93.2%), and four patients died due to bleeding, accounting for 1.8%(n=4) of the total. Four patients' fatal bleeding events were intracranial hemorrhage before hematopoietic reconstruction. The clotting indexes of the four patients were all within the normal range before bleeding; nonetheless, the platelet count was lower than 10×10^9/L. Other adverse reactions involved included allergic shock, diarrhea, dizziness, and headache, which were all judged as mild according to CTCAE 3.0 and tolerable after symptomatic and supportive treatment.

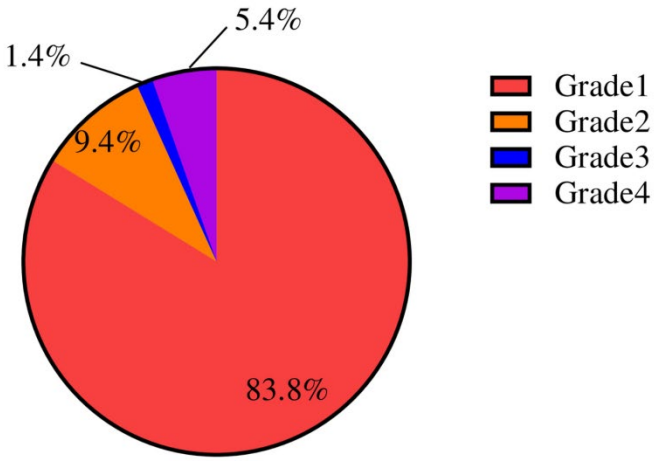

Figure 2. Degree in patients post-HSCT of bleeding（n=74）

The measurement of bleeding severity was characterized according to the CTCAE v.4. Grade 0: no bleeding. Grade 1: minor mucosal bleeding or petechiae not requiring packed red blood cells (PRBC). Grade 2: any bleeding episode requiring transfusion support of 1–2 units of PRBC/episode in 24 hours. Grade 3: any bleeding episode requiring transfusion of > 2 units of PBRC/episode but < 4 units or retroperitoneal bleeding. Grade 4: any bleeding causing hemodynamic instability in a 24h period or any central nervous system bleeding.

5. Discussion

The VOD is a common complication developed after transplantation, especially after allo-HSCT. With the increasing number of allo-HSCT worldwide, as well as the combination of cellular immunotherapy and various novel monoclonal antibodies, the incidence of VOD may be higher. At the same time, VOD generally progresses rapidly, is difficult to treat, is costly, and has a high mortality rate, which is closely related to poor prognosis. Therefore, major transplant centers pay assiduous attention to the prevention and treatment of VOD. In a large number of VOD-related studies, the search for safe and effective VOD prevention programs has been a hot spot.

Currently, there is no consensus on the optimal regimen for VOD prevention, and different drugs that may play a role have been developed as single or multiple-drug combination prophylaxis regimens, demonstrating different preventive effects. A meta-analysis of 135 studies included prospective cohort, retrospective, and randomized controlled studies that statistically analyzed the incidence of VOD following auto (autologous) and allo-HSCT demonstrated an overall VOD incidence of 13.7%(6). A large randomized cohort controlled study on 2572 patients treated with UDCA combined with low-dose heparin or PGE1 to prevent VOD after allo-HSCT resulted in an incidence of 3.4%(5).

Recently, a cohort study involving 1016 patients reported a 2.3% incidence of VOD following allo-HSCT prophylaxis with UDCA and low-dose heparin (13). An open-label phase 3 randomized controlled trial investigating defibrotide as VOD prophylaxis reported a 12% incidence of VOD (21). Furthermore, an 8.8% incidence of VOD was observed in 24 out of 271 patients undergoing reduced-intensity regimen (RIC) prior to allogeneic HSCT (22). A study evaluated 514 patients receiving heparin for VOD prophylaxis after allo-HSCT, giving a VOD rate of 2.7% (20). In a similar vein, a study conducted in China, which analyzed 797 patients undergoing auto- and allo-HSCT using dalteparin sodium combined with PGE1 for VOD prevention, reported a VOD incidence of 7.4% (23).

Overall, the incidence of VOD after allo-HSCT in these studies ranged from approximately 2.3% to 13.7%. Our retrospective clinical observation included 225 allo-HSCT patients from 2008-2022. All patients were uniformly treated with PGE1, dalteparin sodium, LMWD, and UDCA as a regimen to prevent VOD. Among the included patients, all exhibited at least one risk factor for VOD, accounting for 74.2% of high-risk VOD patients. Only two patients eventually developed VOD, one of whom experienced late-onset VOD. The female patient diagnosed with VOD had three risk factors, including a myeloablative conditioning regimen, oral or high-dose Bu-based regimen, and a high-dose TBI-based regimen. The risk factor for VOD in the man diagnosed with VOD was hepatotoxic drugs. Notably, the overall incidence of VOD was only 0.89%, markedly lower than the reported rates in

other studies.

The significantly lower incidence of VOD in our center suggested that the combination of four drugs in the prophylaxis regimen was effective (5,13,20). Pharmacologically, PGE1 acts as a vasodilation and reduces platelet hyperreactivity to achieve anticoagulation. The UDCA can avoid liver cell damage caused by VOD(24). Dalteparin sodium achieves anticoagulant effects based on its antithrombotic properties on the vessel wall or fibrinolytic system. In addition, LMWD increases plasma colloid osmotic pressure, expands blood volume, dilutes blood, and reduces blood viscosity. A wide array of clinical trials investigating the effectiveness of these four drugs for VOD prevention have yielded consistently positive results. The PGE1 has previously been evaluated for efficacy in some studies. A Korean study analyzed 467 patients who underwent auto or allotransplantation and found that although PGE1 alone did not reduce the incidence of VOD, the severity of developing VOD was significantly lower than that of the control group (25). Another study also demonstrated that the use of PGE1 to prevent VOD after allo-HSCT in children reduced the severity of VOD and associated mortality(26).

In a large cohort study by Jae-Ho Yoon et al., the combined use of PGE1 and UDCA significantly reduced the incidence of VOD after allo-HSCT to 4.7% (5). Furthermore, a prospective study evaluating dalteparin sodium combined with PGE1 as VOD prophylaxis after allo-HSCT pinpointed a reduction in VOD mortality (27). The UDCA has been evaluated in randomized controlled trials and meta-analyses, demonstrating a significant preventive effect on VOD after HSCT(28,29). In addition, a prospective phase II study evaluated the efficacy of LMWH monotherapy, illustrating that it was safe and effective for the prevention of VOD after auto- and allo-HSCT(30). Studies from China have also displayed that LMWD has a preventive impact on VOD after auto- and allo-HSCT(31). It is noteworthy that despite the low VOD incidence rate observed in our center, potential differences in race and drug sensitivity cannot be ruled out.

Apart from the remarkably low incidence of VOD, the specific bleeding events were also in the acceptable range. According to statistics, the bleeding rate during treatment was 32.9%, and the degree of bleeding was mainly Grade 1-2 bleeding (93.2%). The incidence of bleeding was the same as that reported in other literature, and the bleeding mortality rate during transplantation was rarely 1.8%, which was significantly lower than that reported in different literature (32,33). When the patient had severe thrombocytopenia and subcutaneous ecchymosis, we promptly discontinued VOD preventive drugs and provided symptomatic treatment for hemostasis. Nevertheless, due to inadequate platelet supply, the patient did not receive timely platelet transfusion for many consecutive days. Consequently, the bleeding events in our study may be closely related to the lack of timely platelet transfusion when the platelet count was extremely low, rather than using VOD preventive drugs since these patients had coagulation parameters in normal levels before bleeding.

From an economic perspective, the duration of the prevention regimen in this study was 3-4 weeks. The total cost of the drug ranges from about 8,500-11,000 RMB, approximately equivalent to 1,100-1,500 dollars. At present, China's national health insurance covers a minimum reimbursement rate of 30% for hospitalized patients, and the consensus of an international expert group suggested using defibrotide to prevent VOD (19). Therefore, the actual cost for patients is less than 8,000 RMB, equivalent to about 1,100 dollars. Defibrotide, which is currently recognized as a drug with a practical effect on VOD (18,21), recommends a therapeutic dose of 25 mg/kg/day for at least 21 days. The total cost of defibrotide can reach up to 520,000 RMB, approximately equivalent to 72,000 dollars when calculated based on a 60-kg patient. Therefore, our four-drug combination prophylaxis regimen is cost-effective. Moreover, defibrotide has not yet been widely adopted globally, and these four drugs that we have selected are available in hospitals that can carry out transplantation. That is why our prophylactic treatment is easier to promote.

The main limitation of this study is the limited number of VOD cases, which hindered further statistical analysis of risk factors in patients with VOD. Furthermore, another limitation is the absence of a control group because all patients who underwent HSCT have received this VOD prevention regimen since the inception of our transplant center. In the future, we will design prospective controlled clinical trials related to this protocol to further verify its efficacy and safety.

6. Conclusion

In conclusion, the results of our cohort study revealed that the four-drug combination regimen of PGE1, dalteparin sodium, LMWD, and UDCA was effective and safe for the prevention of VOD after allo-HSCT, with high-cost performance, which is worthy of promotion and application.

Acknowledgments

None.

Footnotes

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contribution: JPC and QG conceived the project; MLT and LY contributed to data collection. MLT, Le Ma and QG contributed to data analysis (statistics) and drafting manuscript. JPC, QG and LM contributed to the review of manuscript. All authors contributed to the article and approved the submitted version.

Funding: Not applicable.

Ethical Statements: The protocol was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Army Medical University before the initiation of the study [reference number: (B)KY202279]. The study was conducted following the ethical principles of the Declaration of Helsinki. All patients provided written informed consent for the use and publication of the clinical data.

References

1. de Lédinghen V, Villate A, Robin M, Decraecker M, Valla D, Hillaire S, et al. Sinusoidal obstruction syndrome. *Clin Res Hepatol Gastroenterol*. 2020;**44**(4):480-5. doi: 10.1016/j.clinre.2020.03.019. [PubMed: 32253162].
2. Özkan HA, Özkan SG. Hepatic veno-occlusive disease (sinusoidal obstruction syndrome) after hematopoietic stem cell transplantation in adult patients: Diagnosis, incidence, prophylaxis, and treatment. *Transfus Apher Sci.* 2022;**61**(1):103372. doi: 10.1016/j.transci.2022.103372. [PubMed: 35101376].
3. Xia Y, Qin H, Yang J. Hepatic veno-occlusive disease development in the hematopoietic stem cell transplantation patients: incidence and associated risk factors, a meta-analysis. *Eur J Gastroenterol Hepatol.* 2021;**33**(6):872-84. doi: 10.1097/MEG.0000000000001802. [PubMed: 32639417].
4. Mohty M, Malard F, Abecassis M, Aerts E, Alaskar AS, Aljurf M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2016;**51**(7):906-12. doi: 10.1038/bmt.2016.130. [PubMed: 27183098].
5. Yoon JH, Min GJ, Park SS, Park S, Lee SE, Cho BS, et al. Incidence and risk factors of hepatic veno-occlusive disease/sinusoidal obstruction syndrome after allogeneic hematopoietic cell transplantation in adults with prophylactic ursodiol and intravenous heparin or prostaglandin E1. *Bone Marrow Transplant*. 2021;**56**(7):1603-13. doi: 10.1038/s41409-021-01215-y. [PubMed: 33526915].
6. Coppell JA, Richardson PG, Soiffer R, Martin PL, Kernan NA, Chen A, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. *Biol Blood Marrow Transplant*. 2010;**16**(2):157-68. doi: 10.1016/j.bbmt.2009.08.024. [PubMed: 19766729].
7. Hong CR, Choi Y, Oh J, Sunwoo J, Hong KT, Choi JY, et al. Pharmacokinetic analysis of continuous intravenous infusion of lipo-prostaglandin E1 As a prophylaxis of hepatic veno-occlusive disease after hematopoietic stem cell transplantation. *Blood*. 2016;**128**(22):2214. doi: 10.1182/blood.V128.22.2214.2214.
8. Gluckman E, Jolivet I, Scrobohaci ML, Devergie A, Traineau R, Bourdeau-Esperou H, et al. Use of prostaglandin E1 for prevention of liver veno-occlusive disease in leukaemic patients treated by allogeneic bone marrow transplantation. *Br J Haematol.* 1990;**74**(3):277-81. doi: 10.1111/j.1365-2141.1990.tb02583.x. [PubMed: 2159315].
9. Tay J, Tinmouth A, Fergusson D, Huebsch L, Allan DS. Systematic review of controlled clinical trials on the use of ursodeoxycholic acid for the prevention of hepatic veno-occlusive disease in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2007;**13**(2):206-17. Doi: 10.1016/j.bbmt.2006.09.012. [PubMed: 17241926].
10. Imran H, Tleyjeh IM, Zirakzadeh A, Rodriguez V, Khan SP. Use of prophylactic anticoagulation and the risk of hepatic veno-occlusive disease in patients undergoing hematopoietic stem cell transplantation: a systematic review and meta-analysis. *Bone Marrow Transplant*. 2006;**37**(7):677-86. doi: 10.1038/sj.bmt.1705297. [PubMed: 16489362].
11. Attal M, Huguet F, Rubie H, Huynh A, Charlet JP, Payen JL, et al. Prevention of hepatic veno-occlusive disease after bone marrow transplantation by continuous infusion of low-dose heparin: a prospective, randomized trial. *Blood*. 1992;**79**(11):2834–40. [PubMed: 1586733].
12. Or R, Nagler A, Shpilberg O, Elad S, Naparstek E, Kapelushnik J, et al. Low molecular weight heparin for the prevention of veno-occlusive disease of the liver in bone marrow transplantation patients. *Transplantation*. 1996;**61**:1067–71. doi: 10.1097/00007890-199604150-00014. [PubMed: 8623187].
13. Stutz L, Halter JP, Heim D, Passweg JR, Medinger M. Low Incidence of hepatic sinusoidal obstruction syndrome/veno-occlusive disease in adults undergoing allogenic stem cell transplantation with prophylactic ursodiol and low-dose heparin. *Bone Marrow Transplant*. 2022;**57**(3):391-8. doi: 10.1038/s41409-021-01546-w. [PubMed: 34980902].
14. Hao J, Deng L, Li Y. Effect of heparin combined with prostaglandin and compound Danshen on prevention of hepatic vein obstruction after hematopoietic stem cell transplantation. *Chongqing Med*. 2014;**13**:1540-2.
15. Robitaille N, Lacroix J, Alexandrov L, Clayton L, Cortier M, Schultz KR, et al. Excess of veno-occlusive disease in a randomized clinical trial on a higher trigger for red blood cell transfusion after bone marrow transplantation: a Canadian blood and marrow transplant group trial. *Biol Blood Marrow Transplant.* 2013;**19**(3):468-73. doi: 10.1016/j.bbmt.2012.12.002. [PubMed: 23220014].
16. CHS, CMA. The consensus of allogeneic hematopoietic transplantation for hematological diseases in China (2014)--indication, conditioning regimen and donor selection. *Zhonghua Xue Ye Xue Za Zhi.* 2014;**35**(8):775-80. doi: 10.3760/cma.j.issn.0253-2727.2014.08.029. [PubMed: 25152138].
17. SCAG, CSH, CMA. Chinese consensus of allogeneic hematopoietic stem cell transplantation for hematological disease (Ⅲ) -acute graft-versus-host disease (2020). *Zhonghua Xue Ye Xue Za Zhi.* 2020;**9**(7):529-36. doi: 10.3760/cma.j.issn.0253-2727.2020.07.001. [PubMed: 32549120].
18. Bonifazi F, Barbato F, Ravaioli F, Sessa M, Defrancesco I, Arpinati M, et al. Diagnosis and treatment of VOD/SOS after allogeneic hematopoietic stem cell transplantation. *Front Immunol*. 2020;**11**:489. doi: 10.3389/fimmu.2020.00489. [PubMed: 32318059].
19. Mohty M, Malard F, Abecasis M, Aerts E, Alaskar AS, Aljurf M, et al. Prophylactic, preemptive, and curative treatment for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a position statement from an international expert group. *Bone Marrow Transplant*. 2020;**55**(3):485-95. doi: 10.1038/s41409-019-0705-z. [PubMed: 31576023].
20. Sola M, Bhatt V, Palazzo M, Cavalier KE, Devlin SM, Maloy M, et al. Low-dose unfractionated heparin prophylaxis is a safe strategy for the prevention of hepatic sinusoidal obstruction syndrome after myeloablative adult allogenic stem cell transplant. *Bone Marrow Transplant.* 2022;**57**(7):1095-100. doi: 10.1038/s41409-022-01689-4. [PubMed: 35477992].
21. Corbacioglu S, Cesaro S, Faraci M, Valteau-Couanet D, Gruhn B, Rovelli A, et al. Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. *Lancet.* 2012;**379**(9823):1301-9. doi: 10.1016/S0140-6736(11)61938-7. [PubMed: 22364685].
22. Tsirigotis PD, Resnick IB, Avni B, Grisariu S, Stepensky P, Or R, et al. Incidence and risk factors for moderate-to-severe veno-occlusive disease of the liver after allogeneic stem cell transplantation using a reduced intensity conditioning regimen. *Bone Marrow Transplant.* 2014;**49**(11):1389-92. doi:

10.1038/bmt.2014.168. [PubMed: 25068424].
23. Qin CJ, Liu LJ, Zhang ZM, Luo L, Lai YR, Li QC. A clinical analysis of hepatic veno-occlusive disease after hematopoietic stem cell transplantation. *Zhonghua Nei Ke Za Zhi*. 2018;**57**(7):483-6. doi: 10.3760/cma.j.issn.0578-1426.2018.07.003. [PubMed: 29996265].
24. Ohashi K, Tanabe J, Watanabe R, Tanaka T, Sakamaki H, Maruta A, et al. The Japanese multicenter open randomized trial of ursodeoxycholic acid prophylaxis for hepatic veno-occlusive disease after stem cell transplantation. *Am J Hematol.* 2000;**64**(1):32-8. doi: 10.1002/(sici)1096-8652(200005)64:1<32::aid-ajh6>3.0.co;2-n. [PubMed: 10815785].
25. Lee SH, Yoo KH, Sung KW, Koo HH, Kwon YJ, Kwon MM, et al. Hepatic veno-occlusive disease in children after hematopoietic stem cell transplantation: incidence, risk factors, and outcome. *Bone Marrow Transplant.* 2010;**45**(8):1287-93. doi: 10.1038/bmt.2009.349. [PubMed: 20010866].
26. Song JS, Seo JJ, Moon HN, Ghim T, Im HJ. Prophylactic low-dose heparin or prostaglandin E1 may prevent severe veno-occlusive disease of the liver after allogeneic hematopoietic stem cell transplantation in Korean children. *J Korean Med Sci*. 2006;**21**(5):897-903. doi: 10.3346/jkms.2006.21.5.897. [PubMed: 17043426].
27. Kumar S, Deleve LD, Kamath PS, Tefferi A. Hepatic veno-occlusive disease/sinusoidal obstruction syndrome after hematopoietic stem cell transplantation for thalassemia major: incidence, management, and outcome. *Bone Marrow Transplant*. 2021;**56**(7):1635-41. doi: 10.1016/j.bbmt.2015.09.024.
28. Ruutu T, Juvonen E, Remberger M, Remes K, Volin L, Mattsson J, et al. Improved survival with ursodeoxycholic acid prophylaxis in allogeneic stem cell transplantation: long-term follow-up of a randomized study. *Biol Blood Marrow Transplant.* 2014;**20**(1):135-8. doi: 10.1016/j.bbmt.2013.10.014. [PubMed: 24141008].
29. Dalle JH, Giralt SA. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: risk factors and stratification, prophylaxis, and treatment. Biol *Blood Marrow Transplant*. 2016;**22**(3):400-9. doi: 10.1016/j.bbmt.2015.09.024. [PubMed: 26431626].
30. Forrest DL, Thompson K, Dorcas VG, Couban SH, Pierce R. Low molecular weight heparin for the prevention of hepatic veno-occlusive disease (VOD) after hematopoietic stem cell transplantation: a prospective phase II study. *Bone Marrow Transplant*. 2003;**31**(12):1143-9. doi: 10.1038/sj.bmt.1704087. [PubMed: 12796794].
31. FU L, Zhang W, Wang J. Prophylaxis of hepatic veno-occlusive disease after HSC transplantation with lipo-prostaglandin E1 plus dextran 40. *Med J Chin People's Lib Army*. 2008;**33**(7):889-91.
32. Labrador J, Lopez-Anglada L, Perez-Lopez E, Lozano FS, Lopez-Corral L, Sanchez-Guijo FM, et al. Analysis of incidence, risk factors and clinical outcome of thromboembolic and bleeding events in 431 allogeneic hematopoietic stem cell transplantation recipients. *Haematologica*. 2013;**98**(3):437-43. doi: 10.3324/haematol.2012.069559. [PubMed: 22899581].
33. Richardson PG, Riches ML, Kernan NA, Brochstein JA, Mineishi S, Termuhlen AM, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood*. 2016;**127**(13):1656-65. doi: 10.1182/blood-2015-10-676924. [PubMed: 26825712].