Editorial

Biomarkers for hepatic sinusoidal obstruction syndrome after hematopoietic cell transplantation

Je-Hwan Lee, M.D., Ph.D.

Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Hepatic sinusoidal obstruction syndrome (SOS), previously known as veno-occlusive disease, is one of the major complications during the early period after hematopoietic cell transplantation (HCT). The disease is caused by toxic injury of conditioning therapy to sinusoidal endothelial cells, initiating the clinical symptoms of hyperbilirubinemia, tender hepatomegaly, ascites, and weight gain. The incidence and severity of SOS have decreased significantly in recent years, but fatal outcomes of SOS are still observed in clinical practice [1]. SOS has no diagnostic biomarkers, and its diagnosis is depends on clinical criteria. Moreover, the severity of SOS is defined retrospectively, based on the clinical outcome. Single or combinations of parameters have been investigated for their potential as biomarkers for the diagnosis or prognosis of SOS.

Genetic polymorphisms were associated with the occurrence of SOS in several studies. Glutathione S-transferase (GST) is a family of phase II detoxification enzymes that catalyze the conjugation of glutathione to various xenobiotics. Polymorphisms of GST genes have significant influence on the pharmacokinetic parameters of busulfan, which is commonly used in conditioning regimens for HCT. Of 114 patients with β-thalassemia majorundergoing HCT, those with *GSTM1*-null genotypes had significantly higher incidences of hepatic SOS compared with those with *GSTM1*-present genotype (46.5% vs. 18.3%; *P*=0.001) [2]. Heparanase (HPSE) is an enzyme that cuts the saccharide chains of heparin sulfate proteoglycans, interacts with binding proteins, and activates signaling components. Genetic polymorphisms of *HPSE* (rs4693608 and rs4364254) were significantly associated with the incidence of hepatic SOS in 160 children undergoing allogeneic HCT for malignant and non-malignant diseases [3]. Methylenetetrahydrofolate reductase (MTHFR) is one of the main regulatory enzymes involved in homocysteine metabolism. The C677T and A1298C gene polymorphisms in *MTHFR* correlate with MTHFR enzyme activity. *MTHFR* haplotype 677CC/1298CC was significantly associated with the development of hepatic SOS in 62 adult patients with acute myeloid leukemia receiving myeloablative conditioning regimen (busulfan plus cyclophosphamide) for HCT [4]. Interleukin (IL)-1 is involved in the pathophysiology of graft-versus-host diseases, likely through the initiation and maintenance of host tissue inflammation as well as donor cell inflammatory response. IL-1β is a pro-inflammatory cytokine secreted by epithelial tissues early in the inflammatory response. The association of both patient and donor genotypes at the IL-1β - 511 C/T polymorphic site with hepatic SOS and mortality was investigated in 76 children undergoing HLA matched myeloablative allogeneic HCT. The study suggested that the donor, rather than the host, genotype at the IL-1β - 511 polymorphic site might be associated with higher risk of severe SOS after HLA matched allogeneic HCT [5].

The proposed hypothesis of SOS pathophysiology after HCT includes (a) damage of sinusoidal endothelial cells

during conditioning therapy, resulting in the appearance of gaps in the sinusoidal barrier, (b) penetration of red blood cells, leukocytes, and cellular debris into the space of Disse, detaching the endothelial lining, and (c) downstream embolization of the sloughed sinusoidal lining cells, leading to obstruction of the sinusoidal flow [1]. Endothelial injury after conditioning therapy triggers a hypercoagulable state, and various hemostatic parameters have been reported as useful laboratory markers for hepatic SOS after HCT. The decrease in protein C and antithrombin on day 7 after HCT was associated with the development of moderate to severe SOS in 50 patients undergoing allogeneic HCT [6]. Hemostatic parameters were measured at five post-transplant time points in 115 patients (50 of whom developed SOS), and plasminogen activator inhibitor-1 (PAI-1) was identified as a diagnostic marker and a predictor of the severity of SOS after allogeneic HCT [7]. A quantitative mass spectrometry-based proteomics approach was used to identify candidate biomarkers of SOS by comparing plasma pooled from 20 patients with SOS and 20 without SOS, and six candidate proteins were selected. The diagnostic potentials of these six proteins and five other proteins selected from the literature were evaluated in samples from 80 patients. L-Ficolin, hyaluronic acid, and vascular cell adhesion molecule-1 stratified patients at risk for SOS as early as the day of HCT [8].

In this issue of the **Blood Research**, Yeom *et al.* [9] evaluated the association of secondary iron overload with hepatic SOS in animal models of allogeneic HCT with irradiation. Higher levels of lipid hyperoxide (as reactive oxygen species) were observed with higher cumulative iron dose, and the pathologic score of SOS was associated with liver iron content, suggesting that secondary iron overload might induce SOS after HCT with irradiation. Iron overload as a risk factor of SOS after HCT has also been suggested in other studies [1]. Although the mechanism for the association of iron overload with SOS remains poorly understood, hydroxyl radicals (as powerful pro-oxidants) formed by iron-mediated catalysis may attack cellular membrane lipids, proteins, and nucleic acids, thus causing hepatic cellular inflammation and fibrosis. In this situation, high-dose conditioning regimens with chemotherapy and/or irradiation rapidly deplete intracellular anti-oxidants such as glutathione, leading to significant oxidative damages to the liver. Serum ferritin, although not specific, has been used as a measure of iron stores, and several studies reported pre-transplant ferritin level as a risk factor of SOS [10]. Can we use serum ferritin as a biomarker for SOS after HCT? Biomarkers should display objective and quantifiable characteristics of biological processes. If a biomarker is proven to predict clinical outcomes consistently and accurately by solid scientific evidence, it can be a clinically meaningful endpoint. For serum ferritin to be established as a biomarker for SOS, further studies are needed to determine the optimal cutoff value (1,000 ng/mL in many

studies) and to evaluate the usefulness of prophylactic and therapeutic measures with iron chelating agents. Liver magnetic resonance imaging (MRI) scan might be a better biomarker for SOS than serum ferritin in regard to accurate assessment of iron overload.

Hepatic SOS is a potentially life-threatening complication of HCT and is responsible for a significant proportion of non-relapse mortality during the early post-transplant period. Biomarkers for the diagnosis and prognosis of SOS have not yet been established and potential biomarkers for SOS including genetic polymorphisms (*GSTM1*, *HPSE*, *MTHFR*, *IL-1β*), coagulation parameters (protein C, antithrombin, PAI-1), iron overload markers (ferritin, liver MRI), and others (L-Ficolin, hyaluronic acid, VCAM-1) have been assessed. The identification of biomarkers for SOS will contribute to the improvement of post-transplant outcomes through reduction of the incidence and severity of hepatic SOS.

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;50:781-9.

2. Srivastava A, Poonkuzhali B, Shaji RV, et al. Glutathione S-transferase M1 polymorphism: a risk factor for hepatic venoocclusive disease in bone marrow transplantation. Blood 2004;104:1574-7.

3. Seifert C, Wittig S, Arndt C, Gruhn B. Heparanase polymorphisms: influence on incidence of hepatic sinusoidal obstruction syndrome in children undergoing allogeneic hematopoietic stem cell transplantation. J Cancer Res Clin Oncol 2015;141:877-85.

4. Efrati E, Zuckerman T, Ben-Ami E, Krivoy N. MTHFR C677T/A1298C genotype: a possible risk factor for liver sinusoidal obstruction syndrome. Bone Marrow Transplant 2014;49:726-7.

5. Elbahlawan L, McArthur J, Quasney MW, et al. Association of IL-1β -511 polymorphism with severe veno-occlusive disease in pediatric-matched allogeneic hematopoietic stem cell transplantation. J Pediatr Hematol Oncol 2012;34:175-9.

6. Lee JH, Lee KH, Kim S, et al. Relevance of proteins C and S, antithrombin III, von Willebrand factor, and factor VIII for the development of hepatic veno-occlusive disease in patients undergoing allogeneic bone marrow transplantation: a prospective study. Bone Marrow Transplant 1998;22:883-8.

7. Lee JH, Lee KH, Lee JH, et al. Plasminogen activator inhibitor-1 is an independent diagnostic marker as well as severity predictor of hepatic veno-occlusive disease after allogeneic bone marrow transplantation in adults conditioned with busulphan and cyclophosphamide. Br J Haematol 2002;118:1087-94.

8. Akil A, Zhang Q, Mumaw CL, et al. Biomarkers for diagnosis and prognosis of sinusoidal obstruction syndrome after hematopoietic cell transplantation. Biol Blood Marrow Transplant 2015;21:1739-45.

9. Yeom MY, Kim YJ, Chung NG, et al. Hepatic veno-occlusive disease may develop in secondary iron overloaded mice after allogeneic hematopoietic stem cell transplantation with total body irradiation. Blood Res 2015;50:140-6.

10. Maradei SC, Maiolino A, de Azevedo AM, Colares M, Bouzas LF, Nucci M. Serum ferritin as risk factor for sinusoidal obstruction syndrome of the liver in patients undergoing hematopoietic stem cell transplantation. Blood 2009;114:1270-5.