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Review Article

Mechanism of Oxaliplatin-Induced Sinusoidal Obstruction Syndrome along with Therapeutic Strategy

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ABSTRACT

Oxaliplatin is a backbone drug of many regimens for colorectal cancer and colorectal liver metastasis. Most frequent adverse effects in patients with oxaliplatin-based chemotherapy include the peripheral neuropathy, liver dysfunction, splenomegaly, and thrombocytopenia. Recently, the author described a thorough review of the literature on oxaliplatin-induced hepatic complications focusing on Sinusoidal Obstruction Syndrome (SOS), Nodular Regenerative Hyperplasia (NRH), and Focal Nodular Hyperplasia (FNH) in patients with colorectal cancer and colorectal liver metastasis and emphasized the Liver Stiffness Measurement (LSM), elasticity as a novel predictor reflecting splenomegaly by elastography. The underlying mechanisms of oxaliplatin-induced SOS include the activation of inflammation-related pathways, the activated cellular hypoxia, the upregulation of genes involved in coagulation such as Plasminogen Activator Inhibitor-1 (PAI-1) and Von Willebrand Factor (VWF), and the upregulation of angiogenesis-related genes. In this article, current knowledge and trends of the underlying mechanism of oxaliplatin-induced SOS have been reviewed. Additionally, the potential therapies for oxaliplatin-based chemotherapy have been also described. The underlying mechanisms of oxaliplatin-induced SOS showed liver fibrosis, platelet aggregation and adhesion, inflammatory damage, and oxidative stress. The evidence provided that oxidative stress plays a significant role in the pathogenesis of oxaliplatin-induced acute liver injury. Regarding the therapeutic strategy for oxaliplatin-induced SOS, bevacizumab, Vascular Endothelial Growth Factor (VEGF) inhibitor may contribute to the protection of the development of oxaliplatin-induced SOS. Based on the evidence, Glutathione (GSH) might be a potential treatment for oxaliplatin-induced SOS.

Keywords: Mechanism of oxaliplatin-induced SOS; Oxidative stress; Oxaliplatin-induced acute liver injury; Glutathione; Bevacizumab

INTRODUCTION

Recently, the author described a thorough review of the literature on oxaliplatin-induced hepatic complications focusing on SOS, NRH, and FNH in patients with colorectal cancer and colorectal liver metastasis and emphasized LSM, elasticity as a novel predictor reflecting splenomegaly by elastography [1,2]. The LSM exhibits liver elasticity, namely fibrotic status. Most frequent adverse effects in patients with oxaliplatin-based chemotherapy are the peripheral neuropathy, liver dysfunction, splenomegaly, and thrombocytopenia [3]. The mechanism of oxaliplatin-induced SOS includes the activation of inflammation-related pathways, the activated cellular hypoxia, the upregulation of genes involved in coagulation such as PAI-1 and VWF, and the upregulation of angiogenesis-related genes [4,5]. In this article, the current knowledge and trends of the underlying mechanisms of oxaliplatin-induced SOS have been reviewed. Additionally, the author has described the potential therapeutic strategy for oxaliplatin-based chemotherapy.

LITERATURE REVIEW

Clinical and pathological manifestations in oxaliplatin-induced SOS

Recently, the author described a thorough review of the literature on oxaliplatin-induced hepatic complications focusing on SOS, NRH, and FNH in patients with colorectal cancer and colorectal liver metastasis and strengthened LSM, elasticity as

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a novel indicator reflecting splenomegaly by elastography [1,2]. Most frequent adverse effects in patients with oxaliplatin-based chemotherapy are the peripheral neuropathy, liver dysfunction, splenomegaly, and thrombocytopenia. While it is well known that a relationship between hepatic steatosis and SOS has been shown in the oxaliplatin-based chemotherapy [3]. The author previously described an association between chronic liver disease (NAFLD/NASH and HCV infection) and atherosclerosis emphasizing the inflammation as common pathway [6]. Oxaliplatin-induced SOS is a chronic process from hepatic sinusoidal endothelial dysfunction to liver fibrosis leading to portal hypertensin and splenomegaly. In result, thrombocytopenia has been developed [7]. It has been also suggested that oxaliplatin-induced SOS lasts for several months accompanied by NRH, splenomegaly, and thrombocytopenia [8]. The previous study described that the patients with splenomegaly had significantly more severe thrombocytopenia in comparison with patients without splenomegaly [9].

The underlying mechanism in oxaliplatin-induced SOS

Based on the analysis of the gene expression profiles, the previous study indicated that genes of upregulation of oxidative stress, inflammatory injury, liver fibrosis/hepatic stellate cell activation, and platelet aggregation and adhesion have been suggested in oxaliplatin-related SOS in humans [4]. Zhu et al. indicated that pathogenesis of oxaliplatin-induced SOS may include oxidative stress, inflammatory injury, liver fibrosis, platelet aggregation and adhesion, and some other genes associated with the destruction of hepatic vascular homeostasis and the formation of an oxygen-deficient environment [8]. The mechanisms of oxaliplatin-induced SOS also include the activation of inflammation-related pathways, the activated cellular hypoxia, the upregulation of genes involved in coagulation such as PAI-1 and VWF, and the upregulation of angiogenesis-related genes including VEGF-A, VEGF-C, and VEGF-D [4,5]. Three mechanisms for sinusoidal damage induced by oxaliplatin have been also suggested in detail [3]. Firstly, oxaliplatin causes increased porosity of the sinusoidal endothelium and increased cellular fenestrations, stimulated release of free radical and depletion of glutathione transferase, and increased MMP 2-9 have been observed. In result, the migration of the erythrocyte into the Disse space and the perisinusoidal fibrosis have been shown. The hypoxia condition induced the increased angiogenic factors such as vascular endothelial factor, PAI-1, free radicals and MMP 2-9, and perisinusoidal fibrosis. In more detailed, oxaliplatin-induced Sinusoidal Endothelial Cell (SEC) damage causes a coagulation-promoting status in the blood sinus by the activated Metalloproteinases (MMPs). In result, the platelets are aggregated and extravasated platelets secrete growth factors including thromboxane A2 (TXA2), VEGF, TGF-β, and PAI-1 in the central vein [8]. It is known that oxaliplatin induce platelet aggregation and adhesion by the MMPs and growth factors leading to the aggravation of hepatic sinusoidal obstruction [8]. Secondly, NRH easily tends to develop by the chronic hypoxia of the centrilobular areas. Finally, oxaliplatin generates the obliteration of blood capillaries and areas of parenchymal destruction [3].

Platelet aggregation and adhesion in oxaliplatin-induced SOS

It is known that a close association between SOS in patients with Colorectal Liver Metastasis (CRLMs) receiving oxaliplatin chemotherapy and thrombocytopenia and platelet aggregation around the central vein [7]. Regarding animal study, previous report suggested the extravasated platelet aggregation of the liver may be involved in the development of oxaliplatin-induced SOS [10]. Pathological features showed increased platelet aggregation around the central vein in patients with liver metastases receiving oxaliplatin-based chemotherapy suggesting that platelets might be involved in alterations of the sinusoidal endothelial cells [8,10]. In the recent review article, it has been suggested that oxaliplatin-based injury to hepatic sinusoids can attract and activate platelets [11]. It is known that VWF is a multimetric procoagulant plasma glycoprotein mediated platelet adhesion along the endothelium [12]. Endothelial cell function accompanied by hypertension has been most widely quantified by evaluating Flow-Mediated Vasodilation (FMD) examination or measuring plasma VWF level providing that these methods might be useful markers to identify patients at risk of future cardiovascular events [13]. The author previously described an association between VWF level and FMD test reflecting systemic endothelial function in patients without hepatic-associated disease [14]. Whereas several studies have provided the independent prognostic values of VWF-Ag suggesting that a correlation between elevated VWF levels and poorer survival has been shown in patients with colorectal cancer [12]. According to the previous report, Ultra-Large (UL) Multimers, UL-VWF, released upon EC stimulation, is the most biologically active [12]. It is suggested that SOS is caused by the sinusoidal endothelial cell damage leading to the release of Unusual-Large Von Willebrand Factor Multimers (UL-VWFMs) from endothelial cell [15]. Results provided that many microthrombi were positive for both anti-IIb/IIIa and anti-VWF antibodies in immunohistochemical analysis of liver specimens in patients with SOS. They suggested that increased plasma UL-VWFM levels might be by damage to endothelial cells as a result of oxaliplatin-based chemotherapy [15].

Liver fibrosis in oxaliplatin-induced SOS

The author has previously described the oxaliplatin-induced SOS emphasizing the LSM as a novel predictor by elastography [2]. The LSM exhibits liver elasticity, namely fibrotic status. Based on the comparison between LSM and splenic volume index, recent study indicated that measurement of elasticity using shear wave elastography may noninvasively predict oxaliplatin-induced hepatotoxicity [16]. Furthermore, based on the evidence, LSM using US elastography and MR elastography may noninvasively be a promising indicator for SOS as previously described [2].

Inflammatory damage in oxaliplatin-induced SOS

The liver inflammation is regarded as a main driving factor of liver tissue toxicity by oxaliplatin chemotherapy [8]. The levels of TNF-α、IFN-γ, and IL-17 were significantly elevated in the NAFLD mice following oxaliplatin therapy, showing the occurrence of hepatocyte damage *via* triggering strong cytotoxic immunity and apoptosis [17].

Oxidative stress in oxaliplatin-induced SOS

Though the mechanism of oxaliplatin-induced liver damage has not been elucidated, it is known that oxaliplatin-induced liver toxicity may be associated with oxidative stress [18-20]. The previous study indicated that the expression levels of oxidative stress-associated genes such as Metallothionein 1 (Mt1), Heme Oxygenase 1 (HO1), and Superoxide Dismutase 3 (SOD3) were upregulated suggesting that oxidative stress may play an important role in oxaliplatin-induced SOS that can be prevented by the administration of the antioxidant treatment [19]. Previous investigations have focused

on the study of chronic liver damage caused by long-term use of oxaliplatin-based chemotherapy. Regarding Acute Liver Injury (ALI), the study significantly showed the increased levels of MDA and GSH after oxaliplatin-treated cases. Meanwhile SOD and GSH peroxidase levels were reduced after oxaliplatin withdrawal [5]. The evidence provided that oxidative stress plays a significant role in the pathogenesis of oxaliplatin-induced acute liver injury indicating that GSH therapy can decreased oxaliplatin-induced ALI by suppressing oxidative stress in the liver [5]. Another study demonstrated that oxaliplatin causes ALI in NAFLD mice showing that increased levels of ROS and MDA and reduced the levels of SOD and GSH peroxidase in the liver of NAFLD mice [17]. While previous study showed that oxaliplatin-induced oxidative stress causes toxicity in rat liver mitochondria indicating that oxidative stress serves as a significant role in the mitochondrial toxicity of oxaliplatin [21]. Recent study showed the prediction for oxaliplatin-induced liver injury using patient-derived liver organoids suggesting that liver injury associated with oxaliplatin-induced liver damage may be caused by mitochondrial oxidative damage [20].

Therapeutic strategy for oxaliplatin-induced SOS

Bevacizumab, as the representative anti-angiogenic agent has been developed as an anti-VEGF human monoclonal antibody and has contributed to the effective treatment for the colorectal cancer. Whereas the angiogenesis inhibitors mainly effect on the vascular endothelial cell and induce vasoconstriction due to the reduction of the vasodilators such as NO and PGI_2 and increased ET-1 leading to the vascular endothelial dysfunction and plaque formation. In result, drug-induced atherosclerosis including hypertension and thrombosis/atherosclerosis has been developed [22,23]. The clinical study described that the addition of bevacizumab, VEGF inhibitor, to oxaliplatin-based chemotherapy decreased the frequency of splenic enlargement and the development of thrombocytopenia [24]. With regards to the animal study, the previous study provided the evidence on the protection effect of VEGF-inhibition against the development of oxaliplatin induced SOS in mice [25]. Though bevacizumab, VEGF inhibitor may induce atherosclerosis status, it may contribute to the protection of the development of SOS. Further study is needed to verify for the optimal therapy of cancer and the effective intervention as previously described [2]. Recent study revealed that induction chemotherapy combined with a VEGF antibody showed a better pathological response of the primary tumor and a longer recurrence-free survival compared to that with Epidermal Growth Factor Receptor (EGFR) therapy [26]. Regarding GSH therapy, it could decrease the oxaliplatin-induced elevated MDA level, but it had no effect on SOD level in the liver [5]. Using oxaliplatin-induced ALI model, previous study revealed that oxidative stress serves as an important role in oxaliplatin-induced ALI, showing that GSH-based hepatoprotective therapy may inhibit oxidative stress and alleviate oxaliplatin-induced ALI [5]. While another study provided that treatment using exogenous GSH significantly decreased the levels of ROS and MDA [17]. Therapeutics in NAFLD mice with exogenous GSH alleviated oxaliplatin-induced liver damage by ameliorating oxaliplatin-aggravated hepatic oxidative stress and inflammation [17]. Based on these results, it is plausible that GSH drug might be a potential therapy for oxaliplatin-induced SOS.

DISCUSSION

The mechanism of oxaliplatin-induced SOS includes the activation of inflammation-related pathways, the activated cellular hypoxia, the upregulation of genes involved in coagulation such as PAI-1 and VWF, and the upregulation of angiogenesis-related genes including VEGF-A, VEGF-C, and VEGF-D [4,5]. In this article, the current knowledge and trends of the underlying mechanisms of oxaliplatin-induced SOS have been reviewed. Additionally, the author has described the potential therapeutic strategy for oxaliplatin-based chemotherapy setting. Regarding platelet aggregation and adhesion, oxaliplatin-induced Sinusoidal Endothelial Cell (SEC) damage causes a coagulation-promoting status in the blood sinus by the activated MMPs. In result, the platelets are aggregated and extravasated platelets secrete growth factors including TXA2, VEGF, TGF-β, and PAI-1 in the central vein [8]. It is known that oxaliplatin induces platelet aggregation and adhesion by the MMPs and growth factors leading to the aggravation of hepatic sinusoidal obstruction [8]. Concerning liver fibrosis, the author has previously described the oxaliplatin-induced SOS emphasizing the LSM as a novel predictor by elastography [2]. Based on the comparison between LSM and splenic volume index, recent study indicated that measurement of elasticity using shear wave elastography may noninvasively predict oxaliplatin-induced hepatotoxicity [16]. Furthermore, based on the evidence, LSM using US elastography and MR elastography may noninvasively be a promising indicator for SOS as previously described [2]. Regarding inflammatory damage, the levels of TNF-α、IFN-γ, and IL-17 were significantly increased in the NAFLD mice following oxaliplatin therapy, showing the occurrence of hepatocyte damage *via* triggering strong cytotoxic immunity and apoptosis [17]. Previous investigations have focused on the study of chronic liver damage caused by long-term use of oxaliplatin-based chemotherapy. Regarding ALI, the evidence provided that oxidative stress plays a significant role in the pathogenesis of oxaliplatin-induced ALI showing increased levels of MDA and GSH [5]. Another study demonstrated that oxaliplatin causes ALI in NAFLD mice showing that increased levels of ROS and MDA and reduced the levels of SOD and GSH peroxidase in the liver of NAFLD mice [17]. Regarding therapeutic strategy, though an association between bevacizumab, VEGF inhibitor, and atherosclerosis status has been indicated, it may contribute to the protection of the development and severity of SOS. Further study is needed to verify for the optimal therapy of cancer and the effective management as previously described [2]. Meanwhile GSH therapy could decrease the oxaliplatin-induced elevated MDA level, but it had no effect on SOD level in the liver [5]. Using oxaliplatin-induced ALI model, previous study revealed that oxidative stress serves as an important role in oxaliplatin-induced ALI, showing that GSH-based hepatoprotective therapy may inhibit oxidative stress and alleviate oxaliplatin-induced ALI [5]. While another study provided that therapeutics in NAFLD mice with exogenous GSH alleviated oxaliplatin-induced liver damage by ameliorating oxaliplatin-aggravated hepatic oxidative stress and inflammation [17]. Based on these results, it is plausible that GSH drug might be a potential therapy for oxaliplatin-induced SOS.

CONCLUSION

It is plausible that the underlying mechanisms of oxaliplatin-induced sinusoidal obstruction syndrome showed liver fibrosis, platelet aggregation and adhesion, inflammatory damage, and oxidative stress. The evidence provided that oxidative stress plays a significant role in the pathogenesis of oxaliplatin-induced acute liver injury. With regards to the therapeutic strategy for oxaliplatin-induced sinusoidal obstruction syndrome, bevacizumab may contribute to the protection of the development of oxaliplatin-

induced sinusoidal obstruction syndrome. Based on the evidence, glutathione might be a potential treatment for oxaliplatin-induced sinusoidal obstruction syndrome.

CONFLICTS OF INTEREST

Author declares that I have no conflicts of interest.

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