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Review Article

Oxaliplatin-Related Hepatic Sinusoidal Obstruction Syndrome: Updated Biological Pathway Analysis

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ABSTRACT

Oxaliplatin is a backbone drug of many regimens for colorectal cancer and colorectal liver metastasis. The author previously 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 Liver Stiffness Measurement (LSM) as a novel predictor by elastography, recently reviewed the mechanism of oxaliplatin-induced SOS along with potential therapeutic strategy. In this article, the current knowledge and trends of oxaliplatin-induced SOS along with updated biological pathway analysis have been reviewed. Additionally, an association between oxaliplatin-induced SOS and atherosclerotic status has been described. It is plausible that oxaliplatin-induced liver injuries may have the broad spectrum from acute liver injury to long-term liver complications such as NRH. Based on the evidence, gene expression profile revealed several biological pathways including oxidative stress, inflammation, hepatic fibrosis/Hepatic Stellate Cell (HSC) activation, coagulation, angiogenic, and hypoxic factor for oxaliplatin-induced SOS. In particular, inflammatory pathway is significantly upregulated, suggesting a main driving factor of hepatotoxicity by oxaliplatin chemotherapy and a close relationship between oxaliplatin-induced SOS and atherosclerosis. Similar to the association between chronic liver disease (NAFLD/NASH and HCV infection) and atherosclerosis, oxaliplatin-induced SOS may have both liver and systemic inflammation and lead to SOS-related atherosclerosis status. It may be significant to assess the vascular endothelial and smooth muscle cell function using Flow-Mediated Vasodilation (FMD) and Nitroglycerin-Mediated Vasodilation (NMD) procedures for the evaluation of SOS-related atherosclerosis condition in oxaliplatin-induced SOS setting.

Keywords: Oxaliplatin-induced SOS, Oxaliplatin-induced long-term liver complications, Gene expression profiling, Inflammation pathway, SOS-related atherosclerosis

INTRODUCTION

Oxaliplatin is an essential component of many chemotherapies protocol for colorectal cancer and colorectal liver metastasis. Oxaliplatin therapy contributes to the reduction of tumor progression by suppressing synthesis of DNA in cancer cells and impairing cell division and growth [1]. While oxaliplatin-induced hepatic complications including SOS, NRH, and FNH have emerged in patients with colorectal cancer and colorectal liver metastasis [2]. The author recently described a review of the literature on LSM as a novel predictor by elastography and mechanism of oxaliplatin-induced SOS along with potential therapeutic intervention [3,4]. The liver inflammation is regarded as a main driving factor of liver tissue toxicity by oxaliplatin chemotherapy [5]. It is known that the incidence of atherosclerosis status in patients with cancer is very high due to the systemic inflammatory response and impaired vascular endothelial function caused by cancer cell infection and

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chemoradiotherapy [6]. The author previously described an association between chronic liver disease (NAFLD/ NASH and HCV infection) and atherosclerosis emphasizing the inflammation as common pathway [7]. This review outlines the current knowledge and trends of oxaliplatin-related SOS along with updated gene expression profile analysis. In addition, the author has discussed a relationship between oxaliplatin-induced SOS and atherosclerosis condition.

LITERATURE REVIEW

Mechanism of oxaliplatin-induced SOS

Zhu et al. indicated that pathogenesis of oxaliplatin-induced SOS may include some other genes associated with the destruction of hepatic vascular homeostasis and the formation of an oxygen-deficient environment [5]. 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 [8,9]. Puente et al. suggested three mechanisms for sinusoidal damage induced by oxaliplatin in detail [10]. Firstly, oxaliplatin causes increased porosity of the sinusoidal endothelium, stimulated release of free radical and depletion of glutathione transferase, and increased MMP 2-9, leading to the migration of the erythrocyte into the Disse space and the perisinusoidal fibrosis. In result the hypoxia condition has been produced, thereby NRH is tended to develop by the chronic hypoxia of the centrilobular areas. Furthermore hypoxia status induced the increased angiogenic factors such as vascular endothelial factor, PAI-1, free radicals and MMP 2-9, and perisinusoidal fibrosis. 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 [5]. Finally, the obliteration of blood capillaries and areas of parenchymal destruction have been generated by oxaliplatin treatment [10].

Oxaliplatin-induced nodular regenerative hyperplasia

Most frequent adverse effects in patients with oxaliplatin-based chemotherapy are liver dysfunction, peripheral neuropathy, splenomegaly, and thrombocytopenia [10]. It has been also suggested that oxaliplatin-induced SOS lasts for several months accompanied by NRH, splenomegaly, and thrombocytopenia [5]. The previous study described that the patients with splenomegaly had significantly more severe thrombocytopenia in comparison with patients without splenomegaly [11]. The previous study suggested that oxaliplatin-induced SOS may sometimes manifest as new local liver lesion, namely focal chemotherapy-induced hepatopathy, mimicking liver metastasis [12,13]. NRH is regarded as the secondary lesion to SOS-induced alterations in intrahepatic blood flow, resulting in atrophic hypoperfused areas [14]. Previous report described that he changes of SOS and related local disturbance in hepatic perfusion may cause the occurrence of NRH suggesting that this disturbance may also lead to the development of FNH [15,16]. Regenerative nodules include monoacinar regenerative nodules, namely NRH and multiacinar regenerative nodules, known as FNH-like lesions. NRH showed characteristic nodules usually > 3 mm in size, while FNH-like lesions may represent regenerative nodules>5 mm [17]. Regenerative nodules may develop in response to hyperperfusion leading to induce hyperplastic hepatocytes without atypia after chemotherapy [17]. The incidence of NRH of approximately 15-20% has been suggested after oxaliplatin-based chemotherapy, describing that NRH may induce compression and atrophy of the surrounding liver parenchyma, portal hypertension, and postoperative complications [17]. It is known that NRH regress up to nine months after the cession of oxaliplatin-based chemotherapy [18]. Vigano et al. described that oxaliplatin increased the incidence of NRH at multivariate analysis [19]. Regarding image features, NRH may show increased LSM undergoing magnetic resonance elastography [20]. NRH shows hypointense in the T1-weighted images and hyperintense in the T2-weighted images. While enhanced MRI features using the gadoxetic acid showed slightly enhanced areas in the vascular phase and hypointense areas in the hepatobiliary phase. The absence of diffusion restrictions on DW-MRI ruled out the possibility of liver metastases [16].

Oxaliplatin-induced acute liver injury in animal study

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 indicating that GSH therapy can decreased oxaliplatin-induced ALI by suppressing oxidative stress in the liver [9]. Another study demonstrated that oxaliplatin causes ALI in NAFLD mice showing increased levels of ROS and MDA and reduced the levels of SOD and GSH peroxidase in the liver of NAFLD mice [21]. While previous study indicated that oxidative stress serves as a significant role in the mitochondrial toxicity of oxaliplatin in rat liver mitochondria [22]. Recent study showed the prediction for oxaliplatin-induced liver injury using patient-derived liver organoids suggesting that liver injury related to oxaliplatin-induced liver damage may be caused by mitochondrial oxidative damage [23].

Long-term liver complications after oxaliplatin-based chemotherapy

Oxaliplatin-induced liver damage has one of the broadest clinical spectrums in drug-induced liver damage from acute liver failure to NCPH representing more than 10 years later [24]. It is known that oxaliplatin is associated with sinusoidal endothelial injury and induces the development of NRH which causes Non-Cirrhotic Portal Hypertension (NCPH). While NCPH is also caused by other autoimmune, hematological, drug-related factors. The recent study described that the case presented with recurrent variceral bleeding due to NCPH and NRH six years after treatments of colon cancer receiving oxaliplatin-based chemotherapy [25]. Another report showed the isolated gastric variceral bleeding associated with NCPH after oxaliplatin-based chemotherapy [26]. While the term Porto-Sinusoidal Vascular

Disease (PSVD) has recently been introduced showing a group of vascular diseases encompassing the portal venules and sinusoids. Histological features include NRH, obliterative portal venopathy/portal vein stenosis and incomplete septal fibrosis/cirrhosis. It is known that PSVD has been associated with prior use of immunosuppressive or antineoplastic agents such as oxaliplatin and azathioprine [27]. The results showed genes of the *SERPINC1*, Apolipoproteins (APOA, APOB, APOC), ATP synthases, fibrinogen genes, and alpha-2-macrogloburin as differentially expressed in PSVD [27].

Novel indicator in oxaliplatin-induced SOS

The author has previously described the oxaliplatin-induced SOS emphasizing the Liver Stiffness Measurement (LSM) as a novel predictor by elastography [3]. 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 [28]. Furthermore, based on the evidence, LSM using US elastography and MR elastography may noninvasively be a potential indicator for SOS as previously described [3].

It is known that Thrombopoietin (TPO) induces activation of multiple signaling pathways such as JAK, STAT and MAP kinase leading to the enhanced platelet production. Recent data showed that the TPO accumulation in hepatocytes induced a decreased serum level in a mouse model of SOS. The sinusoidal capillarization in SOS has been reported by using CD34 and was suppressed by anti-platelet drugs (PDE III inhibitors) [29]. Recent report described that serum autotaxin is a new surrogate marker for predicting oxaliplatin-induced SOS before surgical resection for CRLM by using multivariate analysis, suggesting that elevated autotaxin level may occur during the early phase of SOS before splenomegaly and thrombocytopenia [30]. Regarding immunohistochemical study, it is putative that the CSI score using CD34, SMA, and GS may play a role in the useful indicator of chemotherapy-induced sinusoidal damage. Increased CD34 expression by SECs has been related to the severity of sinusoidal injury and deterioration of hepatic functional reserve in the cases with oxaliplatin-induced liver injury [31]. Whereas centrilobular perisinusoidal/venular fibrosis has been observed in the cases with oxaliplatin-induced liver damage, showing sporadically SMA expression by HSCs [31]. Previous study showed immunohistochemically HSC activation by diffuse αSM cell expression [8]. The reports showed the Glutamine Synthetase (GS) expression in several lesions such as FNH, suggesting that these conditions are related to altered intrahepatic blood flow caused by shunt vessels or the aberrant vasculature, therefore impaired sinusoidal microcirculation in SOS may result in the GS expression in the hepatic lobules. The previous study suggested that CD34 expression by SECs and positive SMA expression in HSCs pathologically seem to exhibit the sinusoidal endothelial injury, while GS expression of the hepatocytes may reflect impaired sinusoidal microcirculation [31].

Updated biological pathway analysis of oxaliplatin-induced SOS

The previous study provided that several pathway analyses demonstrated major gene upregulation in six pathways in SOS including IL-6, coagulation system (Serpine 1, THBD, and VWF), hepatic fibrosis/hepatic stellate cell activation (COL3a1, COL3a2, PDGF-A, TIMP1, and MMP-2), and oxidative stress. Angiogenic Factors (VEGF-C) and Hypoxic Factors (*HIF1A*) were upregulated and *CCL20* mRNA significantly increased. The result demonstrated several biological pathways. In acute phase response pathway, the relative overexpression of *STAT3* and *IL-6* mRNA by quantitative RT-PCR was confirmed. Regarding coagulation system and oxidative stress pathway, RT-PCR confirmed overexpression of VWF, Serpine 1, and SOD2. In hepatic activation of the hepatic fibrosis/hepatic stellate cell activation pathway, TIMP1 and MMP-2 overexpression, and in cytokine and chemokine mRNAs, considerable overexpression of CCL20 were confirmed by quantitative RT-PCR. With regards to angiogenesis and hypoxia, increased *HIF1a* mRNA and *VEGF-C* RNA were observed by real-time quantitative RT-PCR [8]. The previous study investigated ten genetic polymorphisms in 4 potentially SOS-related genes including *VEGFA*, *MMP9*, *NOS3*, and *GSTP1* describing that they did not significantly show the development of splenomegaly in patients receiving adjuvant oxaliplatin [11]. The recent study revealed that the cytokines and chemokines within the spleen showed significantly temporal upregulation of IL-6, IL-1α, and G-CSF, while IL-1β, IL-12p40, MIP-1β, IL-2 and RANTES were downregulated in mice study. Regarding the flow cytometric analysis, results revealed splenocyte changes with a significant reduction in $CD45^+$ cells [32]. The evidence provided that oxaliplatin may induce acute liver injury and aggravate the exiting hepatic oxidative stress, inflammation, and fibrosis in NAFLD mice. The result showed increased the levels of ROS and MDA, decreased the levels of superoxide dismutase and GSH peroxidase, the upregulation of hepatic inflammatory cytokines including TNF-α, IFN-γ and IL-17, and upregulated expression of TGF-β, α-SMA, and TIMP-1 with collagen fiber depositions after oxaliplatin chemotherapy in NAFLD mice. Oxidative stress serve as an important role in progression of inflammatory disorders suggesting that oxidative stress activates inflammatory pathways leading to induce the expression of TNF-α, IL-1 and TGF-β [21]. Using liver tissues from Non-Human Primate (NHP) model treated with anti-DLL4 or CRLM patients with oxaliplatin, the results showed that NOTCH and IL16 pathways have been implicated in the pathogenesis of drug-induced sinusoidal dilation [33]. The microarray results indicated that mRNA expression after oxaliplatin therapy were related to oxidative stress, coagulation function, steroid anabolism, and pro-inflammatory responses showing that oxaliplatin aggravated oxidative damage in the livers of the mice [34]. Based on the evidence, in particular, inflammatory pathway is significantly upregulated, therefore, showing that a robust relationship between oxaliplatin-induced SOS and atherosclerosis may lead to the SOS-related atherosclerosis status.

Potential therapeutic strategies 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 leading to drug-induced atherosclerosis including hypertension and thrombosis/atherosclerosis [35,36]. 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 [37]. Regarding the animal study, the previous study provided the evidence on the protection effect of VEGF-inhibition against the development of oxaliplatin induced SOS and suggested that changes in the VEGF pathway, VEGF-R2 may be responsible [38]. Though bevacizumab, VEGF inhibitor may induce atherosclerosis status, it may contribute to the protection of the development of SOS. Further investigation is needed to verify for the optimal treatment of cancer and the effective intervention as previously described [3]. Regarding GSH therapy, it could decrease the oxaliplatin-induced elevated MDA level in the liver [9]. 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 [9]. Another study provided that treatment using exogenous GSH significantly decreased the levels of ROS, MDA, and TNF-α, regarding inflammation, it decreased levels of IFN-γ, IL-17, TGF-β, α-SMA, and TIMP-1 [21]. Therapeutics in NAFLD mice with exogenous GSH alleviated oxaliplatin-induced liver damage by ameliorating oxaliplatin-aggravated hepatic oxidative stress and inflammation suggesting that GSH therapy might be a potential intervention for oxidative stress and inflammation status in oxaliplatin-induced SOS [21].

Association between oxaliplatin-induced SOS and atherosclerosis status

It is known that the incidence of atherosclerosis status in patients with cancer is very high due to the systemic inflammatory response and impaired vascular endothelial function caused by cancer cell infection and chemoradiotherapy [6]. Previous study suggested that cancers itself and oncological therapy may damage the endothelial cell system [39]. Some studies have exhibited increased IMT, PWV, and decreased FMD in patients with cancer compared to healthy controls [6]. Recently, cancer therapy-related cardiovascular toxicity has become a prominent clinical challenge [40]. Gene expression profile revealed several biological pathways including oxidative stress, inflammation, hepatic fibrosis/HSC activation, coagulation, angiogenic, and hypoxic factor for oxaliplatin-induced SOS [8]. Based on the evidence, inflammatory pathway is significantly upregulated, therefore, suggesting an essential driving factor of hepatotoxicity after oxaliplatin chemotherapy and a close relationship between oxaliplatin-induced SOS and atherosclerosis. An association between chronic liver disease and atherosclerosis emphasizing the inflammation as common pathway has been described [7]. Similar to the association between chronic liver disease and atherosclerosis, oxaliplatin-induced SOS may have both liver and systemic inflammation along with cancer and lead to SOS-related atherosclerosis status. Endothelial dysfunction is the initial step for atherosclerotic status, therefore, the author will suggest the assessment of vascular endothelial and smooth muscle cell function using Flow-Mediated Vasodilation (FMD) and nitroglycerin-mediated vasodilation (NMD) methods for the evaluation of atherosclerosis condition in the setting of oxaliplatin-induced SOS [41-43].

Future perspective for metastatic colorectal cancer therapy

Oxaliplatin is a backbone drug of many regimens for colorectal cancer and colorectal liver metastasis. Previous 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 [44]. Recently, targeted therapies effect on cancer cells by directly targeting proteins or cells involved in cell growth, proliferation, and metastasis. The VEGF, EGFR, RAS, BRAF, and HER2 pathways have emerged as potential targets suggesting that VEGF, EGFR, and DNA mismatch repair pathways have exhibited promising results for the targeted treatments [45].

DISCUSSION

Recently the author described the mechanism of oxaliplatin-induced SOS along with potential therapeutic strategy [4]. In this review, the author outlined the current knowledge and trends of oxaliplatin-related SOS along with updated gene expression profile analysis. In addition, a relationship between oxaliplatin-induced SOS and atherosclerotic status has been discussed.

Oxaliplatin-induced liver injury showed development of NRH as long-term liver complications. According to the previous report, the changes of SOS and related local disturbance in hepatic perfusion such as chronic hypoxia may cause the occurrence of NRH [15,16]. This phenomenon may be reflected by genetically upregulated hypoxic factor, *HIF1a* mRNA. Regarding a novel indicator, the TPO accumulation in hepatocytes induced a decreased serum level in a mouse model of SOS and serum autotaxin is a new surrogate marker for predicting oxaliplatin-induced SOS before surgical resection for CRLM suggesting that serum TPO and autotaxin may contribute to predict for oxaliplatin-induced SOS. [29,30]. With regards to immunohistochemical study, CD34 expression by SECs and SMA expression in HSCs may show the sinusoidal endothelial injury, whereas GS expression of the hepatocytes may reflect impaired sinusoidal microcirculation as previously reported [31].

The novel surrogate marker such as serum TPO and autotaxin may contribute to predict for oxaliplatin-induced SOS. For potential therapeutic intervention, though bevacizumab, VEGF inhibitor may induce atherosclerosis status, it may contribute to the protection of the development of SOS. Further investigation is needed to verify for the optimal treatment of cancer and the effective intervention. The author previously emphasized the evaluation of vascular endothelial and smooth muscle cell function by FMD and NMD procedures in the setting of oxaliplatin-based chemotherapy [3]. It is known that the incidence of atherosclerosis status in patients with cancer is very high due to the systemic inflammatory response and impaired vascular endothelial function caused by cancer cell infection and chemoradiotherapy [6]. The liver inflammation is regarded as a main driving factor of liver tissue toxicity by oxaliplatin chemotherapy [5]. The gene expression profile revealed several biological pathways including oxidative stress, inflammation, hepatic fibrosis/HSC activation, coagulation, angiogenic, and hypoxic factor for oxaliplatin-induced SOS. Based on the evidence, inflammatory pathway is significantly upregulated, therefore, suggesting a main driving factor of hepatotoxicity after oxaliplatin chemotherapy and a close relationship between oxaliplatin-induced SOS and atherosclerosis [8]. Similar to the association between chronic liver disease and atherosclerosis, oxaliplatin-induced SOS may have both liver and systemic inflammation along with cancer leading to development of SOS-related atherosclerosis. The author will further suggest the assessment of vascular endothelial and smooth muscle cell function using FMD and NMD procedures for the evaluation of SOS-related atherosclerosis condition in oxaliplatin-induced SOS setting.

CONCLUSION

Oxaliplatin-induced liver injury may have the broad spectrum from acute liver injury to long-term liver complications such as nodular regenerative hyperplasia in clinical and animal study. Inflammatory pathway is significantly upregulated, suggesting a close relationship between oxaliplatin-induced SOS and atherosclerosis. Oxaliplatin-induced SOS may induce SOS-related atherosclerosis due to both liver and systemic inflammation.

CONFLICT OF INTEREST

Author declares that I have no conflicts of interest.

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