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Review Article

Hepatic Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease after Hematopoietic Stem Cell Transplantation in Pediatric Patients: A Review of Assessment for Liver Stiffness Measurement by Elastography along with Defibrotide Efficacy

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ABSTRACT

The updated criteria in adult patients with the addition of a new category such as probable Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease (SOS/VOD) included ultrasound and/or elastography criteria. The European Society for Blood and Marrow Transplantation (EBMT) has stated a new classification of the diagnosis and severity for SOS/VOD in pediatric patients, but this did not include elastography criteria. The MEDLINE/PubMed and EMBASE data-bases were systematically searched for studies using elastography for SOS/VOD after Hematopoietic Stem Cell Transplantation (HSCT) in pediatric patients. In this review, the author summarized the current evidence of SOS/VOD in pediatric patients after HSCT for assessment of Liver Stiffness Measurement (LSM) by elastography along with the utility of defibrotide for treatment and prevention. Based on the evidence, Shear Wave Elastography (SWE) and Transient Elastography (TE) are probably potential tools for early accurate diagnosis and disease severity for SOS/VOD after HSCT even in pediatric patients. It is putative that LSM value should be considered as diagnostic criteria for predicting the SOS/VOD in pediatric study. Defibrotide may be a promising therapeutic strategy for SOS/VOD after HSCT in pediatric patients.

Keywords: Sinusoidal obstruction syndrome/Veno-occlusive disease; Hematopoietic stem cell transplantation; Elastography; Pediatric; Defibrotide

INTRODUCTION

Mohty et al. updated the criteria in adult patients with the addition of a new category such as probable SOS/VOD including ultrasound and/or elastography suggestive of SOS/VOD [1]. The recent report described that SWE and TE may be potential tools for early accurate diagnosis, disease severity, and follow-up for SOS/VOD after HSCT in adult patients [2]. The EBMT has stated a new classification of the diagnosis and severity for SOS/VOD in pediatric patients leading to earlier detection and a predictive evaluation of therapeutic efficacy and outcome [3]. Due to an effective indirect predictor for liver fibrosis, the criteria included elastography for predicting the SOS/VOD risk score [4]. With regards to therapeutic strategy, the utility of defibrotide for treatment and protection in SOS/VOD after HSCT in pediatric patient has been described [5]. In this review, the current evidence and trends of SOS/VOD after HSCT in pediatric patients for assessment of LSM by elastography have been outlined. Additionally, the efficacy of defibrotide of treatment and prevention for SOS/VOD after HSCT in pediatric patients has been described.

LITERATURE REVIEW

Association between Busulfan exposure and development of SOS/VOD in pediatric patients undergoing HSCT

A previous study suggested that higher cumulative Busulfan (BU) exposure increased the risk of SOS/VOD in patients with BU as the only alkylator, while the magnitude of BU exposure did not increase this risk in patients treated with multiple alkylators [6]. Further biomedical laboratory research and clinical studies for participant at greater risk are needed to clarify [7]. Recent study showed that pediatric patients with i.v. administration of BU with Therapeutic Drug Monitoring (TDM) achieved a significantly lower incidence of Transplantation-Related Mortality (TRM) and a

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significantly improved Overall Survival (OS) [8]. They showed the relevance of TDM in pediatric patients with malignant diseases, describing the recommendation with a cut-off cumulative AUC of <85.0 mg/L x h to protect the development of SOS/VOD [8].

Updated diagnostic criteria for SOS/VOD after HSCT in pediatric patients

The updated criteria in adult patients with the addition of a new category such as probable SOS/VOD showed ultrasound and/or elastography criteria [1]. Ultrasonography including gray scale and color Doppler US exhibited unspecific hepatosplenomegaly, reversed portal vein flow or high Resistance Index (RI) of the hepatic artery. Regarding Contrast-Enhanced Ultrasound (CEUS) or LSM, a few studies have demonstrated potential features for diagnosis of SOS/VOD [9]. LSM is a useful procedure for assessment such as fibrosis, acute inflammation, and cholestasis. The EBMT has stated a new classification of the diagnosis and severity criteria for SOS/VOD in pediatric patients leading to earlier detection and a predictive evaluation of therapeutic effectiveness and outcome [3]. Imaging features including elastography of SOS/VOD in pediatric patients have been also reported [10]. Lee et al. demonstrated the utility of SWE for diagnosing SOS/VOD suggesting the potential method of elastography for early diagnosis and disease severity [11]. It is known that Pediatric specific European Society for Blood and Marrow Transplantation (pEBMT) criteria are related to improved recognition of SOS/VOD suggesting that the criteria lead to early diagnosis and earlier treatment with defibrotide [12]. Recent study as a retrospective chart review reported the diagnosis and grade of SOS/VOD after HSCT in the pediatric institution with pediatric protocols [13].

Elastography for SOS/VOD following HSCT in pediatric patients

As the conventional US is an operator-dependent examination, some criteria do not suggest as diagnostic criteria in pediatric patients [14,15]. According to the previous study, the characteristics of elastography method make it suitable in pediatric patients [14]. The EBMT has stated a new classification of the diagnosis and severity for SOS/VOD in pediatric patients, but this did not include elastography criteria [3]. Imaging findings including elastography of SOS/VOD in pediatric patients have been also reported [10]. Several reports of LSM values using elastography have been reported in the pediatric patients with SOS/VOD after HSCT [11,16-19]. The median stiffness (kPa) and viscosity (m/s/kHz) values were obtained from the measurements on the SWE map and Shear Wave Dispersion (SWD) map [20]. Zama et al. described three patients with SOS by TE showing 34.3-36.8 kPa in LSM value [16]. Five patients with SOS/VOD undergoing HSCT using SWE have been shown [17]. Canas et al. demonstrated that Point Shear Wave Elastography (pSWE) of the liver is a potential tool for the early diagnosis in pediatric patients with SOS after HSCT showing that a cut-off value is 1.37 m/s with an area under the curve of 0.779 [18]. Lee et al. also have reported the promising method of 2D-SWE for diagnosing SOS, showing that liver stiffness values above 7.2 kPa exhibited sensitivity and specificity of 84.2% and 93.3%, respectively [19]. Recently a feasibility study exhibited SWE and dispersion imaging reflecting the tissue viscosity for SOS/VOD following HSCT prediction in pediatric patients suggesting that liver stiffness showed the highest area under the ROC (AUROC) curves at 0.960, with an optimal predictive value of >6.5 kPa, exhibiting in sensitivity and specificity of 100% and 83.3%, respectively [11]. In addition, they suggested that SWD may be attributed to an additional marker for SOS/VOD [11]. A systematic review and meta-analysis including ten studies with pediatric and adult patients suggested that elastography exhibited non-invasively promising tool for early detection with significant increase in Shear Wave Velocity (SWV) and liver stiffness values [14]. While, to diagnose the accuracy of LSM for SOS/VOD after HSCT, multicentre diagnostic clinical trial including both adult and pediatric patients demonstrated that a diagnostic algorithm was proposed, showing >95% sensitivity and specificity, with a 6 kPa roue-out and 25 kPa rule-in cut-off value [21]. According to the previous study, LSM by SWE may be increased due to fibrosis, inflammation, congestion, portal hypertension, and cholestasis [22]. Recent study reported that the feasibility of comprehensive ultrasound analysis in pediatric patients for the characteristic feature of hepatic fibrosis, inflammation, and steatosis using SWE, SWD, and Attenuation Imaging (ATI) compared to liver biopsies and a control cohort [23]. SWE exhibited a promising diagnostic tool for the early detection and disease severity of SOS/VOD and potentially improved the outcome in pediatric patients. [24]. Whereas SWD provided clinical insights into tissue viscosity related to edema, necrosis, and inflammation [24]. According to the report of gene expression for biological pathway, inflammatory pathway is significantly updated, suggesting a main driving factor of hepatotoxicity by oxaliplatin chemotherapy as previously described [2,25]. Similar to the development of oxaliplatin-induced SOS, LSM value may reflect inflammation even in pediatric patients with SOS/VOD following HSCT. In this review, the current knowledge and trends of SOS/VOD after HSCT in pediatric patients for the estimation of LSM have been summarized (Tables 1 and 2). Based on the evidence, the increased LSM in the acute phase of SOS/VOD may be attributed to the alterations caused by inflammation rather than fibrosis. The results provided that SWE and TE are possibly potential tools for early diagnosis and disease severity indicator of SOS/VOD. As LSM is a very effective predictor of liver fibrosis and/or inflammation this indicator should be regarded as the criteria for predicting the SOS/VOD even in pediatric patients.

Defibrotide for management and prophylaxis in SOS/VOD

SOS/VOD is a life-threatening complication of HSCT belonging to a group of conditions as transplant-related disease and systemic endothelial disease as previously described [3]. The vascular endothelium is the primary target of therapy for hepatic SOS/VOD due to the toxic metabolities from high-dose chemotherapy conditioning for the endothelium, leading to increased adhesion molecular expression, cytokine signaling, and vWF expression [5]. Defibrotide is approved for the therapy in adult and pediatric patients with hepatic SOS/VOD with renal or pulmonary dysfunction after HSCT in the US and Canada. While, in the European Union, the approval for defibrotide is made to treat severe hepatic SOS/VOD after HSCT in adult and pediatric patients age > 1 month [26]. Early administration is significant to maximize the chances of recovering from illness and preventing serious complications as previously described [27]. The mechanism of Defibrotide (DF) for SOS/VOD has been shown. DF provides endothelial protection by the maintenance of sinusoidal vascular integrity and the reduction for heparanase expression, exhibiting anti-inflammatory effects via reductions in TNFα, VCAM-1, p38 MARK, and Akt phosphorylation [5]. Defibrotide has exhibited to protect the endothelial function from cytotoxic and inflammation injury suggesting that it improves thrombotic-fibrinolytic balance.

Richardson et al. described that DF exhibited pleiotropic properties including anti-inflammatory, anti-thrombotic, and fibrinolytic suggesting broad endothelial protective efficacy [5]. Regarding the endothelial function examination, it has been established that Flow-Mediated Vasodilation (FMD) and Nitroglycerin-Mediated Vasodilation (NMD) in the brachial artery are promising methods for evaluating vascular endothelial and Vascular Smooth Muscle Cell (VSMC) function in atherosclerosis status [28-30]. It is known that DF for severe SOS/VOD with MOD/MOF was associated with better results in pediatric patients compared with adults, while DF showed efficacy for prevention of SOS/VOD in a randomized prospective trial [3]. A previous systematic review included findings from 17 prospective and retrospective studies for 2598 patients with SOS/VOD receiving DF. The result provided the day +100 survival rate of 54% overall. While, 56% in patients treated with standard DF was shown. The day +100 survival rate was 44% among patients with MOD and 71% in patients without MOD, respectively. Respective rates in pediatric and adult patients receiving the standard DF dose were 68% and 48% [31]. Meanwhile another systematic review and meta-analysis exhibited effectiveness of DF indicating that DF improves the day +100 survival rate (SR) and Complete Response (CR) in patients with SOS/VOD after HSCT [32]. Further randomized trials and prospective studies are needed to clarify. DF has been also estimated as prophylaxis in patients for preventing SOS/VOD after HSCT [25]. A meta-analysis including retrospective and prospective studies showed a risk ratio of 0.30 for development of SOS/VOD with DF prophylaxis compared to controls [33]. The prospective trials including Pediatric Prevention Trial (NCT00272948) and Harmony Trial (NCT02851407) were conducted exhibiting conflicting results [34,35]. The phase 3 HARMONY trial suggested that DF prophylaxis may offer benefit for SOS/VOD, especially at high-risk patients [35]. The guidelines for pediatric patients at high risk for SOS/VOD suggested that DF prophylaxis is regarded as justification [4]. Based on the evidence, defibrotide for endothelial damage is the promising efficacy for SOS/VOD after HSCT even in pediatric patients.

DISCUSSION

The EBMT has stated a new classification of the diagnosis and severity for SOS/VOD in pediatric patients leading to earlier detection and a predictive evaluation of therapeutic efficacy and outcome [3]. Due to a very effective indirect marker of liver fibrosis, the criteria included elastography for predicting the SOS/VOD risk score in adult patients [4]. Lee et al. also have reported the promising method of 2D-SWE for diagnosing SOS, showing that liver stiffness values above 7.2 kPa exhibited sensitivity and specificity of 84.2% and 93.3%, respectively [19]. Recently a feasibility study exhibited SWE and dispersion imaging for SOS/VOD prediction in pediatric patients following HSCT suggesting that liver stiffness showed the highest area under the ROC (AUROC) curves at 0.960, with an optimal predictive value of >6.5 kPa, exhibiting in sensitivity and specificity of 100% and 83.3%, respectively [11]. In addition, they suggested that SWD may be attributed to an additional marker for SOS/VOD [11]. Meanwhile, based on the evidence for a systematic review and meta-analysis and/or prospective multicentre clinical trial including pediatric and adult patients, LSM is a potential diagnostic tool for early detection [14, 21]. According to the previous study, LSM by SWE may be increased due to fibrosis, inflammation, congestion, portal hypertension, and cholestasis [22]. SWE exhibited a promising diagnostic tool for the early detection and disease severity of SOS/VOD and potentially improved the outcome in pediatric patients [24]. In this review, the current knowledge and trends of SOS/VOD after HSCT in pediatric patients for the estimation of LSM have been summarized (Tables 1 and 2). Based on the evidence, the results provided that SWE and TE may be potential tools for early diagnosis and disease severity indicator of SOS/VOD. As LSM is a very effective indirect predictor of liver fibrosis and/or inflammation, LSM should be considered as the criteria for predicting the SOS/VOD risk score. SOS/VOD is a life-threatening complication of HSCT belonging to a group of diseases as transplant-related disease and systemic endothelial disease [3]. The utility of defibrotide for treatment and prevention has been described in pediatric patient with SOS/VOD after HSCT [5]. Previous study indicated that DF for severe SOS/VOD with MOD/MOF was associated with better results in pediatric patients compared with adults, whereas DF showed efficacy for prevention of SOS/VOD in a randomized prospective trial [3]. Previous systematic review included findings from 17 prospective and retrospective studies for 2598 patients with SOS/VOD receiving DF. The result provided the day +100 survival rate of 54% overall. While, 56% in patients treated with standard DF was shown. The day +100 survival rate was 44% among patients with MOD and 71% in patients without MOD, respectively. Pediatric and adult patients receiving the standard DF dose were 68% and 48%, respectively [31]. Meanwhile another systematic review and meta-analysis exhibited the effectiveness of DF indicating that DF improves the day +100 survival rate and complete response in patients with SOS/VOD after HSCT [32]. Further randomized trials and prospective studies are needed to verify. Regarding DF prophylaxis, a meta-analysis including retrospective and prospective studies showed a risk ratio of 0.30 for development of SOS/VOD with DF prophylaxis compared to controls [33]. Prospective trials including Pediatric Prevention Trial and Harmony Trial were conducted exhibiting conflicting results [4,34,35]. The guidelines for pediatric patients at high risk for SOS/VOD suggested that DF prophylaxis is regarded as justification. Based on the evidence, defibrotide for endothelial injury may be a significant therapeutic strategy and its efficacy is probably promising for SOS/VOD after HSCT in pediatric patients.

Table 1: Assessment of elastography for sinusoidal obstruction syndrome/Veno-occlusive disease in pediatric patients after HSCT.

Study	Design	HSCT patients (N)	SOS patients (N)
Zama et al. [16]	Retrospective, single-institution	NA	3
Reddivalla et al. [17]	Prospective, single-institution	25	5
Canas et al. [18]	Retrospective, single-institution	43	28
Lee et al. [19]	Retrospective, single-institution	34	19
Lee et al. [11]	Prospective, single-institution	38	8

Note: NA: Not Applicable

Table 2: Assessment of elastography for sinusoidal obstruction syndrome/Veno-occlusive disease in pediatric patients after HSCT.

Study	LSM procedure	LSM value	AUC	Sensitivity	Specificity
Zama et al. [16]	TE	34.3-36.8 kPa	NA	NA	NA
Reddivalla et al. [17]	SWE	0.44 m/s	0.853	80%	93%
Canas et al. [18]	pSWE	1.37 m/s	0.779	NA	NA
Lee et al. [19]	2D-SWE	>7.2 kPa	0.925	84.2%	93.3%
Lee et al. [11]	SWE	>6.5 kPa	0.960	100%	83.3%

Note: NA: Not Applicable

CONCLUSION

Shear wave elastography and transient elastography are probably potential tools for early accurate diagnosis and disease severity for SOS/VOD after HSCT even in pediatric patients. It is plausible that liver stiffness measurement value should be considered as the criteria for predicting the SOS/VOD after HSCT in pediatric patients. Defibrotide for endothelial damage may be a significant therapeutic strategy and its efficacy is possibly potential for SOS/VOD after HSCT in pediatric patients. Further randomized trials and prospective studies for defibrotide therapy and prophylaxis are needed to verify.

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