Comparison Between Liver Stiffness Measurement by Fibroscan and Splenic Volume Index as NonInvasive Tools for the Early Detection of Oxaliplatin-induced Hepatotoxicity

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Background: **Oxaliplatin remains an essential component of many chemotherapy protocols for gastrointestinal cancers; however, neurotoxicity and hepatotoxicity may be dose-limiting. The gold standard for the diagnosis of oxaliplatin-induced hepatotoxicity is liver biopsy, which is invasive and costly. Splenomegaly has also been used as a surrogate for liver biopsy in detecting oxaliplatin-induced sinusoidal obstruction syndrome (SOS), but splenic measurement is not routine and can be inaccurate and complex. We investigated the correlation between increased liver elasticity assessed by Fibroscan and the increase in spleen volume on cross-sectional imaging after oxaliplatin as a noninvasive technique to assess liver stiffness associated with oxaliplatin-induced SOS.** ***Methods:*** **Forty-six patients diagnosed with gastrointestinal cancers and planned to take oxaliplatin containing regimens were included in this prospective study at the American University of Beirut Medical Center (AUBMC). Measurement of spleen volume using cross-sectional imaging and of liver elasticity using Fibroscan was performed at baseline, 3 and 6 months after starting oxaliplatin. Mean liver elasticity measurements were compared between patients stratified by the development of splenomegaly using the Student *t*-test. Splenomegaly was defined as 50% increase in spleen size compared with baseline.** ***Results:*** **Patients who developed splenomegaly after oxaliplatin use had significantly higher mean elasticity measurements as reported by Fibroscan at 3 (16.2 vs. 7.8 kPa, $P = 0.036$) and 6 (9.3 vs. 6.7 kPa, $P = 0.03$) months.** ***Conclusion:*** **Measurement of elasticity using Fibroscan could be potentially used in the future as a noninvasive test for predicting oxaliplatin-induced hepatotoxicity. (J Clin Exp Hepatol 2022;12:448–453)**

Oxaliplatin has been the backbone drug of many regimens used for the treatment of gastrointestinal malignancies in the adjuvant and metastatic setting. It was first approved in 2002 by the US Food and Drug Administration for its use in metastatic colorectal cancer.[1] Although the use of oxaliplatin has improved the prognosis of patients especially in stage III colon cancer, it is associated with several side effects including peripheral neuropathy and sinusoidal obstruction syndrome (SOS) of the liver. SOS, also known as veno-occlusive disease or blue liver syndrome, can lead to severe liver damage and thrombocytopenia.[2,3] The concept of SOS was first mentioned in 2004 by Rubbia-Brandt *et al*. who reported that 78% of patients treated with oxaliplatin-based regimen prior to liver surgery were found to have sinusoidal injury on the pathology specimen compared with none in the group who underwent upfront surgery without prior chemotherapy.[2] The pathophysiology remains unclear; however, various hypotheses have been proposed as follows: oxaliplatin causes[1] damage to endothelial cells and releases free radicals that alter the integrity of sinusoidal cells, hence causing perisinusoidal fibrosis,[2] obstruction of blood capillaries, and[3] chronic hypoxia of the centrilobular space responsible for the generation of liver nodular hyperplasia.[4] The periportal

Keywords: fibroscan, oxaliplatin, sinusoidal obstruction syndrome, hepatotoxicity
Received: 3.5.2021; *Accepted:* 5.6.2021; *Available online 15 June 2021*
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Abbreviations: AUBMC: American University of Beirut Medical Center; CAP: Controlled attenuation parameter; CT: Computed tomography; dB/m: decibels/meter; ECOG: Eastern Cooperative Clinical Oncology Group; ICG-R15: indocyanine green retention rate at 15 min (ICG-R15); IRB: Institutional review board; ISP: IntelliSpace Portal; kPa: Kilopascal; MRI: Magnetic resonance imaging; SOS: Sinusoidal obstruction syndrome; SV: Splenic volume; SVI: Splenic volume index; TE: Transient elastography
https://doi.org/10.1016/j.jceh.2021.06.007

fibrosis, together with the diffuse sinusoidal liver injury, leads to backflow portal hypertension, ascites, hyperbiliru binemia, varices, and variceal bleeding in the absence of a parenchymal liver injury.[5–8] Although rarely life-threatening, SOS increases postoperative morbidities and may even lead in rare cases to liver failure.[5,6,9,10]

The gold standard diagnostic test for SOS is liver biopsy. Unfortunately, this diagnostic tool has major limitations including being costly, invasive, and inaccurate with possible sampling errors especially in the absence of diffuse sinusoidal hepatic injury (11). Therefore, less invasive biomarkers to predict and correlate with the hepatic SOS development are needed. Some studies have investigated the levels of hyaluronic acid, aspartate aminotransferase, and the indocyanine green retention rate at 15 min (ICG-R15) as being possible predictive biomarkers for the development of SOS.[12,13] In addition, many studies till date have shown that an increase in spleen volume can be a predictor of oxaliplatin toxicity. Our group at the American University of Beirut Medical Center (AUBMC) previously demonstrated that increase in spleen volume precedes the development of peripheral neuropathy after oxaliplatin use.[14] Most importantly, several studies have shown that an increase in spleen volume constitutes, in particular, an independent predictor and indicator of hepatic sinusoidal injury and SOS.[3,15] As such, given the aforementioned constraints with obtaining a liver biopsy, the increase in spleen volume has been used in many studies as a surrogate marker of SOS; and newly investigated potential diagnostic tools have been compared with splenic volume changes to assess their possible role in detecting SOS.[16]

Fibroscan uses transient elastography to assess the stiffness of the liver in terms of change in elasticity and the steatosis of the liver using controlled attenuation parameter (CAP). Several studies in hematopoietic stem cell recipients have proved that patients who developed SOS had increased liver stiffness as measured by transient elastography.[17,18] In addition, in a pilot study involving only 10 patients, Oki *et al*. showed that transient elastography assessing liver stiffness is effective in identifying oxaliplatin-induced liver injury.[19] Given all of the above and given that splenic volume measurement can be complex and inaccurate, we conducted a prospective study at the AUBMC to evaluate another noninvasive marker for SOS development. We investigated the possible correlation between splenomegaly and increase in liver stiffness measured by Fibroscan before and after the treatment with oxaliplatin. We relied on elasticity measurements, and we discarded the CAP measurements as SOS does not translate pathologically into steatosis, at least in the early stages of the disease. The presence of such a correlation will allow us to consider Fibroscan as a potential, novel, noninvasive predictive tool for oxaliplatin-induced SOS, pushing us to directly investigate its role in comparison with invasive liver biopsy in future studies.

MATERIALS AND METHODS

Study design

A prospective study was conducted at the AUBMC. Patients diagnosed with metastatic or locally advanced gastrointestinal tract cancers and planned to receive oxaliplatin containing regimens were included in the study. Patients above 18 years of age with histology-proven adenocarcinoma of rectal, ascending, descending and transverse colon, esophageal, gastric, and pancreatic cancer, with preserved organ function were included in the study. Eastern Cooperative Clinical Oncology Group (ECOG) performance status of included patients was either 0 or 1. Included patients were planned to start on oxaliplatin-based regimen in metastatic or adjuvant setting. The exclusion criteria were history of liver cirrhosis, steatohepatitis, absence of baseline imaging or prior history of splenectomy, or any other cause of splenomegaly. All patients were identified and included in the study by the primary physician in the outpatient clinic and received oxaliplatin-based regimens (FOLFOX, XELOX, FOLFOXIRI, FLOT, EOX, mFOLFORINOX) after providing written informed consent. The study protocol, recruitment, and consent were reviewed and approved by the Institutional Review Board (IRB) of AUBMC. All methods were performed in accordance with the relevant guidelines and regulations.

Spleen volume calculation

Initial spleen volume was measured at baseline, prior to chemotherapy initiation, using computed tomography (CT) scan and IntelliSpace Portal (ISP) Upgrade System. The latter is a software that draws a 3D representation of the spleen to calculate its volume. Similar steps were performed on repeat CT scans at 3 and 6 months of oxaliplatin treatment using the same software. Splenic volume index SVI was determined at 3 and 6 months from the initial oxaliplatin dose using the following formula, reflecting the percentage change in spleen volume SV compared with baseline[16]:

$$\text{SVI} = \frac{\text{SV at 3 or 6 months} - \text{Baseline SV}}{\text{Baseline SV}}$$

Given that a 50% increase in spleen size was previously shown to correlate with the risk of developing SOS, splenomegaly at 3 or 6 months was defined using a cutoff of ≥50% increase in spleen size at the time of measurement (3 or 6 months) compared with the baseline. As such, patients were classified into two groups: low SVI (SVI < 50%) and high SVI (SVI ≥ 50%). Patients in the high SVI group were considered to have a splenomegaly reflective of SOS. Measurements were performed by experienced radiologists at our institution.

Liver stiffness measurement

All patients were examined using Fibroscan by an experienced operator. The device uses an ultrasound probe to measure shear wave velocity (in meters per second) as the wave passes through the liver. Shear wave velocity measurements are converted into liver stiffness measurements, reported in Kilopascal kPa. Fibroscan also assesses steatosis using CAP reported in decibels/meter (dB/m).

After an overnight or at least 8 hours of fasting, patients were assessed in a lying supine position with the arm in maximal abduction, targeting the right hepatic lobe between the 9th and the 11th intercostal spaces at the midaxillary line. The examination was performed initially with the standard M probe (transducer frequency of 3.5 MHz), with probe switching based on device indication by real-time probe selection software with the XL probe. Liver stiffness measurement were recorded at baseline, 3 months, and 6 months after the first oxaliplatin treatment. Most measurements were done within 2 weeks from the last dose of oxaliplatin. CAP measurements were disregarded in our study as oxaliplatin induces changes in liver stiffness rather than fatty changes.

Patient follow-up

Patients were assessed and clinically followed up on a regular case-by-case basis. Treatment protocol were altered in the case the patient developed treatment-induced side effects as clinically indicated. In the case of increased liver stiffness, each individual case was assessed by the oncology team, and the treatment protocol was modified accordingly.

Statistical analysis

Descriptive statistics was used to analyze the baseline characteristics of the study population. Numerical variables were summarized by their mean and standard deviation. Categorical variables were described by counts and relative frequencies. To assess differences between the two groups we compared age, gender, type of cancer, distant metastasis, the presence of diabetes, and previous cardiovascular disease using the student *t*-test and chi-square tests. The mean change in elasticity was calculated for high and low SVI groups, and means between the two SVI groups were compared using the student *t*-tests at 3 and 6 months, respectively. Analysis was performed using SPSS software IBM v.25, a P value < 0.05 was considered statistically significant in all analyses.

RESULTS

A total of 46 patients were included in our study. A total of 29 (63%) were males, whereas 17 (37%) were females. The median age was 54.5, with a range of 28–78. A total of 17 (37%) patients had colon cancer, 17 (37%) patients with pancreatic cancer, 8 (17.4%) with rectal cancer, 3 (6.5%) with gastric cancer, and 1 (2.2%) with esophageal cancer. We have 20 (43.5%) patients with early-stage disease (stage I, II, III), and 26 (56.5%) patients with more advanced disease (stage IV) (Table 1). The average BMI of included patients was 26.2 (17.9–35.6) Kg/m^2.

Table 1 Patient Characteristics.

	N	%
Number of patients	46	
Gender		
Male	29	63%
Female	17	37%
Stage		
I-II-III	20	43.5%
IV	26	56.5%
Type of cancer		
Colon	17	37.0%
Rectum	8	17.4%
Pancreas	17	37.0%
Gastric	3	6.5%
Esophageal	1	2.2%
Smoking	13	28.3%
History of hypertension	13	28.3%
History of diabetes mellitus	11	23.9%
Metastatic disease to the liver	12	26.1%

Baseline spleen volume and liver elastic properties measured by elastography were recorded for 46 patients. Spleen volume and elastography measurements were reported for 41 and 33 patients at 3 months and 6 months, respectively. Five patients at 3 months and thirteen patients at 6 months were noncompliant to the study protocol as per patient preference and missed their measurements. Only patients with reported measurements at 3 and 6 months were included in the analysis at 3 and 6 months, respectively. The patients were stratified into two groups according to their SVI values using a cutoff of 50% as mentioned above (Table 2). At 3 months, 28 (68%) of the patients had a low SVI, whereas 13 (31.7%) patients had a high SVI. Similarly at 6 months, 23 (69.7%) of the patients had a low SVI and 10 (30.3%) patients had a high SVI. No statistically significant difference was observed between the

Table 2 Number of Patients Classified as High and Low Splenic Volume Index (SVI) at 3 and 6 Months.

	Low SVI	High SVI	Total
3 months	28	13	41
6 moths	23	10	33

Table 3 Mean Liver Elasticity for Patients With High and Low splenic Volume Index (SVI) at 3 and 6 Months, Respectively.

	Mean liver elasticity post–oxaliplatin treatment		*P*-value
	Low SVI	High SVI	
3 months	7.8 kPa	16.2 kPa	0.036
6 months	6.7 kPa	9.3 kPa	0.030

two groups in terms of age, sex, type of cancer, distant metastasis, or other medical history at 3 and 6 months, respectively.

The mean change in AST for all patients was 50% at 3 months and 43.4% at 6 months compared with baseline (P = 0.78). The mean change in ALT for all patients was 57.6% at 3 months and 19.8% at 6 months compared with baseline (P = 0.2). When stratifying patients into two groups based on their SVI, the mean change in ALT at 3 months (69.18% for low SVI and 28.19% for high SVI) and at 6 months (17.02% for low SVI and 25.81% for high SVI) was not significantly different between the two groups, P = 0.49 and 0.67, respectively. Similar results were obtained with AST, with mean changes at 3 months (46.68% for low SVI and 62.59% for high SVI) and at 6 months (17.56% for low SVI and 95.17% for high SVI) being not significantly different between the two SVI groups, P = 0.50 and 0.095, respectively.

At 3 months, the mean elasticity for the low SVI group was 7.8 kPa, compared with a higher mean of 16.2 in the high SVI group (P = 0.036). Similarly at 6 months, the mean elasticity in the low SVI group was 6.7, compared with 9.3 kPa in the high SVI group (P = 0.030) (Table 3).

Around 81% of the patients who had increased liver stiffness at 3 months still had elevated liver stiffness at 6 months (P = 0.009). The remaining 19% had normal values at 3 months but developed de novo increased liver stiffness at 6 months. Two patients had elevated liver stiffness at 3 months but had normal readings at 6 months, and this was attributed to treatment protocol modification.

DISCUSSION

Our study showed that patients who developed splenomegaly as defined by an SVI ≥50% had significantly higher mean elasticity measurements as reported by Fibroscan at 3 (16.2 vs. 7.8 kPa, P = 0.036) and 6 (9.3 vs 6.7 kPa, P = 0.03) months. The aim of this study was to find an additional noninvasive method/measurement tool to predict the hepatotoxicity caused by oxaliplatin that may replace the need for liver biopsy and the measurement of spleen volume. There are many noninvasive ways to evaluate the fibrotic indices in the liver, such as class I and class II biomarkers (AST, ALT, bilirubin, platelets, apolipoprotein A1, etc.), transient elastography (TE or FibroScan), Fibro-CT, MRI, along with other tests and scores.[11,20] In our study, we chose to assess the liver stiffness using Fibroscan, aiming to provide a direct correlation between Fibroscan changes and the development of splenomegaly. The presence of this correlation supports the possibility of using Fibroscan as a new tool to predict oxaliplatin toxicity instead of spleen volume measurement or even liver biopsy.

Many studies reported an increase in spleen volume after oxaliplatin use. A study conducted by Jung *et al.* on 50 patients receiving oxaliplatin-based therapy reported that the incidence of developing an increase in spleen volume was 30% and 67% after a total of 6 and 12 cycles of treatment, respectively.[21] Ohta *et al.* reported an increase in spleen volume in 81% of the patients (n = 59) included in the study after 12 cycles of oxaliplatin-based treatment.[22] Eighty percent of our patients developed an increase in spleen volume after 12 cycles of oxaliplatin-based treatment, which is almost similar to the study conducted by Otha *et al.*[22] Chediak *et al.*, from our group at the American University of Beirut, reported that 74% of their patients treated with oxaliplatin-based regimen had increase in spleen volume, and 66% developed peripheral neuropathy of any grade.[14] They also reported that increase in spleen volume may precede the development of peripheral neuropathy and maybe used as a marker for oxaliplatin-induced toxicity.[14]

These observations shed the light on the use of the increase in spleen volume as an indicator of oxaliplatin-induced hepatotoxicity. Imai *et al.* reported in a multivariate analysis concerning 79 patients receiving oxaliplatin-based therapy that the only independent factor predicting the development of SOS was the increase in spleen volume by more than 25%[15]. Overman *et al.* demonstrated that the use of oxaliplatin-based treatment results in a dose-dependent increase in spleen volume that correlates with hepatic sinusoidal injury and reported that >50% increase in spleen volume may correlate with hepatic sinusoidal injury[3]. As such, an SVI of 50% or 0.5 was used in our study to define splenomegaly that is most reflective of SOS.

These studies support the use of the spleen volume measurement as a noninvasive indicator of oxaliplatin-inducedSOS that may replace the standard of care, which is invasive and costly. However, the measurement of spleen volume is not routinely done, and the imaging modalities used do not always provide accurate estimation of the spleen volume. In fact, the spleen may be incompletely visualized due to the presence of overlying structures especially by using ultrasound as a measurement tool. Moreover, the measurement of the spleen volume using traditional methods is performed using linear measurements that limit the accuracy of the results as the spleen has an irregular shape[23,24].Therefore, novel and more practical predictive tools are needed. To our knowledge, while several studies assessed the role of Fibroscan in SOS after hematopoietic stem cell transplantation, only one study assessed this relationship in the setting of oxaliplatin

use.[17,18] In 2009, Oki *et al*. reported that Fibroscan is a good tool for the detection of hepatic injury induced by FOLFOX.[19] They reported that changes in liver stiffness detected by Fibroscan were noted after 48 hours of treatment with FOLFOX, and these changes can be reversible after 2 weeks of treatment.[19] In our study, we were able to prove that an increase in elasticity as reported by Fibroscan correlates with the development of splenomegaly, which is as mentioned above a used indicator of SOS. As such, Fibroscan could be potentially used as an additional noninvasive marker to predict oxaliplatin-induced SOS. The next step would be to establish a study directly comparing Fibroscan measurements with liver biopsy results to establish a direct correlation between this noninvasive test and the gold standard but invasive and costly liver biopsy.

Early detection of oxaliplatin-induced SOS is of clinical relevance, especially when surgical resection is planned after chemotherapy administration. Oxaliplatin-induced hepatotoxicity is underestimated and has been previously overlooked in many cases. Most altered liver function tests were attributed to liver metastases.[5,6] However, SOS was shown to be associated with increased short-term postoperative complications, including the increased need of blood transfusion during and directly after surgery.[25] In addition, several cases of pre- and postoperative liver failures were attributed to oxaliplatin-induced SOS.[5,6] As such, careful consideration of prehepatectomy chemotherapy should be suggested. For patients with initially unresectable disease, liver surgery is considered as soon as chemotherapy-induced tumor downsizing allows margin-negative resection.[25] However, for patients with resectable disease at diagnosis, and given that worse SOS outcomes, were associated with longer chemotherapy duration, long-course chemotherapy for such an indication should be avoided.[25] In addition, we suggest routinely assessing the presence of oxaliplatin-induced hepatotoxicity before directly proceeding to surgery to prevent the possible intra- and postoperative complications. In this regard, and pending further studies, Fibroscan may be possible used in the future as a noninvasive assessment tool for oxaliplatin-induced hepatotoxicity before proceeding to hepatectomy.

Our study, however, has several limitations. First, the sample size in our study was relatively small, and a larger sample size study is needed to better define the role of Fibroscan in detecting oxaliplatin-induced hepatotoxicity. In addition, not all patients were compliant to the planned measurements at 3 and 6 months, reducing the number of patients included in the statistical analysis. Finally, our study compared elasticity measurements with splenic volume changes. In fact, and as mentioned above, splenomegaly is a predictor but not the gold standard diagnostic test for SOS. As such, until directly assessing the relationship between Fibroscan measurements and liver biopsy results, Fibroscan cannot be used clinically as a diagnostic tool for oxaliplatin-induced liver injury.

In conclusion, despite being invasive and costly, liver biopsy remains the gold standard to detect the SOS. The measurement of spleen volume is another noninvasive tool used to measure oxaliplatin-induced hepatotoxicity based on previous studies. Our study showed that patients who developed splenomegaly postoxaliplatin treatment had higher liver elasticities as measured by Fibroscan. As such, the role of Fibroscan in this setting should be further investigated in a larger sample size study and by directly comparing it with liver biopsy outcomes, being the gold standard test. In addition, further noninvasive accurate methods should be explored to have a noninvasive gold standard method for toxicity prediction particularly for patients planned for liver resection.

ETHICAL APPROVAL

This study was designed and performed in accordance with the declaration of Helsinki. Patients provided written informed consent to participate in the study. The study protocol, recruitment, and consent were reviewed and approved by the Institutional Review Board (IRB) of AUBMC.

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CONFLICTS OF INTEREST

The authors have none to declare.

ACKNOWLEDGEMENT

None.

FUNDING

None.

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