Digestive and Liver Disease 51 (2019) 1348–1356

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Correspondence

## Incidence of portal hypertension in patients exposed to oxaliplatin

### 1. Introduction

Oxaliplatin is an alkylating agent used for gastrointestinal neoplasia [1]. Case descriptions showed that oxaliplatin may lead to the development of portal hypertension (PH) [2–4] with histological alterations similar to those found in idiopathic non-cirrhotic portal hypertension (NCPH).

We observed 4 patients with NCPH secondary to oxaliplatin. Their clinical features on disease evolution are reported in Table 1. To establish the incidence and presentation of NCPH we reviewed the database of patients consecutively treated with oxaliplatin.

Five hundred and seven patients admitted to the Oncology Unit between January 2011 and March 2017 and treated with oxaliplatin for gastrointestinal neoplasia were reviewed (Fig. 1). Among them, 347 were excluded because of CT scans not performed at our Radiology Unit and 80 because of signs of PH before therapy or for the presence of other conditions potentially related to PH. Four patients were excluded because affected by some conditions potentially associated with NCPH (celiac disease, IBD and AIDS) and 13 patients had a history of abdominal surgery potentially causing thrombosis and PH. Finally, 14 patients were excluded because of contemporaneous presence of portal vein diameter > 15 mm and longitudinal spleen diameter > 12 cm and 11 because of ascites in the CT scan performed before oxaliplatin

In the remaining 143 patients, the CTs performed before and $7.5 \pm 3.1$ months after oxaliplatin treatment were carefully evaluated by an expert radiologist (MDM). The development of portal hypertension was defined as the presence of one of the following radiological signs: (1) contemporaneous increment of portal vein diameter > 15 mm and of longitudinal spleen diameter > 12 cm; (2) development of esophago-gastric varices; (3) development of spontaneous porto-systemic shunts, where these parameters were absent at CT scan performed before the treatment.

### 2. Results

Before chemotherapy no patients had radiological signs of portal hypertension. Both longitudinal spleen diameter (10.3 vs 10.9 cm; $p = 0.002$) and spleen volume (25.9 vs 29.8 $cm^3$; $p = 0.004$) significantly increased after oxaliplatin. Six patients (4.2%; CI:95%; 1.5–8.9) developed radiological signs of portal hypertension. Among them, one patient developed isolated gastric varices, and another one esophago-gastric varices and ascites (Fig. 1). The presence of esophago-gastric varices in these two patients was confirmed with upper endoscopy.

A third CT scan performed $15 \pm 8.8$ months after the initial CT was available in 57 patients. Two further patients developed a contemporaneous increment of portal vein and spleen diameter. Thus, a total of 8 patients developed PH after oxaliplatin. These 8 patients had a decrease of the platelets count after therapy ($261 \pm 77$ vs $145 \pm 76$; $p = 0.01$) and received a higher number

**Table 1**
Clinical characteristics, presentation and evolution of PH in the four cases first observed because of portal hypertension secondary to oxaliplatin therapy.

| | N° of cycles and regimen of therapy | First clinical manifestation | Time interval between the end of therapy and clinical manifestation | Histological features | Follow up |
|---|---|---|---|---|---|
| 47Y, M | 6 cycles of adjuvant therapy (XELOX regimen) | Splenomegaly, portal vein enlargement, splenorenal shunt at follow-up CT scan | 6 months | OPV[a], paraportal shunts, NRH[b], sinusoidal dilatation | Development of large esophageal varices 2 years later |
| 67Y, M | 5 cycles of adjuvant therapy (XELOX regimen) | Esophageal variceal bleeding treated by endoscopic ligation and beta-blockers | 4 years | Paraportal shunts, sinusoidal dilatation | Persistence of small varices 2 years later |
| 50Y, F | 8 cycles of adjuvant therapy (FOLFOX regimen) | Splenomegaly, portal vein enlargement and umbelical vein recanalization at follow-up CT scan | 6 months | Sinusoidal dilatation, OPV[a], paraportal shunts | Reduction of radiological signs but persistence of splenomegaly and of histological features of NCPH[c] 1 year later |
| 78Y, M | 6 cycles of adjuvant therapy (FOLFOX regimen) | Esophageal variceal bleeding treated by endoscopic ligation and beta-blockers | 3 years | OPV[a], paraportal shunts, sinusoidal dilatation | Recurrence of large varices re-treated with ligation and development of acute portal and splenic vein thrombosis 2 years later |

[a] OPV: obliterative portal venopathy.
[b] NRH: nodular regenerative hyperplasia.
[c] NCPH: non-cirrhotic portal hypertension.

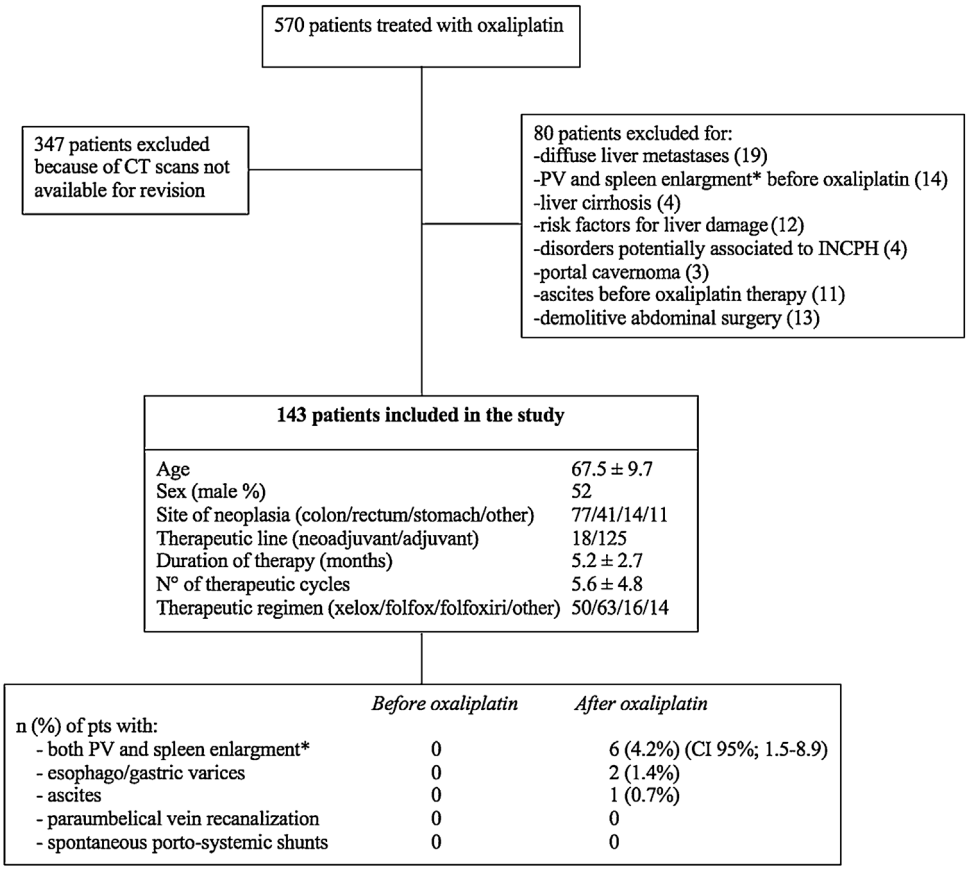


**Fig. 1.** Design of the study, characteristic and main results obtained from the analysis of the 143 patients included in the study. Median ± Standard deviation, *portal vein (PV) diameter > 15 mm and longitudinal spleen diameter > 12 cm.

of cycles of chemotherapy (9.7 ± 6.1 vs 5.4 ± 4.7; p = 0.01) compared to the 135 patients not developing PH.

## 3. Discussion

To our knowledge, some case reports suggested that oxaliplatin may induce vascular liver disease [5] including portal hypertension. Our study represents the first description of the incidence of PH in an oncological population consecutively treated with oxaliplatin.

Since the study was retrospective and the diagnosis of portal hypertension based on radiological data, the patients included in the original database were subjected to a very narrow selection (Fig. 1) aimed at excluding the patients potentially affected by PH before therapy. The retrospective nature of the study did not allow to obtain a histological confirmation but the study shows that PH may develop in a significant number of patients after oxaliplatin treatment. Adding patients who have developed splenomegaly plus portal dilatation with those who have developed esophagogastric varices it can be concluded that the hepatic vascular damage responsible for the development of portal hypertension is quite frequent in patients receiving oxaliplatin therapy and that this side effect should be taken into consideration by subjecting patients to controls that highlight their onset. Thus, at least in patients who developed thrombocytopenia after therapy and with unexplained development of splenomegaly, dilatation of portal vein and other radiological signs of portal hypertension, non-cirrhotic portal hypertension secondary to oxaliplatin must be actively excluded. Moreover, the data from our series show that the development of non-cirrhotic portal hypertension after therapy seems to be dose-dependent, confirming what has been observed in other studies [6,7].

Finally, given the small number of patients having a second or third CT-scan after the therapy, consistent conclusions about the natural history of the disease can't be postulated. The evolution of PH in the four patients described in Table 1 and in the oncological series suggests that, once identified, the patients with PH due to oxaliplatin should be followed-up accurately. In fact, while in some patients the regression of signs of portal hypertension can be observable, in other patients the disease persists and progresses with its complications also many years after the end of the therapy.

The suspicion should arise in the patients developing unexplained splenomegaly and thrombocytopenia, especially if submitted to higher doses of oxaliplatin. In these patients a prompt search for portal vein dilatation and other signs of PH should be performed with CT scan that, if positive, must be followed by endoscopy and liver biopsy. In this setting the use of non-invasive strategies such as liver stiffness has limited application, helpful only to further exclude liver cirrhosis, and it cannot replace the role of the biopsy. The retrospective nature of the study did not allow to obtain a histological confirm but the liver biopsy remains mandatory to assess the presence of NCPH and eventually to exclude other liver diseases.

## Conflict of interest

None declared.

## References

[1] André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343–51.
[2] Slade JH, Alattar ML, Fogelman DR, Overman MJ, et al. Portal hypertension associated with oxaliplatin administration: clinical manifestations of hepatic sinusoidal injury. Clin Colorectal Cancer 2009;8(4):225–30.

[3] Lawal TO, Farris AB, El-Rayes BF, et al. Oxaliplatin-induced hepatoportal sclerosis, portal hypertension, and variceal bleeding successfully treated with transjugular intrahepatic portosystemic shunt. Clin Colorectal Cancer 2012;11(3):224–7.
[4] Morris-Stiff G, White AD, Gomez D, et al. Prasad Nodular regenerative hyperplasia (NRH) complicating oxaliplatin chemotherapy in patients undergoing resection of colorectal liver metastases. The Journal of Cancer Surgery 2013: 1–5.
[5] Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004;15:460–6.
[6] Politano S, Pathak P, Hoff PM, et al. The use of 5-fluorouracil and oxaliplatin (FOLFOX) for colorectal cancer is associated with the development of splenomegaly and thrombocytopenia. Presented at: The American Society of Clinical Oncology Annual Meeting; May 30-June 3 2008. Abstract 4102.
[7] Overman MJ, Maru DM, Charnsangavej C, Loyer EM, Wang H, Pathak P, et al. Oxaliplatin-mediated increase in spleen size as a biomarker for the development of hepatic sinusoidal injury. J Clin Oncol 2010;28(15):2549–55.

Stefania Gioia*
*Dipartimento di Medicina Traslazionale e di Precisione, "Sapienza" University of Rome, Italy*
*Hypertension, "Sapienza" University of Rome, Italy*

Michele Di Martino
*Department of Radiological, Oncological and Pathological Sciences, Department of Radiology, "Sapienza" University of Rome, Italy*

Marina Minozzi
*Department of Radiological, Oncological and Pathological Sciences, Department of Oncology, "Sapienza" University of Rome, Italy*

Silvia Nardelli
*Dipartimento di Medicina Traslazionale e di Precisione, "Sapienza" University of Rome, Italy*
*Hypertension, "Sapienza" University of Rome, Italy*

Enrico Cortesi
*Department of Radiological, Oncological and Pathological Sciences, Department of Oncology, "Sapienza" University of Rome, Italy*

Oliviero Riggio
*Dipartimento di Medicina Traslazionale e di Precisione, "Sapienza" University of Rome, Italy*
*Hypertension, "Sapienza" University of Rome, Italy*

* Corresponding author.
*E-mail address:* stensgioia@hotmail.com (S. Gioia)

10 June 2019

https://doi.org/10.1016/j.dld.2019.06.020

## How will artificial intelligence affect diagnosis and treatment of liver disease?

### 1. Introduction

Recent years have seen a dramatic increase in computational capacity and the volume of data stored which has fuelled progress in machine learning methodology. Increasing attention is turning towards the use of artificial intelligence (AI) in healthcare; AI is facilitating the diagnosis of several conditions, from atrial fibrillation to stroke, and the treatment of others, such as depression and anxiety. Hepatology could see significant change with the introduction of AI but there are important challenges to consider for ensuring successful integration and implementation.

### 2. What is medical artificial intelligence?

The term 'artificial intelligence' encompasses many techniques, from advanced statistical modelling to 'black box' deep learning algorithms. The area providing the most exciting new applications in healthcare is machine learning (ML), where the *'machine'* is able to *learn* complex and non-linear relationships between variables and outcomes of interest. To do so, self-updating algorithms are fed with large quantities of data, which include variables mapped to outcomes of interest. In doing so, they may elucidate previously unidentified relationships, that traditional statistical methods were unable to detect. ML is also able to analyse types of data not previously amenable to advanced computer-based analysis, such as imaging and text data.

Such techniques have many potential uses in hepatology, from finding new patterns of blood marker variation for predicting or diagnosing liver disease to automating image analysis; from identifying liver regions at risk of irradiation toxicity to using drug structure to predict risk of liver injury. AI could increase diagnostic accuracy, improve decision-making by enhancing predictive capabilities and increase efficiency through automation.

### 3. AI & new routes of diagnosis

Many liver conditions represent a diagnostic challenge, such as liver cancer which can be difficult to detect at an early stage. One reason is difficulty gaining direct access for visualisation. Commonly preferred modalities of investigation, therefore, are liver function tests (LFTs), ultrasound scans and, when required, biopsies.

LFTs can lack disease-specificity and ultrasound can lack sensitivity and have inter-operator variability. Liver biopsy is the gold standard method of diagnosis for many conditions, such as acute hepatitis and alcohol-related liver disease, however it can cause infection or bleeding and can have sampling errors. In acute or advanced disease, these risks are deemed more permissible due to the imminent need for diagnosis to facilitate treatment. In conditions with a lower risk-benefit, however, the absence of reliable, non-invasive diagnostic tests, can reduce rates of diagnosis. This is true in NAFLD, which is usually asymptomatic but can lead to cirrhosis and HCC. It has thus been a focal point for research, exploring the use of AI to improve diagnosis through enhanced blood test analysis and automated ultrasound analysis.

#### 3.1. Enhanced blood test analysis

AI models can analyse temporal variations of blood test measurements, with other relevant factors such as gender, BMI and genetic profile, to diagnose and predict disease. Numerous models have been developed for diagnosing NAFLD with such data, including Ma et al.'s Bayesian network which obtained an $F_1$ score of 0.655 [1]. Similar models could be developed for other conditions and may play a role as screening tools, to facilitate earlier treatment. Such analysis may be automated, reducing time doctors spend analysing results and potentially increasing reliability of interpretation. However, we must also guard against over-reliance on such algorithms.

Analysis of key biomarkers using machine learning could also provide deeper insight into the pathophysiology of liver diseases. Ma et al.'s study identified the five strongest predictors of NAFLD as BMI, triglycerides, $\gamma$GT, ALT and uric acid [1].

#### 3.2. Automation of ultrasound imaging

Use of ultrasound for diagnosis is constrained by technical expertise, equipment availability and inter-operator variability.