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Liver failure in patients treated with chemotherapy for colorectal liver metastases: Role of chronic disease scores in patients undergoing major liver surgery. A case-matched analysis

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Abstract

Aim: An accurate and noninvasive tool to predict Chemotherapy Associated Liver Injury (CALI) still lacks. Study aimed to evaluate chronic liver disease scores (Aspartate aminotransferase to Platelet Ratio Index, APRI and Fibrosis-4, FIB-4) as Postoperative Liver Failure (PLF) predictors in patients treated with Oxaliplatin for Colorectal Liver Metastases (CLM).
Methods: 8 patients who developed PLF after major hepatectomy (Group B) were compared to 24 patients who did not develop PLF (Group A) in a case-matched analysis for patients and disease characteristics. ROC curves analysis was performed to assess score accuracy.
Results: In Group A number of CT cycles was lower, (6 vs 9, p NS), interval between treatment and surgery was longer (11 vs 7 weeks, $p < 0.05$) and bevacizumab was more frequently administered (66.7% vs 37.5%, $p < 0.05$). In Group B median APRI score was 0.53 (range: 0.86–4.26) whereas in Group A was 0.30 (range: 0.06–2.21, $p < 0.05$). Median FIB-4 score was 2.46 (range: 0.86–13.65) in Group B and 1.58 (range: 0.27–7.68) in Group A ($p < 0.001$). Multivariate analysis showed a significant correlation between APRI and the onset of PLF. A good accuracy of APRI score was evident in ROC curves with an area under the curve of 0.72 (p 0.003).
Conclusions: APRI score is calculated considering both liver damage and platelet count, it is cost effective and easily available. This study demonstrates that there is a good accuracy in PLF prediction and consequently in CT induced liver damage evaluation.

Keywords: Chemotherapy; Liver surgery; Sinusoidal obstruction; postoperative liver failure; Metastases

Introduction

Almost 50% of patients affected by colorectal cancer develop liver metastases (CLM) and the only curative treatment for this subset of patients is represented by surgical removal of lesions[1]: hence the need for a multidisciplinary management of these patients, together with radiologists, radiotherapists and medical oncologists, to increase resectability rate, therefore improving long term outcome. An optimal timing for systemic ChemoTherapy (CT) administration has not been defined yet: despite this, usefulness and advantages resulting from NeoAdjuvantChemoTherapy (NACT) are well recognized.[2] Indeed, it allows tumor downstaging, expanding both rate of R0 resections and number of candidates to surgery among patients with initially unresectable disease. In addition, preoperative identification of good responders is possible, while patients with disease progression during therapy might be excluded from surgery.[3]

In spite of its benefits, CT may induce liver injury on non-neoplastic parenchyma leading to increased morbidity and mortality after liver resection in patients who received oxaliplatin or irinotecan based regimens.[4–7] Oxaliplatin in particular is associated with Sinusoidal Obstruction Syndrome (SOS), responsible for a significant risk of bleeding and Postoperative Liver Failure (PLF).[8] PLF is one of the most severe causes of mortality following liver surgery[9]: indeed the capability of the liver in tolerating extended resections is based

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upon parenchymal functional reserve, that can be potentially impaired as a result of prolonged chemotherapy.[4–8]

A non-invasive and accurate tool to predict Chemotherapy Induced Liver Injury (CALI) still lacks, but should be essential to evaluate risk of PLF resulting from parenchymal impairment, therefore allowing better patients selection before major resections. APRI (Aspartate aminotransferase to Platelet Ratio Index)[10] and FIB-4 (Fibrosis-4)[11] scores have been reported to grade liver fibrosis in patients with hepatitis C virus infection, even though their importance has been recently high lightened in prediction of high grade lesions of SOS.[12–14]

Aim of the study was to identify clinical and biochemical factors associated to PLF in patients affected by CLM who underwent major liver surgery and previous oxaliplatin based CT in a case-matched analysis. Analysis was focused on chronic liver disease scores. Secondary aim was to assess accuracy of chronic liver disease scores as predictors of PLF.

Methods

Patients

From January 2004 to December 2012, 1413 liver resections were performed at the Hepatobiliary Surgery Unit of San Raffaele Hospital. Data from these patients have been collected in a prospective database and are now retrospectively reviewed.

463 (32.8%) liver resections were performed in patients affected by CLM. Of these, 258 patients were treated with systemic chemotherapy before resection and in 161 (34.7%) of them oxaliplatin-based regimens were used. Out of 101 patients who underwent oxaliplatin based NACT within 4 months before liver resection, without demonstrated chronic liver disease, 54 major or extended hepatectomies were performed. Among this last group, 8 patients developed PLF according to ISGLS definition (in particular all patients had grade B or C PLF, while none of them had grade A PLF)[15] and were compared in a case-matched analysis to 24 patients, belonging to the same population, who did not develop PLF in the postoperative period.

The two groups (Group A including 24 patients who underwent major hepatectomy without PLF and Group B including 8 patients who underwent major hepatectomy and developed PLF) were compared in a case-matched analysis with a 3:1 ratio according to patients baseline characteristics as shown in Table 1.

Table 1
Baseline characteristics.

Variable	Group A	Group B	*P*
	24	8	
Age (yr), mean ± SD	62 ± 8	59 ± 12	NS
Gender (M/F), *n* (%)	13/11 (54.2/45.8)	5/3 (62.5/37.5)	NS
Body mass index (kg/m^2), mean ± SD	22.9 ± 3.6	25.5 ± 5	NS
Primary cancer (colon/rectum)	15/9 (62.5/37.5)	6/2 (75/25)	NS
Liver metastases at diagnosis			
Sinchronous/metachronous	14/10 (58.3/41.7)	5/3 (62.5/37.5)	NS
Number of liver lesions, median (range)	4 (1–10)	2 (1–4)	NS
Total tumor diameter in cm, mean ± SD	7.7 ± 4.1	5.1 ± 4.5	NS
Resectable/unresectable	19/5 (79.1/20.9)	6/2 (75/25)	NS
Preoperative portal vein embolization	3 (12.5)	1 (12.5)	NS
Two stage hepatectomy program	3 (12.5)	1 (12.5)	NS
ASA > 2	4 (16.7)	2 (25)	NS

Neoadjuvant systemic chemotherapy

Patients with unresectable or marginally resectable disease were candidates to CT to downsize liver metastases and convert them to resectability. All the patients were treated by a combination of fluorouracil, leucovorin and oxaliplatin. In most of them a biologic agent (bevacizumab) was used in addition to CT as a first line treatment. Response to CT was evaluated every 4–6 weeks using computed tomography, according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Preoperative workup

Before surgery, all patients were evaluated by thoraco-abdominal and pelvic imaging, blood tests including serum tumor markers, colonoscopy and/or rectal echoendoscopic ultrasound (EUS). Selected patients also underwent Positron Emission Tomography (PET), to exclude presence of extrahepatic disease.

The following biochemical data were assessed before liver resection: hemoglobin level, serum creatinine level, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, gamma glutamyltransferase and alkaline phosphatase levels, serum total bilirubin level, serum albumin level and International Normalized Ratio (INR). APRI score was calculated for every patient as follows:

$$\frac{\left[\text{AST level}\,\frac{\frac{\text{U}}{\text{L}}}{\text{ULN}}\right]}{\left[\text{Platelet count}\left(\frac{10^9}{\text{L}}\right)\right]}\times 100.$$

FIB-4 score was instead calculated as follows:

$$\frac{\left[\text{age}\left(\text{years}\right)\times \text{AST}\left(\frac{\text{U}}{\text{L}}\right)\right]}{\left[\text{Platelet count}\left(\frac{10^9}{\text{L}}\right)\times\sqrt{(ALT)\left(\frac{\text{U}}{\text{L}}\right)}\right]}.$$