Original research

Preoperative assessment of chemotherapeutic associated liver injury based on indocyanine green retention test

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HIGHLIGHTS

- ICG test can predict the diagnosis of SOS but does not give any information on nodular regenerative hyperplasia and steatohepatitis.
- High preoperative ICGR15 values are more common in elderly male patients and after bevacizumab administration.
- High preoperative ICGR15 values not represent a contraindication to liver surgery.

ARTICLE INFO

ABSTRACT

Background: The aim of the study was to assess the capacity of indocyanine green retention test at 15 min (ICGR15) to predict chemotherapeutic-associated liver injuries (CALI).
Methods: Patients undergoing liver resection for CLM that received preoperative oxaliplatin and/or irintecan-based chemotherapy within 3 months before surgery and scheduled first hepatectomy were considered.
Results: 166 out of 983 patients treated between 01/2001 and 04/2014 fulfilled the inclusion criteria. The median number of cycles of preoperative chemotherapy was 6.0 ± 4.87. Chemotherapy was mainly based on oxaliplatin in 123 (74.1%). Bevacizumab was associated in 51(31%) patients. A total of 102 (61.4%) patients had at least 1 CALI. Grade 2–3 steatosis occurred in 56 (33.7%) patients and steatohepatitis in19(11.5%). Sinusoidal obstructive syndrome (SOS) was presented in 93 (56%) patients. 23(13.8%) patients had nodular regeneration hyperplasia. At multivariate analysis the only predictive factor of ICGR$\geq$10% was age$\geq$65 years (p = 0.001). A median split (ICGR15 = 8%) was used to categorized ICGR15 value. Multivariate analysis showed that age$\geq$ 65 [OR 2.530 (CI95% 1.28–4.97) p < 0.001], male sex [OR 2.614 (CI95% 1.31–5.20) p < 0.001], SOS [OR 1.954 (CI95% 1.00–3.81) p = 0.050] and administration of Bevacizumab [OR 2.201 (CI95% 1.07–4.50) p = 0.031] were predictive factors for ICGR$\geq$8%.
Conclusions: ICGR15 test can predict the diagnosis of SOS. High ICGR15 value is more common in elderly male patients and after bevacizumab administration.

1. Introduction

During recent years an increasing number of patients with colorectal liver metastases receive chemotherapy before hepatectomy [1–3]. As side effect the number of patients who develop chemotherapy associated liver injury (CALI) is consensually increased [4–7]. Two types of CALI have been identified [8,9]: injury to sinusoidal endothelial cells and non-alcoholic fatty liver disease. The first type of injury include a range of histological changes like sinusoidal obstructive syndrome (SOS) and nodular rigenerative hyperplasia (NRH) and is strictly correlated to administration of Oxaliplatin. Non-alcoholic fatty liver disease includes steatosis, steatohepatitis and cirrhosis and it is more common in patients that received Irinotecan based chemotherapy as described by Fong in 2006 [10]. Many studies showed that CALI can reduce liver functional reserve and worsen postoperative course after liver resection

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[4,11–13]. In particular higher rates of overall morbidity [11], transfusion rate [4] and hepatic dysfunction with ascites [12] were descriptive in patients with SOS. NRH was associated to an increasing risk of portal hypertension and hepatic morbidity [13]. Finally one study reported that steatohepatitis has been associated to higher 90-day mortality [14]. Obviously the preoperative diagnosis of CALI could be crucial in patients selection before liver resection. For these reasons many authors tried to identify predictive factors of CALI [6,12,13,15–18]. The indocyanine green retention test at 15 min (ICGR15) is largely used to assess hepatic functional reserve in patients with chronic liver diseases and cirrhosis [19,20]. Consequently the ICG value is currently incorporate in decision tree algorithm of patients with hepatocellular carcinoma [21,22]. The aim of this study is to assess the capacity of indocyanine green retention test to predict preoperatively CALI in a large series of patients all treated with modern chemotherapy.

2. Patients and methods

All consecutive patients affected by colorectal liver metastases scheduled for liver resection between 01/2001 and 04/2014 were considered. Patients data were obtained from a prospective maintained database. Inclusion criteria were preoperative oxaliplatin and/or irinotecan-based chemotherapy within 3 months before surgery and scheduled first hepatectomy. Patients lacking complete data concerning chemotherapy, preoperative ICGR15 and histology features of CALI were excluded. Also patients with viral and alcoholic chronic liver diseases were excluded.

2.1. Chemotherapy associated liver injury definition

Steatosis was estimated as the percentage of involved hepatocytes and categorized as follows: absent (0%), mild (1%–30%), moderate (31%–60%), and severe (>60%). SOS was graded semi-quantitatively according to the histological scoring systems published by Rubbia-Brandt et al. [8]: 0, absent; 1, mild (centrilobular involvement limited to one-third of the lobular surface); 2, moderate (centrilobular involvement in two-thirds of the lobular surface); and 3, severe (complete centrilobular involvement). Steatohepatitis was defined as the concomitant presence of steatosis, lobular inflammation, and hepatocellular ballooning. Steatohepatitis activity was scored according to Kleiner score [23].

2.2. Indocyanine green retention rate test

ICGR15 was determined preoperatively in all patients with total bilirubin levels in the reference range (<2 mg/dl). After a basal blood-sample ICGR15 (Pulsion® medical Systems, Italy) at a dose of 0.5 mg/kg, was administered by the antecubital vein of the opposite arm. Then, venous peripheral blood samples were collected every 5 min for 15 min. ICGR15 were calculated by fitting the serum disappearance curve by a single exponential decay equation [24].

2.3. Statistical data

All statistical analysis were performed with Stat Soft version 7.0 (Verona-Italy). Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables were compared between groups by the unpaired *t*-test or Mann-Whitney *U* test, as appropriate. Statistical significance was determined at p < 0.05. Receiver operating characteristic curves were plotted to identify the value of ICGR in predicting SOS with a high sensitivity and specificity. The study was approved by the local ethical committee.

2.4. Patients management

The management of patients with colorectal liver metastases at our Institution has been previously reported [25,26]. Briefly, patients undergoing neoadjuvant chemotherapy underwent restaging after 4–6 cycles. Surgery was scheduled if no progression occurred. The ICGR15 test was performed before surgery. In patients scheduled to portal vein embolization or ligation the ICG test was performed before portal occlusion.

2.5. Definition

Major hepatectomy was defined as the resection of ≥3 Couinaud's segments [27]. Operative mortality was defined as death within 90 days after surgery or before discharge from the hospital. Morbidity included all postoperative complications and was classified according to Dindo classification [28]. Complications of grade III or higher were defined as major morbidity. Hepatic insufficiency was defined as an increased international normalized ratio and concomitant hyperbilirubinemia ≥5 days postoperatively [29]. CALI was defined as presence of almost one of the following histology features: grade 2/3 steatosis, grade 2/3 SOS, NRH and steatohepatitis [30]. ICGR15 value higher than 10% was considered abnormal [21].

3. Results

3.1. Patients characteristics and chemotherapy details

166 out of 983 patients with colorectal liver metastases treated during the study period (11.8%) fulfilled the inclusion criteria
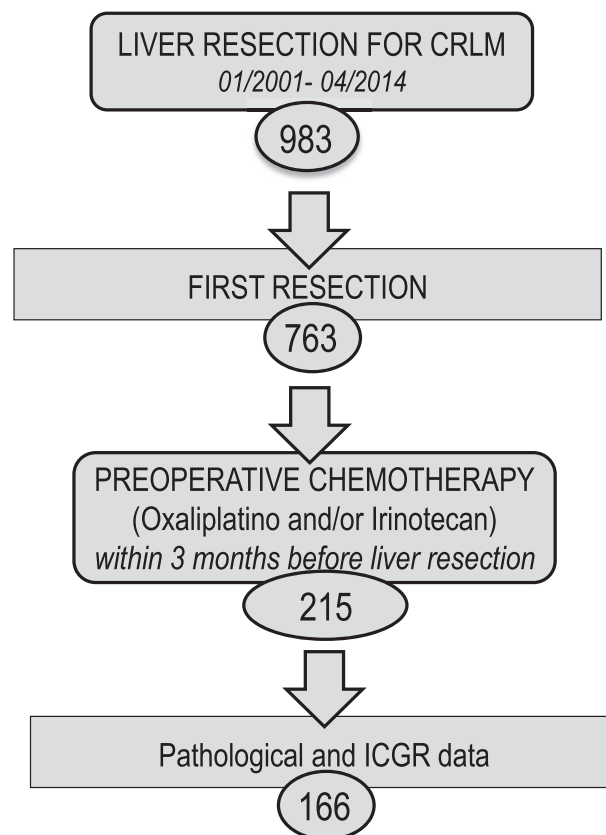

Fig. 1. Flow chart of patients considered suitable for the study. CRLM: colon-rectal liver metastases; ICGR15: indocyanine green retention test at 15 min.