http://dx.doi.org/10.1016/j.hpb.2017.08.030 HPB

ORIGINAL ARTICLE

Impact of chemotherapy-associated liver injury on tumour regression grade and survival in patients with colorectal liver metastases

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Abstract

Background: An inverse relation between chemotherapy-associated liver injury (CALI) and tumour response to chemotherapy has been reported. The aim was to validate these findings, and further investigate the impact of CALI on survival in patients who underwent partial hepatectomy for colorectal liver metastases (CRLM).

Methods: Patients who received neoadjuvant chemotherapy and underwent partial hepatectomy for CRLM between 2008 and 2014 were included. Liver and tumour specimens were histologically examined for CALI (steatosis, steatohepatitis, sinusoidal dilatation [SD], nodular regeneration) and tumour regression grade (TRG). TRG 1–2 was defined as complete tumour response.

Results: 166 consecutive patients were included with a median survival of 30 and 44 months for recurrence-free and overall survival, respectively. Grade 2–3 SD was found in 44 (27%) and TRG 1–2 was observed in 33 (20%) patients. Of studied CALI, only grade 2–3 SD was associated with increased TRG 3–5 (odds ratio 3.99, 95% CI 1.17–13.65, $p = 0.027$). CALI was not significantly related to survival. TRG 1–2 was associated with prolonged recurrence-free (hazard ratio 0.47, 95% CI 0.25–0.89, $p = 0.020$) and overall survival (hazard ratio 0.35, 95% CI 0.18–0.68, $p = 0.002$).

Conclusion: CALI was not directly related to survival. CALI was, however, associated with diminished complete tumour response, and diminished complete tumour response, in turn, was associated with decreased survival.

Received 26 June 2017; accepted 31 August 2017

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Introduction

Neoadjuvant chemotherapy is used to downsize colorectal liver metastases (CRLM) with the aim of facilitating future hepatic resection.[1–3] Tumour downsizing relies on the tumour response to chemotherapy, as expressed by the tumour regression grade (TRG).[4] CRLM patients with complete tumour response have been shown to have better survival than those with poor response.[5]

Systemic chemotherapy may have beneficial effects, but frequently causes undesired liver parenchymal damage,

The paper is not based on a previous communication to a society or meeting.

Please cite this article in press as: Zhao J, et al., Impact of chemotherapy-associated liver injury on tumour regression grade and survival in patients with colorectal liver metastases, HPB (2017), http://dx.doi.org/10.1016/j.hpb.2017.08.030

collectively referred to as chemotherapy-associated liver injury (CALI). For instance, oxaliplatin-based treatment appears to be related to the development of sinusoidal obstruction syndrome[6–8] and nodular regeneration,[9] whereas irinotecan-based regimens are associated with increased occurrence of steatohepatitis.[10–12] The authors have recently demonstrated that chemotherapy-associated sinusoidal dilatation was related to increased major morbidity, and therefore advised adaptation of surgical management in case of its presence.[8] Moreover, the authors[13] and others[5] have previously shown that chemotherapy-associated sinusoidal dilatation is associated with poor tumour response to neoadjuvant chemotherapy.

Despite the significant inverse relation between CALI and tumour response, few studies have examined the effect of CALI on the long term survival of patients who undergo liver resection for CRLM. Although one study claimed that chemotherapy-associated sinusoidal dilatation was associated with shortened survival,[14] another study could not reproduce this.[5] Therefore, it remains unclear whether CALI influences survival. The first aim of the present study was to validate the relation between CALI and tumour response in an independent large cohort. The second aim was to explore whether sinusoidal dilatation, nodular regeneration, steatosis, and steatohepatitis were associated with survival in CRLM patients after partial hepatectomy.

Methods

Inclusion of patients

Consecutive patients who had undergone partial hepatectomy for CRLM at Maastricht University Medical Centre between January 2008 and December 2013 were considered for this study. Inclusion criteria were: (i) patients treated with neoadjuvant chemotherapy; (ii) availability of adequate histopathology assessment of non-tumour bearing liver tissue (i.e. presence of non-tumour-bearing liver at a distance of more than 2 cm from the tumour). Patients with cirrhosis were excluded from the study.

Definition and data collection

Comorbidity was defined as any disease affecting the patient apart from colorectal liver metastases (e.g. diabetes mellitus, and pulmonary, renal, cardiovascular, and other diseases). Overall morbidity was defined as any complication occurring within 30 days after surgery or during hospital stay and graded according to the classification of Dindo *et al.*[15] Major morbidity was defined as Dindo-Clavien score IIIa (requiring invasive intervention) or higher. The concept of a liver surgery-specific complication was in correspondence to the liver surgery-specific composite endpoint (CEP) developed in 2011, and included one or more of the following events: ascites, postoperative liver failure, bile leakage, intra-abdominal abscess, intra-abdominal haemorrhage, and operative mortality.[16] 90-day mortality rate was used as it has been shown to be an equivalently specific measure of surgery-related death and represents a legitimate measure of surgical quality.[17] Because postoperative infectious complications have been shown to be significant prognostic factors for long-term survival after hepatectomy for colorectal liver metastases,[18] they were included as confounders when studying factors related to survival in multivariable Cox regression models. Postoperative infectious complications were prospectively collected daily by an independent infection-control nurse based on the following definitions, and defined as a combination of surgical site infections,[19] remote site infections, and systemic sepsis. Radical resection was defined as resected tumour lesions with a surgical margin of more than 1 mm, and confirmed to have absent tumour cells on the margin from routine pathology reports. With respect to tumour recurrence, patients were followed up by monitoring blood levels of carcinoembryonic antigen (CEA) every three months together with liver radiologic imaging half-yearly in the first 2 years, and CEA half-yearly together with liver radiologic imaging annually up to 5 years after surgery. The date of last follow-up was November 2, 2016.

Pathology assessment of non-tumour-bearing liver and metastases

Sinusoidal dilatation, nodular regeneration, steatosis, and tumour regression grade were semi-quantitatively assessed by two experienced liver pathologists (AW and CV). Diagnosis of nodular regeneration was made only when confirming liver fibrosis was absent or minor. Assessment of steatohepatitis was performed by another experienced liver pathologist (JV) independently. All pathologists were blinded to clinical information concerning the patients.

The tissue was fixed in formalin, embedded in paraffin, and stained with haematoxylin & eosin and reticulin. Sinusoidal dilatation was graded according to Rubbia-Brandt *et al.*[20] Nodular regeneration was graded according to the Wanless scoring system.[21] Steatosis was graded according to Kleiner *et al.*[22] Grade 2–3 liver injuries (i.e. sinusoidal dilatation, steatosis, and nodular regeneration) were defined as severe lesions, respectively. Patients presenting with at least grade 1 of each of the three features (steatosis, hepatocellular ballooning, and lobular inflammation) were classified as having steatohepatitis according to the recently established SAF scoring system.[23] Tumour regression was graded as described by Mandard *et al.*,[4] for the assessment of tumour regression after preoperative chemoradiotherapy for esophageal carcinoma, and modified for liver metastases. Grade 1 is characterized by the absence of histologically identifiable residual tumour and extensive fibrosis; grade 2 shows the presence of rare residual tumour cells scattered through the fibrosis; grade 3 represents a substantial amount of residual tumour cells but fibrosis dominated; grade 4 reflects residual tumour cells outgrowing fibrosis; and grade 5 indicates the absence of any tumour regression. Tumour regression grade 1–2 was defined as complete tumour response, and grade 3–5 was defined as poor tumour response.

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