Histological Liver Injury and Surgical Outcome after FOLFOX Followed by a Hepatectomy for Colorectal Liver Metastases in Japanese Patients

Hiroyuki Komori, Toru Beppu, Yoshihumi Baba, Kei Horino, Choi Imsung, Toshiro Masuda, Hiromitsu Hayashi, Hirohisa Okabe, Ryuu Ootao, Masayuki Watanabe, Hiroshi Takamori, Kenichi Iyama, and Hideo Baba,

Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University

Kenichi Iyama Department of Surgical pathology, Graduate School of Medical Sciences, Kumamoto University

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Correspondence to: Hideo Baba, MD,PhD, FACS
hdobaba@kumamoto-u.ac.jp
Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University
Honjyo 1-1-1, Kumamoto, 860-8556, Japan
TEL: 96-373-5212, FAX: 96-371-4378

Abbreviations; FU, fluorouracil; LV, leucovorin; FOLFOX, chemotherapy with oxaliplatin plus fluorouracil and leucovorin; FOLFIRI, chemotherapy with irinotecan plus fluorouracil and leucovorin; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis;

Influence of chemotherapy on liver function and resections

Abstract

Background.

To clarify the influence of preoperative chemotherapy on the liver function and the correlation between histological hepatic injury and the postoperative outcome in patients with colorectal liver metastases who underwent a hepatic resection.

Methods.

Twenty-seven patients who underwent a hepatic resection for colorectal liver metastases were included. Fifteen patients with initially unresectable colorectal liver metastases were able to undergo a tumor resection after FOLFOX (Oxaliplatin plus fluorouracil and leucovorin, with a mean of 7.7 cycles) were compared to 12 patients underwent a hepatectomy with no preoperative chemotherapy. The postoperative mortality, morbidity, changes in liver function tests, and pathology of the resected liver were examined.

Results.

Pre-operative FOLFOX therapy was significantly associated with the macroscopic appearance of oxaliplatin-associated blue liver ($p=0.02$), and a tendency toward sinusoidal dilatation (33.3 % in FOLFOX group versus 8.3% in the no chemotherapy

group, p= 0.056). The preoperative liver function tests, showed that the albumin and ICGR15 test were significantly worse after FOLFOX therapy, however intraoperative events, postoperative values of liver function tests and morbidity rate were similar in the two groups. There was no postoperative mortality in any of the patients.

Conclusions.

Although preoperative FOLFOX administration for the patients with colorectal liver metastasis caused macroscopic blue liver, microscopic sinusoidal dilatation in the liver parenchyma and a significant decrease in liver function, there was no increase in the morbidity and mortality rate, in comparison to patients without preoperative chemotherapy.

Introduction

Liver metastases are among the most common metastases from colorectal cancer leading to death from this disease. Depending on the stage of the primary colorectal cancer, liver metastases occur in 20% to 70% of the patients (1, 2). A hepatic resection remains the only treatment that can yield 5-year survival rates of 20% to 50% (3-6), if the liver metastases can be curatively resected without nonresectable extrahepatic disease. Recently, various new therapeutic drugs have been introduced. These include irinotecan, a topoisomerase I inhibitor (7), and oxaliplatin, a platinum derivative with significant activity in colorectal cancer (8). These drugs can yield high response rates of 34~50% with a median survival of 15~19.5 months in patients with stage IV colorectal cancer (9, 10). With such high response rates, 10 to 13% of primary-unresectable colorectal liver metastases can became resectable (11-13). In Japan, a CPT-11 based regimen known as “FOLFIRI” (CPT-11 plus fluorouracil and leucovorin), or oxaliplatin based regimen “FOLFOX”(Oxaliplatin plus fluorouracil and leucovorin) have became widely used for metastatic colorectal cancer patients.

On the other hand, the widely used chemotherapeutic agents, 5-FU and its

derivatives or irinotecan, have been reported to induce steatosis of the liver (14, 15). In addition, CPT-11 and oxaliplatin can be associated with liver injury (16-20). Vauthey et al. reported a close association between preoperative CPT-11 administration and steatohepatitis (17). Rubbia-Brandt et al. and Karoui et al. have suggested that an oxaliplatin based regimen could induce sinusoidal obstruction (20, 21).

The aim of this study was to clarify the influence of preoperative chemotherapy using FOLFOX on the morphological changes in the liver parenchyma as well as changes in liver function and surgical outcome in Japanese patients with liver metastases from colorectal cancer.

Patients and methods

Patients

Forty-one patients underwent a hepatic resection for liver metastases from colorectal carcinoma between April 2005 and November 2007, in the Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Japan. Seven patients that underwent a hepatic resection with a preoperative chemotherapy regimen other than FOLFOX within 6 months were excluded. In 22 patients who were administered FOLFOX, more than three months after the last FOLFOX (2 patients), or followed by other chemotherapy (5 patients), were also excluded. Twenty-seven patients were included in the current study (17 men and 10 women). The median age was 61 years (range, 39-83). The primary tumor location was the colon in 15 patients (60%) and the rectum in 10 patients (40%). Liver metastases were synchronous in 13 patients (52%). The preoperative mean CEA value was 241 ng/ml ± 476 (range; 2.3-3157). Patients were classified into two groups; the FOLFOX group and no chemotherapy group. The liver metastases that were initially considered to be unresectable in all patients treated with FOLFOX subsequently became resectable

after chemotherapy.

Protocol of Systemic Chemotherapy

The FOLFOX4 regimen administered before a hepatectomy included LV+5FU+ oxaliplatin (FOLFOX4; Day1: oxaliplatin 85mg/m^2, LV 100mg/ m^2, 5FU 400mg/ m^2 bolus, 5FU 600mg/m^2 continuous infusion for 22 hr. Day2: LV 100mg/ m^2, 5FU 400mg/ m^2 bolus, 5FU 600mg/m^2 continuous infusion for 22 hr. and repeat this regimen every two weeks.)(22).

Clinical assessments and the surgical procedure

All patients underwent pre and postoperative assessments including liver function tests, blood counts, coagulation tests, and measurement of serum urea, creatinine, and electrolytes. Indocyanine green retention rate at 15 minutes (ICG-R15) and the ratio of liver to heart-plus-liver radioactivity of Tc-GSA 15 minutes (LHL15) were evaluated preoperatively. The most impaired values during the postoperative hospital days were analyzed among the parameters of liver function (prothrombin time activity, albumin, total-bilirubin, aspartase aminotransferase (AST),

alanine aminotransferase (ALT)). The correlation between the cycles of FOLFOX or the total dose of oxaliplatin, and damage of liver function was also evaluated.

The resectability of the hepatic lesions was assessed by abdominal ultrasound and chest and abdominal CT scans after every three cycles. The tumor regression effect was calculated with CT according to the RECIST criteria. During the surgery, a complete examination of the liver was performed with intraoperative ultrasonography to determine the number and the location of the lesions and their anatomical relationship to the vascular system. A liver transection was performed using an ultrasonic dissector. Biliary and vascular pedicles were secured by ligation and clipping, and hemostasis of the liver cut surface was completed with a dissecting sealer (Valley Lab, Boulder, Colorado, USA) or a VIO soft coagulation system (ERBE, Elektromedizin GmbH, Germany). The duration of the surgery, the amount of blood loss, blood transfusion requirements (packed red cell units), the type of liver resection and the vascular interruption time were recorded individually.

Pathologic Examination

Several samples of non tumorous tissue from the resected liver specimen were taken and fixed, paraffin-embedded, and stained with hematoxylin and eosin. The samples were blindly investigated by two pathologists (I.K, and B.Y.). The presence of sinusoidal dilatation (SD) was recorded using the Rubbia-Brandt Score (20) as follows: 0, absent; 1, mild (centrilobular involvement limited to one-third of the lobular surface); 2, moderate (centrilobular involvement extending in two-thirds of the lobular surface); 3, severe (complete lobular involvement). The liver steatosis was graded from 0 to 3: absent~5% (grade 0), 5%~33% of hepatocytes (grade 1), between 33% and 66% (grade 2), and >66% (grade 3). The steatohepatitis was evaluated using the NAFLD Activity Score (NAS), scored from 0 to 2: not NASH , 3 to 4: borderline NASH and >5: NASH (23).

In addition, peliosis, hemorrhagic centrilobular necrosis and regenerative nodular hyperplasia were evaluated as previously described (24). The correlation between histological hepatic injury and FOLFOX cycles, degree of pathologic effects of the tumor, adverse effects, surgical insult and postoperative morbidity were also evaluated.

Statistical Analysis

Quantitative data were expressed as the means ± SD. Comparisons between the groups were analyzed using the χ^2 test with the Yates correction, or Students' *t*-tests for quantitative and qualitative variables as appropriate, and comparisons of the pathological scores of steatosis, steatohepatitis and sinusoidal dilatation between two groups were analyzed using the Mann Whitney U test. The correlations between the Rubbia-Brandt Score and vascular exclusion time, the number of cycles of chemotherapy, preoperative liver function, intraoperative blood loss, postoperative days, and also between the total dose of oxaliplatin and the damage of liver function were analyzed using the Spearman rank correlation. All statistical significance was performed at a p-value of 0.05. Statistical analyses were made using the StatView 5.0 software package (Abacus Concepts, Calabasas, CA).

Results

Patients, Tumors and Surgical Procedures

The clinical characteristics of the 27 patients in the FOLFOX (n=15) or no chemotherapy group (n=12) are summarized in Table 1. In the FOLFOX group, the mean age of the patients was significantly older, and platelet counts, serum albumin level and ICG-R15 were significantly worse in comparison to the no chemotherapy group (Table1). The mean preoperative tumor size after FOLFOX was significantly smaller, and the synchronous liver metastases were more frequently than in the no chemotherapy group. The number of metastases were larger in the FOLFOX group (5.9 ± 5.6 vs. 2.4 ± 2.2), but the difference was not significantly. (Table 2).

The liver resections included 7 or more right hepatectomies or more and 1 left hepatectomy and 9 sectionectomies. Partial resections were performed in combination with wedge resections in 10 patients. Radio-frequency ablation (RFA) was additionally performed in three patients in the FOLFOX group, and one in the no chemotherapy group. Vascular interruption was performed during surgery in 22/27 patients. No significant differences were observed in the types of hepatic resection,

vascular interruption time, surgical time, blood loss, and the ratio of patients requiring blood transfusions between the two groups (Table 3).

Pathological findings

The pathological examinations in the non-tumorous liver are summarized in Table 4. The frequency of macroscopic “blue liver” was significantly high in the FOLFOX group. No steatosis >grade 2 was observed in the patients of the FOLFOX group. There were no significant differences in the NAS score for steatohepatitis. Steatohepatitis (NAS >5) was observed in two patients (14%) only in the no chemotherapy group. Sinusoidal dilatation (Rubbia-Brandt Score >2) was seen in 5 of 15 patients (33.3%) in the FOLFOX group, and a tendency toward a higher score of sinusoidal dilatation was observed in the FOLFOX group. (Table 4) (Fig1). No significant correlation was observed between the Rubbia-Brandt Score and the vascular exclusion time, the number of cycles of chemotherapy, intraoperative blood loss, and the postoperative days, Peliosis, hemorrhagic centrilobular necrosis and regenerative nodular hyperplasia were not detected in either groups.

Post-operative course

No significant difference was observed between the two groups in the postoperative value of liver function tests (Table 5). There was no postoperative mortality. Postoperative complications occurred in two (1 aspiration pneumonia, 1 biliary fistula requiring drainage >1 month) of 15 patients in the FOLFOX group and three (1 intestinal hemorrhage, 2 biliary fistula requiring drainage >1 month) of 12 patients in the no chemotherapy group (Table 6). There was no significant difference in the duration of post-operative hospital stay between the two groups.

Discussion

The use of preoperative chemotherapeutic agents has numerous theoretical benefits ; however the effect of these agents on the underlying liver parenchyma remains unclear. Some reports have showed that preoperative chemotherapy had no influence on either liver function or the risk of liver resection (21, 25, 26). In the current study there was no patient who could not undergo a hepatectomy because of liver injuries after chemotherapy. However, the liver function, including the serum albumin level and ICG-R15 levels, were significantly worse in comparison to the no chemotherapy group. The administration of FOLFOX might influence the preoperative laboratory data, although the total dose of oxaliplatin did not correlate with the damage of the liver function.

It has recently, it has been reported that new chemotherapeutic agents could cause sinusoidal dilatation in the liver. Sinusoidal dilatation (Rubbia-Brandt score showed >Grade 2) was observed in up to 63% patients treated with pre-operative chemotherapy (27). Karoui M *et al*. reported that sinusoidal dilatation was present in 49% of patients in the chemotherapy group (only 25% in the control group, $p = 0.005$), although it was not stratified by the type of chemotherapy regimen type, and the

correlation between the type of chemotherapeutic agent and the pathological changes was not evaluated.(21) Vauthey *et al*. demonstrated that a chemotherapeutic regimen with or without oxaliplatin was a key factor in the development of sinusoidal dilatation, (17) but Aloia T *et al*.(24) reported that 19% (10/52) of the patients administered an oxaliplatin containing regimen showed sinusoidal alteration (vasodilatation and congestion), similarly the rate was 12% as opposed to (2 /17) patients who did not. In the current study, blue liver was observed in 7 of 15 patients of the FOLFOX group ($p=0.02$). Sinusoidal dilatation (>Grade 2) was detected 5 in 15 patients (33.3%) of the FOLFOX group, and the distribution of high-grade patients with sinusoidal dilatation was more frequent in comparison with the no chemotherapy group.

Venoocclusive disease (VOD) of the liver, including sinusoidal dilatation, is a clinical syndrome in patients with blood transplantation or bone marrow transplantation resulting from liver damage by pre-transplant radiation and chemotherapy (28). In addition, the clinical course of severe VOD frequently progresses into lethal results. In contrast, oxaliplatin containing chemotherapy causes sinusoidal dilatation without such a severe complications as reported before (17, 24).

Blue liver and sinusoidal dilatation might cause an increased amount of bleeding during a hepatic resection for colorectal liver metastasis. Karoui M *et al*. reported that sinusoidal dilatation was detected in 49% in the chemotherapy group, but there was no impact on the intraoperative blood transfusion (3±1.9 packed red cell units). Aloia T et al. reported that patients who received oxaliplatin based chemotherapy before hepatic resection for colorectal liver metastases were more likely to receive intraoperative RBC transfusions (24). They did not address the relationship between sinusoidal dilatation (FU/LV; 30%, FU/LV/I-OHP; 19%) and oxaliplatin. Although the presence of surgical necrosis, hemorrhagic centrilobular necrosis and regenerative nodular hyperplasia in the nontumor-bearing liver after systemic chemotherapy was significantly related to the oxaliplatin regimen, these pathologic changes were never observed in either group in the current study. Perioperative transfusions are reported to be a risk factor for poor outcome after a liver resection for metastatic colorectal cancer (29). In the current study, the mean blood loss was 435 ml and the RBC transfusion rate was 15.4% in FOLFOX group which was comparable to the no chemotherapy group. No increased risk was not encountered in intraoperative blood loss and RBC transfusion

due to preoperative FOLFOX administration. Recent advances in surgical techniques and perioperative managements might reduce the risk of liver resections and contribute to better prognosis. The postoperative mortality was less than 0-4% in recent series of reports of hepatic resection for colorectal liver metastases (30, 31). The postoperative morbidity, including transient liver failure, hemorrhage, subphrenic abscess, and biliary fistula, occur in 20% to 40% of patients (30-34). In the current study, the use of new devices (a dissecting sealer and a VIO soft coagulation system) during liver transection might have contributed to the reduced blood loss, and thus made it possible to perform safe liver resection despite the significant preoperative liver function damage.

Morbidity after a hepatectomy is correlated with the number of cycles of preoperative chemotherapy but not to the type of chemotherapeutic agent (21). The percentage of postoperative morbidity was 61.5% when the chemotherapy was repeated over 10 cycles. In the current study, an average of 7.7 cycles (range 5~10) of FOLFOX were administered before the hepatic resections. Although three patients in the FOLFOX group received 10 cycles of chemotherapy, the postoperative liver function was approximately equal to the no chemotherapy group and no postoperative mortality

was encountered. The mean number of the cycles of FOLFOX was less than that reported by Karouis', and this differencemay have contributed to the lower morbidity (13%). Recently, a correlation has been reported between sinusoidal injury and postoperative morbidity was reported (35). Sinusoidal injury was significantly associated with a decreased liver functional reserve before a hepatectomy, and increased postoperative morbidity. The preoperative ICG-R15 values became higher, and number of postoperative hospital days tended to be longer in the oxaliplatin-based chemotherapy group. In contrast, no positive correlation between sinusoidal dilatation and morbidity was recognized in the current study. A larger number of patients might be necessary to confirm the true correlation (data not shown).

In conclusion, the FOLFOX regimen influenced the preoperative laboratory data, and caused gross blue liver and histological sinusoidal dilatation in the background liver, nevertheless the surgical outcome and postoperative mortality and morbidity rates were equivalent to the no chemotherapy group. FOLFOX as preoperative chemotherapy can be safely administered as preoperative chemotherapy for Japanese patients with initially unresectable colorectal liver metastases.

Figure Legends

Figures1. Sinusoidal distention and congestion in a patient who received FOLFOX. Only scattered macro vesicular steatosis is present. Compare the zone with sinusoidal distention (arrows) to the normal parenchyma in the left lower quadrant. Hematoxylin and eosin, X100.

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