

Effect of age on the development of chemotherapy-associated liver injury in colorectal cancer liver metastasis

TAIICHI WAKIYA¹, DAISUKE KUDO¹, KEINOSUKE ISHIDO¹, NORIHISA KIMURA¹,
YUTA YAKOSHI¹, YOSHIKAZU TOYOKI¹, HIROSHI KIJIMA² and KENICHI HAKAMADA¹

Departments of ¹Gastroenterological Surgery and ²Pathology and Bioscience, Hirosaki
University Graduate School of Medicine, Hirosaki, Aomori 036-8562, Japan

Received March 13, 2017; Accepted May 10, 2017

DOI: 10.3892/mco.2017.1314

Abstract. With the prolongation of the mean lifespan, the number of elderly individuals undergoing liver resection for colorectal cancer liver metastasis (CRLM) following chemotherapy has increased. However, the effect of age on the development of chemotherapy-associated liver injury (CALI) in CRLM remains unclear. The aim of the present study was to elucidate the effect of age on the development of CALI in CRLM. A total of 64 patients undergoing liver resection for CRLM following oxaliplatin-based chemotherapy (OBC) were investigated. The patients were divided into three groups (group A: <65 years, group B: 65-74 years and group C: >75 years) according to age at surgery, and the development rate of CALI was compared between the groups. The patients underwent pathological assessments to determine the degree of histopathological injury of the non-cancerous liver parenchyma. Group A included 37 cases, group B 17 cases and group C 10 cases. There were no significant differences among the groups regarding the number of OBC cycles and duration of OBC cessation. Sinusoidal injury was observed in 27.0, 29.4 and 30.0% of the cases in groups A, B and C, respectively; the differences were not statistically significant ($P=0.479$). Steatohepatitis was observed in 35.1, 35.3 and 40.0% of the cases in groups A, B and C, respectively; the differences were not statistically significant ($P=0.958$). There was no significant correlation between age and sinusoidal

pathological score ($r=-0.102$, $P=0.423$) or non-alcoholic fatty liver disease activity score ($r\leq 0.001$, $P=0.997$). Therefore, the development of CALI following OBC treatment in CRLM was not found to differ by age.

Introduction

Liver resection with systemic chemotherapy is the only treatment offering the possibility of long-term survival in patients with colorectal cancer liver metastasis (CRLM) (1-4). However, systemic chemotherapy for CRLM has been shown to cause chemotherapy-associated liver injury (CALI), including sinusoidal injury (SI) and steatohepatitis (SH), which may increase the morbidity and mortality following major liver resection (5-10). Therefore, it is crucial to prevent the development of CALI and identify the associated risk factors. With the prolongation of the average life span, the number of elderly individuals undergoing liver resection for CRLM following chemotherapy has increased. However, the effect of age on the development of CALI in CRLM remains unclear. The aim of the present study was to elucidate the effects of age on the development of CALI in CRLM.

Patients and methods

Patients. Patients undergoing liver resection for CRLM following chemotherapy between April 2009 and March 2015 were considered for inclusion in this study. A total of 64 patients met the inclusion criteria and comprised the study population. The inclusion criteria were as follows: First liver resection, administration of oxaliplatin-based chemotherapy (OBC) within 4 months prior to liver resection, absence of preoperative jaundice, and availability of formalin-fixed, paraffin-embedded liver parenchymal tissue from the non-cancerous parenchyma for pathological analysis. The study protocol was approved by the Institutional Review Committee of the Hirosaki University Graduate School of Medicine (Hirosaki, Japan).

Pathological assessment. All histological slides that were originally prepared from formalin-fixed and paraffin-embedded tissues were reviewed. The morphological analyses were performed using slides stained with hematoxylin and eosin.

Correspondence to: Professor Kenichi Hakamada, Department of Gastroenterological Surgery, Hirosaki University Graduate School of Medicine, 5 Zaifu-cho, Hirosaki, Aomori 036-8562, Japan
E-mail: hakamada@hirosaki-u.ac.jp

Abbreviations: BMI, body mass index; CALI, chemotherapy-associated liver injury; CapeOX, capecitabine+ oxaliplatin; CRLM, colorectal liver metastasis; FOLFOX, 5 fluorouracil + leucovorin + oxaliplatin; NAFLD, non-alcoholic fatty liver disease; OBC, oxaliplatin-based chemotherapy; SH, steatohepatitis; SI, sinusoidal injury; SOX, S-1 + oxaliplatin

Key words: colorectal liver metastasis, chemotherapy, drug-induced liver injury, risk factor, aging

The slides were examined by 3 pathologists who were blinded to the clinical data. SI was graded according to the sinusoidal pathological score reported by Rubbia-Brandt *et al* (7). SI was classified as follows: 0, absent; 1, mild (centrilobular involvement limited to one-third of the lobule); 2, moderate (centrilobular involvement extending to two-thirds of the lobule); and 3, severe (complete lobular involvement). SH was graded according to the non-alcoholic fatty liver disease (NAFLD) activity score, as defined by Kleiner *et al*, based on steatosis, lobular inflammation and ballooning (11). Sinusoidal pathological scores of 0 and 1 were diagnosed as non-SI, and an NAFLD score of <3 was diagnosed as non-SH.

Comparison of perioperative factors. The 64 patients were divided into three groups (group A: <65 years, group B: 65-74 years and group C: >75 years) according to age at surgery. The medical records of all the patients were retrospectively reviewed and the development rate of CALI was compared between the groups. In addition, the association between the pathological score (SI and SH) and age at surgery was analyzed.

Preoperative chemotherapy. The systemic chemotherapy regimens consisted of three patterns: 5-fluorouracil + leucovorin + oxaliplatin (FOLFOX), capecitabine + oxaliplatin (CapeOX) and S-1 + oxaliplatin (SOX). In 52 patients, cytotoxic chemotherapy was combined with molecularly targeted therapy. In the present analysis, regimens of molecularly targeted therapy + FOLFOX, CapeOX or SOX were referred to as FOLFOX, CapeOX or SOX regimens, respectively. Chemotherapy regimens, including dose reduction, were selected at the discretion of the treating physician.

Statistical analysis. Continuous variables were expressed as median (range) and analyzed using non-parametric methods for non-normally distributed data (Mann-Whitney U-test). Categorical variables were reported as number (percentage) and analyzed using the Chi-squared test or Fisher's exact test, as appropriate.

For comparing the three groups, the Kruskal-Wallis test and Bonferroni correction were used. Univariate and multivariate analyses were performed using logistic regression analysis to determine the risk factors associated with CALI. In analyses of the preoperative parameters, the median value was used to determine the cut-off level. Any variable with $P < 0.1$ on univariate analysis using the abovementioned test was considered to be a candidate for the multivariate analysis.

Correlations between the pathological score and age at surgery were assessed using Spearman's correlation. A correlation was considered statistically significant when the correlation coefficient (r) was >0.3 . A difference was considered to be significant when the P -value was <0.05 . The statistical analysis was performed using the Predictive Analytics Software Package, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics. The characteristics of the patients are summarized in Table I. There were 44 male and 20 female

Table I. Patient characteristics.

Characteristics	No. (%)
Gender (male/female)	44/20 (68.8/31.3)
Age, years [median (range)]	62 (42-81)
Body mass index, kg/m ² [median (range)]	21.6 (17.3-37.9)
Body surface area, m ² [median (range)]	1.63 (1.27-2.10)
Primary lesion	
Colon/rectum	27/37 (42.2/57.8)
Chemotherapeutic regimen	
FOLFOX	28 (43.8)
CapeOX	29 (45.3)
SOX	7 (10.9)
Molecularly targeted therapy	52 (81.3)
Bevacizumab	47 (73.4)
No. of OBC cycles [median (range)]	5 (2-22)
Duration of OBC cessation, weeks [median (range)]	7 (3-16)
Pathological response	
1a	19 (29.7)
1b	26 (40.6)
2	16 (25.0)
3	3 (4.7)
Sinusoidal pathological score ≥ 2	18 (28.1)
NAFLD activity score ≥ 3	23 (35.9)

OBC, oxaliplatin-based chemotherapy; FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; CapeOX, capecitabine + oxaliplatin; SOX, S-1 + oxaliplatin; NAFLD, nonalcoholic fatty liver disease.

subjects, with a median age of 62 years (range, 42-81 years). The primary lesions were colon cancer in 27 patients and rectal cancer in 37 patients. The OBC regimens were FOLFOX, CapeOX and SOX. Multiple regimens were required in 16 patients, 4 of whom (4/64, 6.25%) had a history of irinotecan-based chemotherapy. Molecularly targeted therapy was administered to the majority of the patients (52/64), 47 of whom received bevacizumab. The median duration of OBC cessation was 7 weeks. Approximately 28 and 36% of the cases in each group had SI and SH, respectively.

Comparison of preoperative characteristics by age at surgery. Group A included 37 cases, group B 17 cases and group C 10 cases. A comparison of the preoperative characteristics prior to liver resection is shown in Table II. The body surface area decreased with age; however, the difference was not statistically significant. There were no significant differences among the groups regarding the number of OBC cycles or the duration of OBC cessation.

Comparison of preoperative blood tests by age at surgery. Table III shows a comparison of the preoperative blood test results prior to liver resection. The prothrombin time-international normalized ratio, total bilirubin, aspartate aminotransferase and alanine aminotransferase levels

Table II. Comparison of preoperative characteristics according to age at surgery.

Characteristics	Group A (<65 years)	Group B (65-74 years)	Group C (≥75 years)	P-value
Patient total	37	17	10	
Gender (male/female)	24/13	12/5	8/2	0.65
Median age, years	57.0	69.0 ^a	78.0 ^a	<0.01
Median body mass index, kg/m ²	21.3	21.8	21.6	0.82
Median body surface area, m ²	1.69	1.61	1.59	0.31
Median no. of OBC cycles	5.0	5.0	6.5	0.44
Median duration of OBC cessation, weeks	7.0	7.0	7.0	0.57
Molecularly targeted therapy (+)	31 (83.8)	12 (70.6)	9 (90.0)	0.56
Bevacizumab (+)	30 (81.1)	9 (52.9)	8 (80.0)	0.26
Antiplatelet therapy (+)	4 (10.8)	2 (11.8)	3 (30.0)	0.14

^aP<0.01 vs. the <65 group. OBC, oxaliplatin-based chemotherapy.

Table III. Comparison of preoperative blood test results according to age at surgery.

Variables (median)	Group A (<65 years)	Group B (65-74 years)	Group C (≥75 years)	P-value
Patient total	37	17	10	
Plt, 10 ⁴ /μl	19.5	18.4	16.1	0.45
PT-INR	1.02	1.02	1.03	0.73
ALB, g/dl	4.3	4.1	3.7 ^a	<0.01
AST, U/l	25.0	26.0	22.5	0.67
ALT, U/l	25.0	21.0	18.5	0.19
T-Bil, mg/dl	0.6	0.6	0.5	0.18
ICG-R15, %	13.0	11.0	13.0	0.72
APRI score	0.36	0.43	0.40	0.69
FIB-4 score ^b	1.58	2.23	2.42 ^a	<0.01

^aP<0.01 vs. the <65 group. ^bAge (years) x AST (U/l)/[Plt (10⁹/l) x (ALT (U/l))^{1/2}. FIB, fibrosis; Plt, platelet; PT-INR, prothrombin time-international normalized ratio; ALB, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-Bil, total bilirubin; ICG-R15, indocyanine green retention rate at 15 min; APRI, aspartate aminotransferase to platelet ratio index.

were not significantly different among the three age groups. Furthermore, the indocyanine green retention rate at 15 min did not exhibit any consistent trends with aging.

Comparison of pathological score by age at surgery. A comparison of the pathological score of liver parenchymal tissue from non-cancerous regions is shown in Fig. 1. SI was observed in 10, 5 and 3 patients from groups A, B and C, respectively, which was not significantly different (P=0.479). SH was observed in 13, 6 and 4 patients of groups A, B and C, respectively, which was also not significantly different (P=0.958).

Correlation between age at surgery and pathological scores. There was no significant correlation between age and the sinusoidal pathological score (r=-0.102, P=0.423) or

non-alcoholic fatty liver disease activity score (r=<0.001, P=0.997).

Risk factors for SI. Based on the results of the univariate analysis, a high body mass index (BMI), large number of OBC cycles, bevacizumab-containing regimens and long duration of OBC cessation were considered candidates for the multivariate analysis. The multivariate analysis revealed that a large number of OBC cycles was an independent risk factor for SI (Table IV).

Risk factors for SH. Based on the results of the univariate analysis, a high BMI and a large number of OBC cycles were considered candidates for the multivariate analysis. The multivariate analysis did not identify any variables as independent risk factors for SH (Table IV).

Table IV. Multivariate analysis of the risk factors for CALI.

Variables	Univariate analysis	Multivariate analysis		
	P-value	Odds ratio	95% CI	P-value
Risk factors for SI				
BMI >21.6 kg/m ²	0.095	1.819	0.506-6.543	0.36
No. of OBC cycles >5	<0.01	3.725	1.020-13.601	0.047
Duration of OBC cessation >7 weeks	0.09	0.227	0.049-1.050	0.06
Bevacizumab-containing regimens	0.046	0.327	0.083-1.291	0.11
Risk factors for SH				
BMI >21.6 kg/m ²	0.07	0.488	0.160-1.486	0.21
No. of OBC cycles >5	0.02	3.045	0.962-9.638	0.06

CALI, chemotherapy-associated liver injury; SI, sinusoidal injury; BMI, body mass index; OBC, oxaliplatin-based chemotherapy; SH, steatohepatitis.

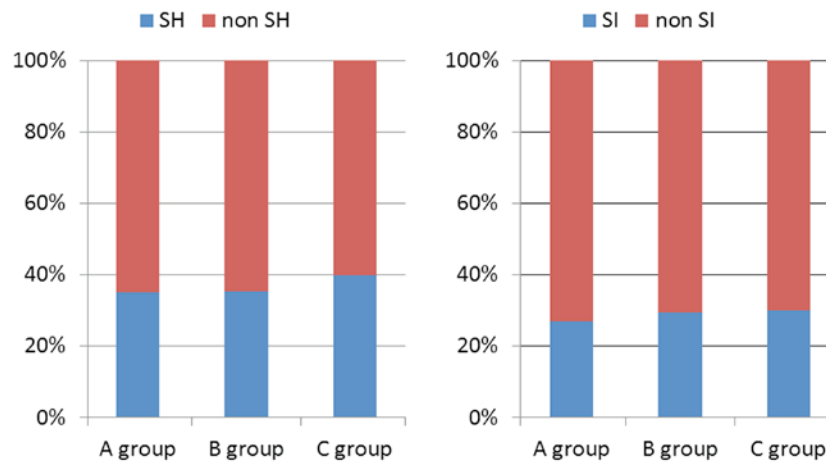


Figure 1. Frequency of chemotherapy-associated liver injury in patients with liver metastasis from colorectal cancer according to age at surgery. SI, sinusoidal injury; SH, steatohepatitis.

Discussion

Systemic chemotherapy for metastatic colorectal cancer may cause non-specific as well as specific damage to the non-cancerous liver parenchyma. OBC plays a central role in the treatment of patients with CRLM and may induce SI, which may increase the risk of liver resection for CRLM (5,6,9,12-14). Although there is no established guideline to prevent the development of chemotherapy-associated SI, the following factors have been identified as risk factors for SI: Female gender, a high number of chemotherapy cycles, and a short interval between cessation of chemotherapy and liver resection (5,15). However, the effect of age on the development of chemotherapy-associated SI remains unclear.

In previously published reports comparing two groups according to the histopathological assessment of SI, the development of chemotherapy-associated SI did not differ by age (5,14,16,17). However, it is difficult to conclude that these findings are sufficient, as those studies did not focus on

age. Furthermore, in a previous large study on the safety of OBC in elderly patients with colorectal cancer, CALI was not sufficiently investigated (18). Understandably, the pathological evaluation of CALI is likely difficult in such a large study. Therefore, the aim of the present study was to specifically focus on the age of the patients and pathological evaluation of SI.

There was no significant difference in the pathological score of the liver parenchymal tissue of the non-cancerous region among the groups. Furthermore, there was no strong correlation between age at surgery and the pathological score of SI or SH. These results suggested that the rate of development of severe CALI, which increases the morbidity and mortality following hepatectomy after OBC in CRLM, does not differ markedly by age. Unfortunately, detailed information on the relative dose intensity was not available, as nearly all cases were introduced from other institutions. However, a previous pooled analysis of elderly patients with colorectal cancer suggested that increasing age did not adversely affect drug delivery (18). Therefore, the effect of age alone on severe

CALI appears to be limited, provided that chemotherapy is appropriately conducted.

Although the present study provides insight into the management of CRLM among elderly patients in routine clinical practice, there were certain limitations, including the small sample size and retrospective design. In addition, the elderly patients included in this study were operable patients in good physical condition with few complications. Thus, patients who do not undergo surgery must also be evaluated to confirm our findings regarding the effect of age on the development of CALI in CRLM. However, in such cases, a liver biopsy would be required for the pathological examination of CALI, but this may not be possible for all cases due to ethical considerations.

In conclusions, the development of CALI following OBC in CRLM did not differ by age. The effect of increasing age on the development of severe CALI appears to be limited, provided that chemotherapy is appropriately conducted.

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