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Liver

Impact of statin use on the prognosis of patients with hepatocellular carcinoma undergoing liver resection: a subgroup analysis of patients without chronic hepatitis viral infection

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ABSTRACT

Background. Statins have been reported to reduce the risk of hepatocellular carcinoma (HCC). The effect of perioperative statin use on the prognosis of HCC patients undergoing liver resection remains unclear.
Methods. We retrospectively analyzed 643 patients who underwent curative liver resection for HCC. Patients negative for hepatitis B surface antigen and hepatitis C antibody were classified as the non-B non-C HCC subgroup (n = 204). Perioperative statin users were defined as patients preoperatively receiving statin medications and maintaining > 28 cumulative defined daily doses after liver resection. The recurrence-free survival (RFS) and overall survival (OS) according to statin use were analyzed in the overall HCC cohort or in the non-B non-C HCC subgroup.
Results. Among a total of 643 (HCC) patients, 43 patients (6.7%) received perioperative statin medications. In statin users, the proportion of non-B non-C HCC patients was significantly higher than in nonstatin users. Statin users had a high prevalence of obesity and diabetes, as well as dyslipidemia. The liver function of statin users was better than that of nonstatin users. The multivariate survival analysis revealed that use of statins was significantly associated with improvement of RFS (hazard ratio [HR], .42; 95% confidence interval [CI], 0.25–0.71; $P = .001$), but not with OS (HR, 0.62; 95% CI, 0.30–1.27; $P = .19$). In the subgroup analysis of the non-B non-C HCC cohort, statin use was significantly associated with improvement of RFS (HR, 0.47; 95% CI, 0.22–0.99; $P = .04$).
Conclusion. Perioperative statin use was associated with an improvement of RFS in HCC patients undergoing curative liver resection.

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer-related death worldwide.[1,2] Liver resection has been established as a safe and effective therapeutic option in patients with HCC[3,4] by virtue of advances in operative techniques and perioperative management.[5,6] On the other hand, cancer recurrence after curative resection and progression of underlying liver disease remain major concerns.

Recently, the use of statins, cholesterol-lowering 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, has been reported to reduce the risk of HCC in patients with chronic hepatitis B virus (HBV) or hepatitis C (HCV) infection.[7-12] Statins have received attention for their protective effect against cancer, including HCC, as well as melanoma, colorectal cancer, and breast cancer.[11-14] The suppressive effects of statins on carcinogenesis could involve their pleiotropic effects through both HMG-CoA-dependent and HMG-CoA -independent pathways, such as effects on inflammation, immunomodulation, angiogenesis, apoptosis, and proliferation.[14-17] Regarding their effects on underlying liver diseases, statins have been shown to reduce fibrosis progression and cirrhosis, as well as portal hypertension in HBV and HCV patients.[8,18-22] Although studies have demonstrated the protective effect of statins on the incidence of HCC and fibrosis progression based on underlying chronic hepatitis viral infection, little is known about the impact of statins on the prognosis of HCC patients who undergo curative liver resection.

Infection with chronic HBV or HCV has been the dominant risk factor of HCC development[23,24]; whereas the incidence of HCC unrelated to hepatitis virus, also termed non-B non-C HCC (NBNC HCC), has rapidly increased.[25,26] The recent epidemics of obesity and metabolic syndrome are associated with the increasing prevalence of nonalcoholic fatty liver disease (NAFLD),[27-29] which we previously

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reported to be a major etiological component of NBNC HCC.[26] Statins are used as cholesterol-lowering medications to manage or prevent coronary disease and stroke.[30] Obesity, insulin resistance, and diabetes, associated with the pathogenesis of NAFLD and an increased risk of HCC, are the main components of metabolic syndrome, and patients with those conditions are likely to exhibit a high prevalence of dyslipidemia.[31,32] Therefore, statins are postulated to be frequently used in HCC patients with metabolic syndrome–associated etiology, which might account for a significant proportion of NBNC HCC.

In this study, we aim to investigate the effect of perioperative statin use on the prognosis of HCC patients undergoing curative liver resection. Furthermore, we performed a subgroup analysis focusing on patients with NBNC HCC, based on the assessment of their unique characteristics associated with the high prevalence of obesity- and metabolic syndrome–related comorbidities.

Methods

Patients

We analyzed retrospectively 643 patients who underwent initial and curative liver resection for HCC at Kyoto University Hospital, Kyoto, January 2000–December 2014. Underlying liver diseases were categorized according to the presence of chronic hepatitis virus infection as reported previously[26]: patients negative for hepatitis B surface antigen and hepatitis C antibody were classified as the NBNC HCC group (n = 204), and the others were included in the HBV- or HCV- related HCC (B/C HCC) group (n = 439). The defined daily dose (DDD), the average maintenance dose per day of a drug recommended by World Health Organization, was used to define statin use.[11] Patients preoperatively receiving statin medications and maintaining > 28 cumulative DDDs (cDDDs) after liver resection throughout the study observation period were enrolled in the statin-use group. The diagnosis of metabolic syndrome–related comorbidities was based on the international criteria with slight modification to suit the Japanese criteria as follows: diabetes mellitus (fasting glucose ≥ 126 mg/dL or HbA1c ≥ 6.5%), dyslipidemia (increased triglycerides ≥ 150 mg/dL or reduced HDL cholesterol < 40 mg/dL in men or < 50 mg/dL in women) and hypertension (systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg).[26,32] Drug treatment for diabetes, dyslipidemia, or hypertension was an alternative indicator. In addition to conventional liver function indicators, serum alpha-fetoprotein level was measured before surgery. Tumor characteristics and pathological findings of nontumor-bearing liver parenchyma were evaluated. Liver fibrosis progression was assessed using the Metavir score and F4 was defined as pathological cirrhosis.[33] Surgical procedures (≥sectionectomy or not), surgical time and blood loss were recorded, and postoperative complications were diagnosed according to the Clavien-Dindo classification.[34] Patients underwent regular postoperative follow-up with measurements of tumor markers (alpha-fetoprotein and des-gamma-carboxy prothrombin) and radiologic examinations with computed tomography or magnetic resonance imaging at 3- to 6-month intervals. Recurrences were diagnosed primarily based on radiologic studies. Patients enrolled in the study cohort were subjected to an annual prognosis survey and the information was updated in December 2016. This study was in accordance with the ethical guidelines for epidemiological research in Japan and was approved by the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine (approval code: E2029/R0261).

Statistical analysis

Numbers and percentages of patients were presented in categorical variables. Continuous variables were presented as the mean ± standard deviation. Differences in categorical variables were analyzed using the Pearson χ^2 test. Continuous variables were compared using Student *t*-test. The recurrence-free survival (RFS) was defined as the period from the date of surgery to the date of diagnosis of recurrence or death; the overall survival (OS) was defined as the period from the date of surgery to the date of death. The RFS and OS curves were determined using the Kaplan-Meier product-limit method, and groups were compared using the log-rank test. Cox proportional hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated in the categorized variables including use of statins; underlying liver disease; sex; age (≥65 or not); body mass index (≥25 kg/m^2 or not); daily ethanol intake (>70 g/day or not); prevalence of diabetes, dyslipidemia, and hypertension; Child-Pugh classification (A or B); serum alpha-fetoprotein (≥20 ng/ml or not); tumor size (≥5 cm or not); tumor number (solitary or multiple); tumor differentiation (well to moderately or poorly differentiated); presence of microvascular invasion and liver cirrhosis (F4 or not); and variables that were associated with survival at $P < .10$ in univariate analysis were included in a multivariate analysis. All statistical analyses were 2-tailed and we used $P < .05$. JMP Pro 12 software (SAS Institute Inc., Cary, NC) was used in all statistical analyses.

Results

Patients' characteristics according to statin use

In the overall population of 643 HCC patients, 43 patients (6.7%) received perioperative statin medications, including 23 patients (3.6%) taking at least 365 cDDDs and 20 patients (3.1%) taking fewer than 365 cDDDs after surgery. Specifically, 17 patients were medicated with pravastatin, 15 patients with atorvastatin, 7 patients with rosuvastatin, and 4 patients with pitavastatin.

The patient characteristics of the overall HCC cohort according to the use of statins are shown in Table 1. In statin users, the proportion of NBNC HCC patients was significantly higher than in nonstatin users. Statin users had a higher body mass index (BMI) and a higher prevalence of diabetes and hypertension, as well as dyslipidemia. The liver function of statin users was better than that of nonstatin users, as indicated by lower levels of alanine aminotransaminase, higher prothrombin activity, and higher albumin levels; they also exhibited a lesser proportion of cirrhosis than nonstatin users. The rate of surgical complication of Clavien-Dindo classification grade ≥ III was lower in statin users; whereas surgical procedures, time, and blood loss did not show significant differences.

Impact of statin use on outcomes in overall HCC population

The impact of perioperative statin use on prognosis in the overall HCC population was analyzed. The comparison using the Kaplan-Meier method resulted in the significant improvement of both RFS (5-yr RFS rate, 55.4% in the statin group versus 25.0% in the nonstatin group) and OS (5-yr OS rate, 73.1% versus 56.7%, respectively) in statin users (Fig 1). The RFS and OS rates did not show a significant difference between statin users with cDDDs ≥ 365 and those with cDDDs < 365 (5-yr RFS rate, 52.5% versus 60.4%; 5-yr OS rate, 74.5% versus 71.3%, respectively) (Supplemental Fig S1). The statin medication was closely related to the prevalence of dyslipidemia; analysis in patients with dyslipidemia (n = 43 in the statin group; n = 46 in the nonstatin group) also resulted in the significant effect of statins on the improvement of RFS (Supplemental Fig S2). The multivariate analysis revealed that use of statins was significantly associated with RFS (HR, 0.42; 95% CI, 0.25–0.71) besides the tumor characteristics including alpha-fetoprotein level, tumor number, and microvascular invasion (Table 2). On the other hand, perioperative