that type 2 diabetes increases the risk of developing HCC in those who are HCV negative or have a high level of total cholesterol [26]. Second, Nakano et al. reported that epidemiological studies on diabetes mellitus revealed that the number of patients with diabetes mellitus is gradually increasing in Japan along with development of car society and westernization of food intake. Since prevalence of diabetes mellitus increases with aging, proportion of individuals with diabetes mellitus aged over 60 has exceeded two-third of estimated total number of patients (7.40 million in 2002) in Japan where aging of society is rapidly progressing [27]. In a word, the number of type 2 diabetes people is increasing in Japan and they were regarded as a high risk for HCC. Then, the number and the proportion of HCC patients with nonBC have been increased recent twelve years in Japan.

It is known that 2 to 4 decades of chronic HCV infection are required to develop cirrhosis and subsequent HCC [28–31]. The number of HCC cases has increased in Japan, because individuals infected with HCV during the past have grown old and have reached the cancer-bearing age. The prevalence of HCV infection in young Japanese individuals is low and the incidence of HCVAb is very low because of preventative actions against HCV infection such as the screening of blood products for HCV and the use of sterile medical equipment [32]. Additionally, we showed that the number and proportion of patients with HCC-C cases decreased, whereas the number and ratio of HCC-nonBC steadily increased during the studied period. These findings may be expected that the incidence of HCC patients with nonBC in Japan may continue to increase even after the consequence of the HCV epidemic level off, a country that is far advanced with regard to HCC patients with HCV infection, in the near future.

Conclusions

In summary, HCC patients had increased from 1996 to 2000 and this increase was originated from HCC patients with HCV infection. The number and proportion of HCC patients with HCV infection reached a peak in 2000 and thereafter decreased and became stabilized. The incidence of hepatocellular carcinoma associated with hepatitis C infection decreased after 2001 in Kyushu area. This change was due to the increase in the number and proportion of the HCC not only nonBC patients but also B patients.

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EDITORIAL

Insulin resistance and chronic liver disease

Takumi Kawaguchi, Eitaro Taniguchi, Minoru Itou, Masahiro Sakata, Shuji Sumie, Michio Sata

Takumi Kawaguchi, Michio Sata, Department of Disease Information & Research, Kurume University School of Medicine, Kurume 830-0011, Japan
Takumi Kawaguchi, Eitaro Taniguchi, Minoru Itou, Masahiro Sakata, Shuji Sumie, Michio Sata, Department of Medicine, Kurume University School of Medicine, Kurume 830-0011, Japan
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Correspondence to: Takumi Kawaguchi, MD, PhD, Department of Digestive Disease Information & Research, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan. takumi@med.kurume-u.ac.jp
Telephone: +81-942-31-7902 Fax: +81-942-31-7820
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Abstract

Increased insulin resistance is frequently associated with chronic liver disease and is a pathophysiological feature of hepatogenous diabetes. Distinctive factors including hepatic parenchymal cell damage, portal-systemic shunting and hepatitis C virus are responsible for the development of hepatogenous insulin resistance/diabetes. Although it remains unclear whether insulin secretion from pancreatic beta cells is impaired as it is in type 2 diabetes, retinopathic and cardiovascular risk is low and major causes of death in cirrhotic patients with diabetes are liver failure, hepatocellular carcinoma and gastrointestinal hemorrhage. Hemoglobin A1c is an inaccurate marker for the assessment and management of hepatogenous diabetes. Moreover, exogenous insulin or sulfonylureas may be harmful because these agents may promote hepatocarcinogenesis. Thus, pathogenesis, cause of death, assessment and therapeutic strategy for hepatogenous insulin resistance/diabetes differ from those for lifestyle-related type 2 diabetes. In this article, we review features of insulin resistance in relationship to chronic liver disease. We also discuss the impact of anti-diabetic agents on interferon treatment and hepatocarcinogenesis.

Key words: Viral hepatitis; Hyperinsulinemia; Hypoglycemic drug; Hepatoma

Peer reviewers: Papandreou Dimitrios, PhD, MD, RD, Assistant Professor of Nutrition, Department of Health Science, University of Nicosia, Cyprus; Head of Pediatric Obesity Unit, Aristotle University of Thessaloniki, School of Medicine, Ahepa General Hospital, P. Mela 22 GR 54622, Greece; Ignazio Grattagliano, MD, General & Internal Medicine, University of Bari, P.zza G. Cesare, 111, 70043 Bari, Italy

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INTRODUCTION

An association between diabetes mellitus (DM) and liver cirrhosis was first described by Bohan[1] and named as hepatogenous diabetes by Megyesi *et al*, in which 57% of cirrhotic patients showed increased insulin resistance[2]. Various pathogenetic factors are involved in development of the insulin resistance[3-7]. Serum insulin levels are higher in diabetic patients with chronic liver disease than those in patients with lifestyle-related DM[8], suggesting that besides over-eating, obesity and physical inactivity, distinctive factors may underlie the pathophysiology of hyperinsulinemia in patients with chronic liver disease.

Since blood glucose is delivered to the liver through the portal vein, hyperinsulinemia in patients with liver cir-

rhosis may be secondary to either hepatic parenchymal cell damage or to portal-systemic shunting[9-12]. The rate at which insulin is degraded in the liver is reduced in patients with liver cirrhosis[11,12]. Moreover, despite peripheral hyperinsulinemia, insulin levels in the portal and hepatic veins are decreased in cirrhotic patients with portal systemic shunting[9,10]. However, hyperinsulinemia is also seen in patients with chronic hepatitis C virus (HCV) infection who do not show both severe hepatic parenchymal cell damage and portal-systemic shunting[6,8,13-16], indicating that increased hepatic insulin resistance is another factor related to hyperinsulinemia in patients with liver disease, particularly in HCV-related chronic liver disease[8,13,17-21].

PATHOGENESIS OF INSULIN RESISTANCE IN PATIENTS WITH CHRONIC HEPATITIS C

Insulin resistance parallels the liver fibrosis stage[22-26] and is associated with a reduced level of sustained virological response (SVR) to pegylated interferon and ribavirin[27-30]. Thus, insulin resistance is involved in the disease progression and success of treatment and it is important to understand the pathogenesis of insulin resistance in patients with chronic hepatitis C.

Changes in serum levels of leptin, adiponectin, tumor necrosis factor-alpha and interleukin-6 are known to be associated with the development of insulin resistance[31-36]. However, in patients with chronic hepatitis C, changes in these cytokines are not always correlated with insulin resistance[37-39]. On the other hand, insulin resistance is increased in the HCV core cDNA-transfected hepatoma cell lines and mice[8,40] and serum levels of HCV core protein are associated with the development of insulin resistance in patients with chronic hepatitis C[14,41]. Furthermore, insulin resistance is correlated with HCV viral kinetics[42,43] and is improved by clearance of HCV by interferon therapy[44-47]. These findings suggest that HCV *per se* is an important factor for the development of insulin resistance.

Recently, the relationship between HCV genotype and insulin resistance has been revealed. HCV genotypes 1, 3 and 4 associated with more severe insulin resistance[24,42,48]. In human hepatoma cell lines, HCV genotype 1 up-regulates suppressor of cytokine signaling (SOCS) 3 and causes ubiquitination of insulin receptor substrate (IRS)1/2, which subsequently suppresses insulin-induced phosphorylation of the p85 subunit of phosphatidylinositol 3-kinase and Akt and reduces glucose uptake (Figure 1)[8]. These changes are not seen in hepatoma cell lines infected with HCV genotype 2, suggesting that IRS1/2 degradation through up-regulation of SOCS3 is a genotype-specific mechanism[49]. In agreement with these results of basic research, hepatic expression of SOCS3 is higher in patients with HCV genotype 1 than in those with genotype 2 and increased hepatic expression of SOCS3 is correlated with poor response to antiviral treatment[50,51]. Two further mechanisms are reported in HCV genotype 1: activation of

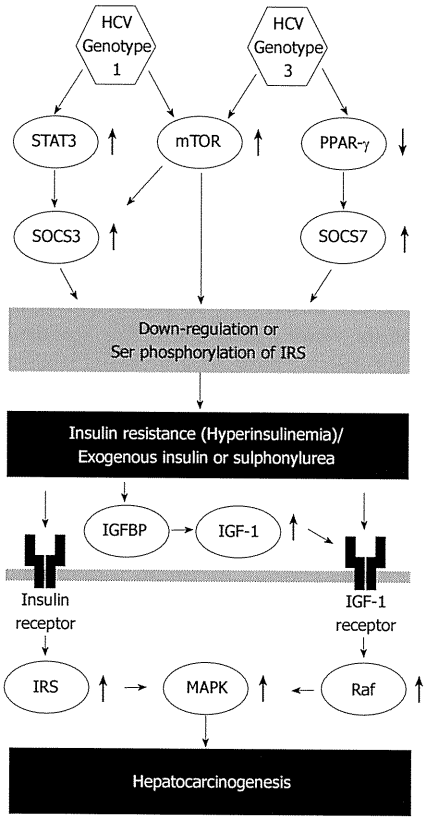

Figure 1 Scheme for HCV genotype difference in the molecular pathogenesis of insulin resistance and hepatocarcinogenesis. HCV: Hepatitis C virus; STAT: Signal transducer and activator of transcription; SOCS: Suppressor of cytokine signaling; mTOR: Mammalian target of rapamycin; PPAR: Peroxisome proliferator-activated receptor; IGFBP: Insulin-like growth factor binding protein; IGF: Insulin-like growth factor; IRS: Insulin receptor substrate; MAPK: Mitogen-activated protein kinase.

the mammalian target of rapamycin[52] and up-regulation of serine phosphorylation of IRS1(Figure 1)[43]. In addition, amino acid substitutions in the core region of HCV genotype 1b [Gln70 (His70) and/or Met91] have recently been reported as significant predictors of severe insulin resistance[53,54]. Although the underlying molecular mechanisms remain unclear, these findings indicate a unique molecular pathogenesis for insulin resistance in HCV genotype 1.

HCV genotype 3 also causes down-regulation of IRS1; however, the molecular pathogenesis differs from that of HCV genotype 1. HCV genotype 3 promotes down-regulation of IRS1 by up-regulating SOCS7 but not SOCS3 (Figure 1)[52]. SOCS-7 mRNA expression is independent of signal transducer and activator of transcription 3 and is modulated by peroxisome proliferator-activated receptor gamma activity (Figure 1)[52,55]. HCV genotype 4 is the most common variant in the Middle East and Africa and is increasing in prevalence in Western countries[56]. Infection with HCV genotype 4 is associated with a high prevalence of hepatic steatosis and obesity; however, the impact of

adiponectin on insulin resistance remains controversial[57,58] and specific mechanisms of insulin resistance in HCV genotype 4 infection also remain unclear.

Besides direct association of HCV with intracellular insulin signaling, hepatic steatosis is associated with increased BMI and insulin resistance and HOMA index is reported to be a predictor of SVR in patients with HCV non 3 genotypes[27,59-62]. In patients with HCV genotype 3, hepatic steatosis directly correlates with circulating and hepatic viral load, which is mediated by an impaired very-low-density lipoprotein assembly and secretion and by an up-regulation of the sterol depending protein signaling pathway, which regulates de novo lipogenesis and inhibits mitochondrial fatty acid b-oxidation[63,64].

CHANGES IN PANCREATIC BETA CELLS IN PATIENTS WITH LIVER DISEASE

A decrease in islet mass and/or beta-cell dysfunction is a pathogenesis for type 2 DM[65,66]. In patients with chronic liver disease, impairment of insulin secretion is also reported[11,67]; however, insulin resistance/hyperinsulinemia is also characteristic in such patients[8,13,17-21] and it therefore remains unclear whether the pathogenesis of hepatogenous DM is same as that of type 2 DM.

Pancreatic islet hypertrophy is reported in surgical biopsy tissue of patients with liver cirrhosis[68]. Islet hypertrophy and hyperplasia are also reported in thioacetamide-treated rats[69] and in HCV-core transgenic mice[40]. Moreover, Takei *et al* reported that islets in patients with cirrhosis show higher proliferation and lower apoptosis compare to those in patients with no chronic liver disease[70]. These findings suggest that hyperinsulinemia in cirrhotic patients may be caused by an adaptive response of the pancreatic beta cells to increased insulin resistance.

Although cross-talk between the pancreas and liver is an important issue in the development of insulin resistance, little is known about this relationship. Further studies regarding morphological and pathological changes of pancreatic alpha-or beta cells are required to characterize the pathogenesis of insulin resistance in patients with liver disease.

CAUSES OF DEATH IN DIABETIC PATIENTS WITH LIVER DISEASE

The prevalence of DM in patients with chronic liver disease is reportedly 18%-71%[18,20,71-73]. DM leads to several complications including cardiovascular disease. Generally, the therapeutic strategy in DM is to reduce the incidence of cardiovascular disease and to prevent a subsequent decrease in quality of life and improve prognosis. However, hepatogenous DM is less often associated with a positive family history, retinopathy and cardiovascular diseases[18,74-76]. In fact, major causes of death in cirrhotic patients with DM relate to liver disease or its complications, such as chronic liver failure, hepatocellular carcinoma (HCC) and gastrointestinal hemorrhage[18,19,77-79]. Therefore, the management of DM in patients with liver cirrhosis should aim to reduce such hepatic complications and to improve prognosis. Because the incidence of HCC has been well demonstrated to relate to DM[80], a major target in the management of DM should be to reduce the incidence of HCC in patients with liver cirrhosis.

ASSESSMENT OF DM IN PATIENTS WITH LIVER DISEASE

Plasma glucose and hemoglobin A1c (HbA1c) are generally used for routine assessment and management of patients with type 2 DM, whereas there is less information regarding the association between these markers and HCC incidence or prognosis in patients with liver cirrhosis. HbA1c level in patients with HCC is higher than in patients with liver cirrhosis or in control subjects[81]. In patients with liver cirrhosis, however, HbA1c does not properly represent glycemic control status in cirrhotic patients because of the short lifespan of erythrocytes caused by hypersplenism[82-86]. These data indicate that assessment and management of hepatogenous DM using HbA1c is inaccurate, although poor glucose control is associated with HCC incidence.

Strict control of blood glucose levels may improve survival in HCV patients. In patients with HCV-related liver cirrhosis, the prognosis for patients with hyperglycemia (fasting plasma glucose $\geq$ 7.0 mmol/L; 126 mg/dL) was worse than for those with normoglycemia[19]. Therefore, fasting plasma glucose < 7.0 mmol/L (126 mg/dL) appears to be meaningful in hepatogenous DM.

Fasting serum insulin and homeostasis model assessment of insulin resistance (HOMA-IR) are also used as markers of glucose tolerance. In patients with HCV infection, HCC development is associated with increased fasting serum insulin level and by HOMA-IR[87]. Moreover, HCC recurrence has also been demonstrated to be related to HOMA-IR[88,89]. In addition, prognosis is worse in HCC patients with increased fasting serum insulin level or HOMA-IR[90]. These data suggest that the assessment of insulin is also meaningful in patients with liver cirrhosis. Taken together, fasting plasma glucose and either serum insulin or HOMA-IR are candidate markers for the assessment of hepatogenous insulin resistance/DM. However, further studies are required to clarify the utility of these markers and their target values in terms of complications induced by liver cirrhosis including HCC or prognosis.

IMPACT OF ANTI-DIABETIC AGENTS IN PATIENTS WITH LIVER DISEASE

Exogenous insulin and sulphonylureas

Despite the recognition of this potential link between insulin resistance and life-threatening complications including HCC, there is no common therapeutic strategy for

Table 1 Effects of anti-diabetic agents in patients with chronic liver disease

Anti-diabetic agent	Subjects	Outcome	Reference
Exogenous insulin or sulphonylurea	Patients with liver cirrhosis or HCC	Increased HCC risk	[100]
Exogenous insulin or sulphonylurea	Patients with chronic hepatitis C	Increased HCC risk	[101]
Exogenous insulin	Chronic viral hepatitis patients who had undergone curative resection for HCC	Increased risk of HCC recurrence	[102]
Metformin	Treatment-naïve female patients with HCV genotype 1-related chronic hepatitis and insulin resistance	Increased SVR rate	[16]
Metformin	Patients diabetes mellitus and liver cirrhosis or HCC	Decreased HCC risk	[101]
Metformin	Patients with liver cirrhosis or HCC	Decreased HCC risk	[112]
Pioglitazone	Chronic hepatitis C patients who had previously failed to respond to antiviral therapy	No increase in EVR rate	[115]
Pioglitazone	Treatment-naïve chronic hepatitis C patients with insulin resistance	Increased SVR rate	[116]

HCC; hepatocellular carcinoma, EVR; early virological response, SVR; sustained virological response.

insulin resistance in patients with chronic liver disease. Since insulin is a growth-promoting hormone with mitogenic effects[91], exogenous insulin and sulphonylureas, which increase serum insulin levels, are considered to enhance carcinogenesis. In fact, a large-scale cohort study has reported that exogenous insulin increases the risk of malignancies in patients with DM[92,93]. Exogenous insulin and sulphonylureas are known to promote breast cancer[94], colorectal cancer[95,96] and pancreatic cancer[95,97] in patients with DM. Recently, a possible link between anti-diabetic agents and the risk of cancer is noted in the consensus statement from the American Diabetes Association and the American Cancer Society[98].

An association between anti-diabetic agents and hepatocellular carcinoma (HCC) was first described in 1986 by Lawson *et al*[99]. In addition, we, along with others, have recently shown that use of exogenous insulin or sulphonylurea increases the development and recurrence of HCC in patients with chronic hepatitis C (Table 1)[80,100-102]. Exogenous insulin or second-generation sulphonylurea increases serum insulin levels. Since insulin has mitogenic and cell proliferative effects, these anti-diabetic agents could be a carcinogenic factor. Insulin binds to insulin receptors and activates the mitogenactivated protein kinase pathway[91,103]. Insulin also cross-reacts with insulin like growth factor (IGF)-1 receptor and activates the Raf cascade, leading to mitosis and cell proliferation[104]. Moreover, excess insulin binds to IGF-binding proteins, resulting in increased levels of free serum IGF-1 (Figure 1)[87,105-107]. Thus, hyperinsulinemia induced by use of exogenous insulin or sulphonylurea may enhance hepatocarcinogenesis through multiple pathways.

The association of exogenous insulin or second-generation sulphonylurea with HCC was more evident in females than in males[101]. Sex affects the development of HCC and females are less prone to HCC than males[108,109]; therefore, we assume that use of exogenous insulin or a 2nd-generation sulfonylurea may accelerate development of HCC mainly in patients who have negative factor for the development of HCC.

Metformin

Metformin is an oral biguanide with insulin-sensitizing effects. However, biguanides are reported to predispose patients with liver cirrhosis to lactic acidosis and are considered as a contraindication in this situation[110]. Recently, Romero-Gomez *et al* first reported that adding metformin to peginterferon and ribavirin is safe and improved insulin sensitivity in treatment-naïve patients with HCV genotype 1 infection and DM[16]. In an intent-to-treat analysis, no beneficial effects of metformin on SVR were seen; however, in female patients with insulin resistance, adding metformin to antiviral treatment doubled the SVR rate (58% *vs* 29%)[16]. Although the reason for this sex difference is still unclear, elevated estradiol-to-testosterone ratio is known to be associated with better response to metformin treatment[111], suggesting a possible association between sex hormones and metformin-induced high SVR rate. Donadon *et al* and our research group have reported that metformin reduced risk of HCC in patients with DM and chronic liver disease[101,112]. Metformin is also known to attenuate the response of cancer cells to insulin *in vitro*[113,114]. Thus, metformin has potential benefits as an insulin sensitizer for patients receiving antiviral treatment or those with liver cirrhosis(Table 1).

Pioglitazone

Pioglitazone is a thiazolidinedione with insulin-sensitizing effects. Recently, Overbeck *et al* reported that adding pioglitazone to pegylated interferon-alpha and ribavirin improves insulin resistance; however, none of the patients achieved a satisfactory virological response after 12 wk of treatment (Table 1)[115]. On the other hand, Khattab *et al* reported that pioglitazone improves sustained virological response to antiviral therapy in hepatitis C patients with insulin resistance (Table 1)[116]. The effect of pioglitazone on SVR therefore remains controversial; however, a difference in enrolled subjects may account for this discrepancy. The study by Overbeck *et al* enrolled patients with chronic hepatitis C who previously failed to respond to peginterferon plus ribavirin therapy[115], whereas the

study by Khattab *et al* enrolled naïve chronic hepatitis C patients with insulin resistance[116]. Thus, pioglitazone may not enhance the effect of antiviral therapy in intractable chronic hepatitis C. However, insulin resistance is reduced in both studies and pioglitazone may therefore be able to improve insulin resistance-related complications in patients with HCV infection. Further study will need to focus on the effects of pioglitazone, not only on antiviral treatment but also on the development of hepatic fibrosis, hepatocarcinogenesis and patient prognosis.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase (DPP)-4 inactivates incretin hormones including glucagon-like peptide-1 (GLP-1)[117,118], which enhances insulin secretion and reduces body weight[119,120]. DPP-4 inhibitors are therefore used as anti-diabetic agents[117,118]. DPP-4 is also known as CD26, an immune-regulation molecule expressed on T-cells[121], and transfection of a HCV non-structural genome region is reported to increase DPP-4 expression in a hepatoma cell line[122]. Treatment of HCV-infected patients with interferon decreases serum DPP-4 activity, which is related to interferon-induced immune activation[123]. Although changes in DPP-4 activity after interferon treatment may just represent indirect evidence, one would think that changes in DPP-4 activity could be involved in the pathogenesis of HCV-related insulin resistance.

Although changes in GLP-1 and DPP-4 remain unclear in hepatogenous insulin resistance, we previously investigated changes of these molecules in patients with HCV infection[124]. The serum level of the active GLP-1 in HCV-infected patients is significantly lower than that in hepatitis B virus-infected patients and healthy subjects. On the other hand, DPP-4 is up-regulated in the serum, ileum and liver of HCV-infected patients more than that of hepatitis B-infected patients and healthy subjects. Taken together, it seems that inactivation of GLP-1 through up-regulation of DPP-4 is a possible pathogenetic mechanism for HCV-related insulin resistance.

DPP-4 inhibitors are now available in the clinical setting and decrease plasma glucose levels as well as HbA1c levels with a low incidence of hypoglycemia in patients with type 2 diabetes mellitus[125,126]. Unlike other anti-diabetic agents, DPP-4 inhibitors are metabolized in the kidney and rarely cause hepatic dysfunction[127,128]. Moreover, GLP-1 analogs improve insulin sensitivity in insulin-resistant obese fa/fa Zucker rats[129] and DPP-4 inhibitors increase hepatic glucose uptake[130]. Thus, further study will be focus on the effects of DPP-4 inhibitors on HCV-related insulin resistance.

COFFEE CONSUMPTION

In various studies including a large prospective study, patients with HCV-related liver disease with a regular coffee consumption show a lower rate of disease progression such as hepatic fibrosis[131-133] and HCC[134-138]. Recently, it was also reported that more than 3 cups per day coffee drinkers are three times more likely to have a virological response to peginterferon plus ribavirin treatment than non-drinkers[139]. Since coffee consumption increases insulin sensitivity[140] and inhibits the development of non-alcoholic fatty liver disease in healthy subjects[141], coffee intake may be protective by mechanisms modulating insulin sensitivity and resulting in a reduced extent of liver steatosis in patients with HCV infection.

CONCLUSION

In this paper, we summarize the features of insulin resistance in relationship to chronic liver disease. Pathogenesis, assessment and cause of death in insulin resistance related to liver disease differ from those of lifestyle-related insulin resistance. Furthermore, exogenous insulin or sulfonylureas may be harmful because these agents may promote hepatocarcinogenesis. There is, therefore, a need for a unique therapeutic strategy for hepatogenous insulin resistance.

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Case Report

Development of intrahepatic cholangiocarcinoma after a 14-year follow-up of a patient with primary sclerosing cholangitis and ulcerative colitis

Takumi Kawaguchi,[1,2] Ryohei Kaji,[2] Hiroyuki Horiuchi,[3] Tomotake Shirono,[2,6] Yusuke Ishida,[2] Yoshinobu Okabe,[2] Minoru Itou,[2] Keiichi Mitsuyama,[2] Jun Akiba,[4] Osamu Nakashima,[4] Hirohisa Yano,[4] Masayoshi Kage,[5] Masaru Harada,[7] Shotaro Sakisaka[8] and Michio Sata[1,2]

Department of [1]Digestive Disease Information & Research, [2]Medicine, [3]Surgery and [4]Pathology, Kurume University School of Medicine, [5]Department of Diagnostic Pathology, Kurume University Hospital, Kurume, [6]Digestive Disease Center, Asakura Medical Association Hospital, Asakura, [7]Third Department of Internal Medicine, University of Occupational and Environmental Health, Japan, School of Medicine, Kitakyusyu, and [8]Department of Gastroenterology and Medicine, Fukuoka University Faculty of Medicine, Fukuoka, Japan

Intrahepatic cholangiocarcinoma (ICC) is one of the life-threatening complications of primary sclerosing cholangitis (PSC). However, the incidence of ICC in Japanese PSC patients is low, and the association between the development of ICC and morbidity duration of PSC is largely unknown. Here, we describe a case of ICC that developed after a long-term follow-up of a patient with PSC and ulcerative colitis (UC). At the age of 10 years, the patient was first diagnosed with UC and its remission was achieved with systemic steroid therapy. Since then, he was routinely followed-up. At the age of 19 years, laboratory tests showed abnormalities in liver function parameters, and the patient was diagnosed with PSC. Although treatment with ursodeoxycholic acid improved the abnormalities in serum levels of biliary enzymes and no PSC-related symptoms were seen for 13 years, calculous cholecystitis frequently occurred in the patient since the age of 32 years. He developed ICC, which expressed some hepatic progenitor cell markers such as CD133, neural cell adhesion molecule, keratin 7, and keratin 19 at the age of 33 years. ICC was treated by curative partial hepatectomy and adjuvant chemotherapy with gemcitabine. Eight months later, however, the patient developed multiple metastases in the abdominal lymph nodes and lungs, and died 21 months after the onset of ICC. Here, we report a case of ICC that developed after a 14-year follow-up of a patient with PSC and UC.

Key words: cholangiocarcinoma, Japanese, long-term follow-up, primary sclerosing cholangitis, ulcerative colitis.

INTRODUCTION

PRIMARY SCLEROSING CHOLANGITIS (PSC) is a cholestatic liver disease characterized by multiple fibrotic strictures of the intra- and extrahepatic biliary tree.[1–3] Although PSC is generally slow progressive, it is refractory to therapy, and frequently results in advanced liver cirrhosis.[1–3] Intrahepatic cholangiocarcinoma (ICC) is the most feared complication of PSC and the occurrence of ICC leads to a poor prognosis for PSC patients.[4,5]

The prevalence of ICC in patients with PSC is reported to be approximately 7–15% in the USA.[2] While, a Japanese national survey disclosed the prevalence of ICC to be only 3.6% in PSC patients (14/391).[5] The survey also revealed two clinical characteristics for PSC-associated ICC in Japan. First, the average follow-up period between PSC and ICC diagnoses is relatively short (average period, 2.6 ± 3.5 years).[5] Second, PSC patients with inflammatory bowel disease (IBD) are less likely to develop ICC.[5] However, PSC-associated ICC is a rare disorder in Japan, and limited information is available about the clinical characteristics of this devastating disorder. Here, we report a case of ICC, which developed

Correspondence: Dr Takumi Kawaguchi, Department of Digestive Disease Information & Research, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan. Email: takumi@med.kurume-u.ac.jp
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after a 14-year follow-up of PSC and ulcerative colitis (UC).

CASE REPORT

A 10-YEAR-OLD Japanese male visited Kurume University Hospital because of abdominal pain and hematochezia. The patient was diagnosed with UC by colonic biopsy. Since the patient had an allergic reaction to 5-aminosalicylic acid, remission of UC was achieved by systemic steroid therapy. After withdrawal of steroid therapy, exacerbation of UC occurred, and he was administered a continuous 5 mg/day of prednisolone (Fig. 1).

At the age of 19 years, laboratory tests of the patient showed abnormalities in liver function parameters with elevated serum levels of biliary enzymes, including alkaline phosphatase (ALP) (Fig. 1). Multiple strictures and dilatation of the intrahepatic bile ducts were seen on endoscopic retrograde cholangiography (ERC). His liver biopsy showed concentric periductal fibrosis (Fig. 2). Thus, the patient was diagnosed with PSC associated with UC. After treatment with 600 mg/day of ursodeoxycholic acid (UDCA), his serum levels of biliary enzymes were decreased (Fig. 1).

At the age of 25 years, the patient complained of abdominal pain and hematochezia. Colonoscopy revealed diffuse mucosal inflammation and ulcerations

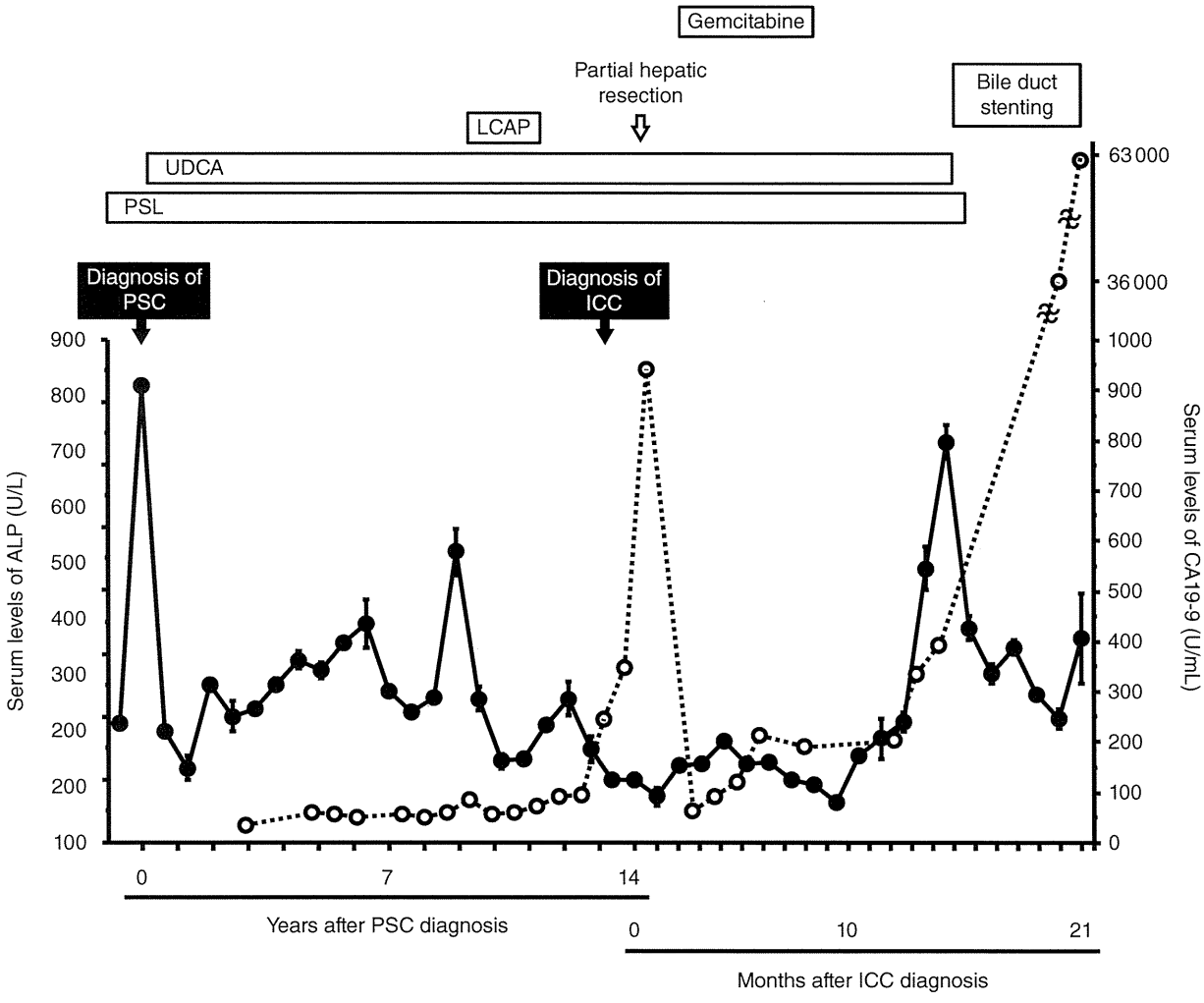

Figure 1 Clinical course and changes in serum alkaline phosphatase (ALP) and carbohydrate antigen 19–9 (CA19-9) levels. Serum levels of ALP (black circle) are shown as mean ± standard deviation (SD) of the all data measured in the indicated year or month, and serum levels of CA19-9 (white circle) are shown as absolute values. PSC, primary sclerosing cholangitis; ICC, intrahepatic cholangiocarcinoma; PSL, prednisolone; UDCA, ursodeoxycholic acid; LCAP, leukocytapheresis. (—●—): ALP; (···○···): CA19-9.

in the descending colon. Simultaneously, laboratory tests showed elevated serum levels of biliary enzymes, including ALP and total bilirubin levels, indicating exacerbation of both UC and PSC. Leukocytapheresis therapy was initiated and marked improvement in clinical symptoms and colonoscopic findings were noted (Fig. 1). Furthermore, serum levels of biliary enzymes decreased, as previously reported.[6]

At the age of 32 years, the patient complained of abdominal pain with no hematochezia. After evaluation of biochemical and diagnostic images, the patient was diagnosed with calculous cholecystitis. His abdominal pains and biochemical abnormalities were improved by a conservative therapy of total parenteral nutrition. Although brush cytology using ERC showed suspected adenocarcinoma, ICC was not detected by computed tomography (CT) and ERC (Fig. 3). Thereafter, frequent recurrence of calculous cholecystitis was observed.

When the patient was 33 years of age, a hepatic space-occupying lesion (SOL; diameter, 35 mm) was detected by the abdominal ultrasonography (Fig. 4a). His biochemical parameters are summarized in Table 1. His serum carbohydrate antigen 19–9 (CA 19–9) level was 72.6 U/mL. On CT, contrast enhancement was not seen in the hepatic SOL (Fig. 4b). The hepatic SOL showed an accumulation of fluoro-2-deoxyglucose on positron emission tomography (Fig. 4c). On the basis of these findings, the hepatic SOL was clinically diagnosed as ICC. Since bile duct histology demonstrated no malignancy under ERC, curative partial hepatectomy was performed. The pathological diagnosis of the cancerous lesion was ICC and that of non-cancerous lesion was non-cirrhotic PSC (Inuyama classification A1, F1) (Fig. 4d–f). No infiltration of IgG4-positive cells was found in his liver specimens (Fig. 4g). We also performed immunohistochemistry for hepatic progenitor cell (HPC) markers such as CD133, neural cell adhesion molecule (NCAM), keratin 7 (K7), and K19 of the resected tissue (Fig. 5a–h). Some of ICC cells were weak immunoreactive for CD133 (Fig. 5b) and NCAM (Fig. 5d), and most of the ICC cells were strong immunoreactive for K7 and K19 (Fig. 5f,h).

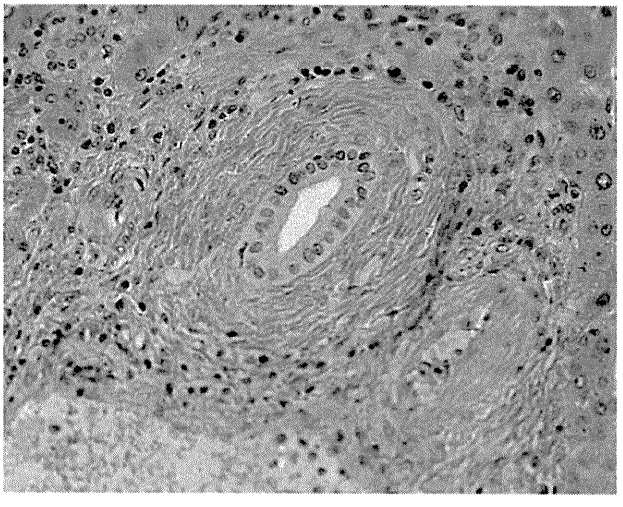

Figure 2 Histology of liver biopsy. Examination of liver biopsy specimen shows concentric periductal fibrosis, "onion-skin appearance". Original magnification × 200.

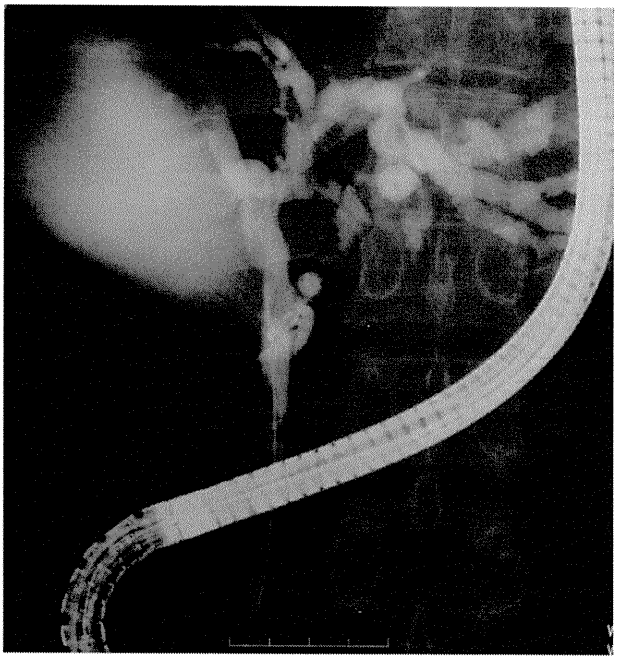

Figure 3 Endoscopic retrograde cholangiography shows multiple strictures and dilatation of the intrahepatic bile ducts. There are no findings indicating cholangiocarcinoma.

After partial hepatectomy, he was administered gemcitabine (1400 mg/day) every 2 weeks for 6 months as adjuvant chemotherapy. However, 2 months after termination of chemotherapy, he developed multiple metastases in the liver, abdominal lymph nodes, and lungs and died 21 months after the onset of ICC (Fig. 1).

DISCUSSION

THE CHARACTERISTICS OF ICC in patients with PSC are different depending on the geographical location.[2,3,5] In this report, we presented a case of ICC that developed after a 14-year follow-up of PSC and UC in Japan.

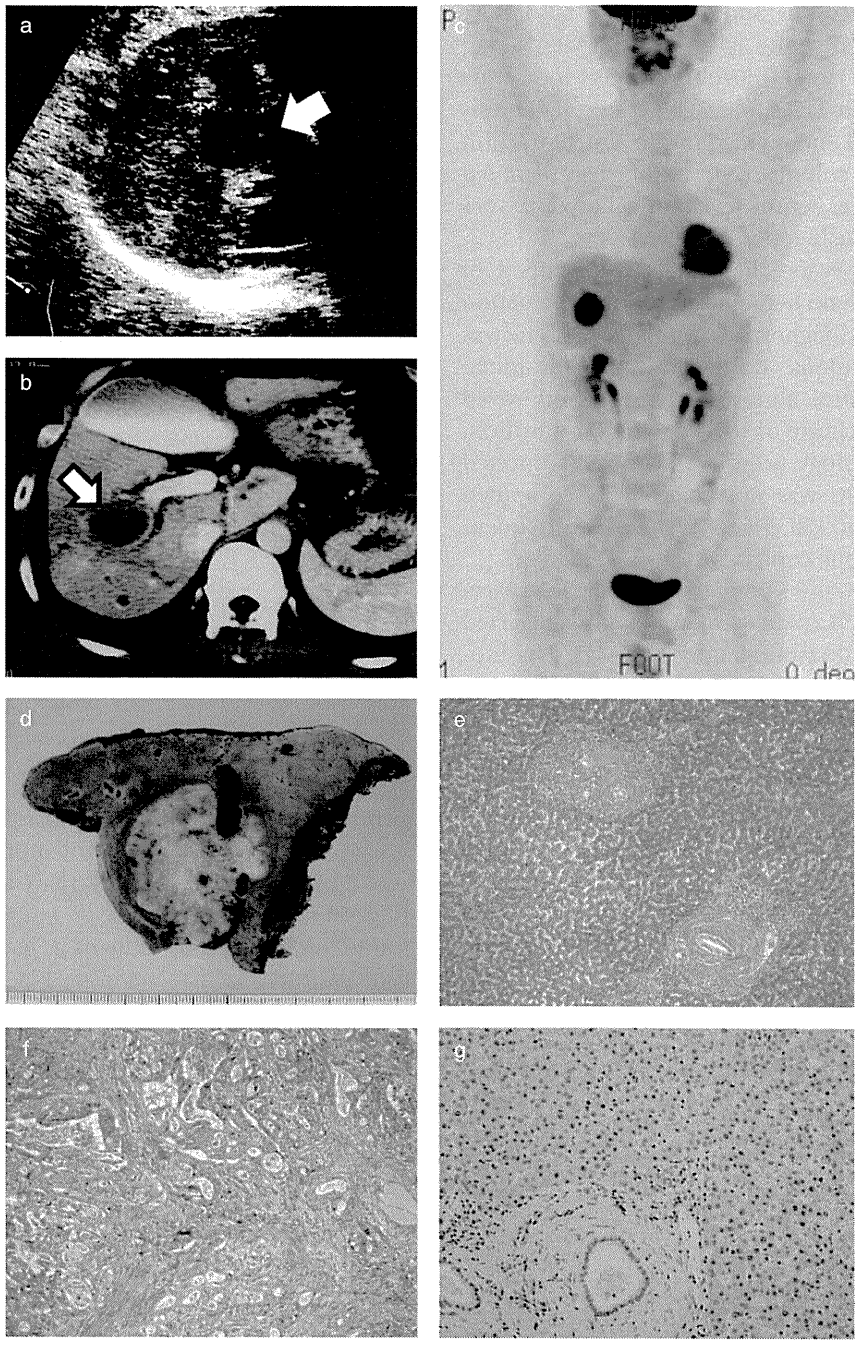

Figure 4 (a) Abdominal ultrasonography shows hypoechoic a space-occupying lesion (SOL; diameter, 35 mm) in the liver (arrow). (b) The hepatic SOL shows no contrast enhancement in the early phase of computed tomography (arrow). (c) The hepatic SOL shows accumulation of fluoro-2-deoxyglucose on positron emission tomography scan. (d) Macroscopic view shows a mass with a blurred border arising in a non-cirrhotic liver. (e) Liver histology demonstrates concentric periductal fibrosis, mild inflammation, and fibrous expansion of the portal area (Inuyama classification A1, F1). Hematoxylin-eosin staining. Original magnification × 20. (f) Tumor histology shows an adenocarcinoma showing small tubular, acinar or cord-like structures with a slit-like lumen. Hematoxylin-eosin staining. Original magnification × 100. (g) No infiltration of IgG4-positive cells is seen in the liver specimens. Immunostaining for IgG4. Original magnification × 100.

Table 1 Biochemical parameters measured at the onset of cholangiocarcinoma

Examination	Reference value	Value
Red blood cell ($\times 10^4$/mm^3)	430–570	567
Hemoglobin (g/dL)	14.0–18.0	15.7
White blood cell (/mm^3)	4000–9000	6000
Platelet ($\times 10^4$/mm^3)	13–36	29.6
Aspartate transaminase (U/L)	13–33	32
Alanine aminotransferase (U/L)	8–42	49
Lactate dehydrogenase (U/L)	119–229	161
Alkaline phosphatase (U/L)	115–359	286
γ-glutamyl transpeptidase (U/L)	10–47	101
Total protein (g/dL)	6.70–8.30	7.64
Albumin (g/dL)	4.00–5.00	3.90
Total bilirubin (mg/dL)	0.30–1.50	0.89
C-reactive protein (mg/dL)	<0.40	0.17
Total cholesterol (mg/dL)	128–220	190
Fasting blood glucose (mg/dL)	80–109	102
Hemoglobin A1c (%)	4.3–5.8	4.9
Prothrombin activity (%)	60–130	97
α-fetoprotein (ng/mL)	<8.7	6.1
Protein induced by vitamin K absence (mAU/mL)	<40	30
Carcinoembryonic antigen (ng/mL)	<5.0	3.6
Carbohydrate antigen 19–9 (U/mL)	<37.0	76.2
DuPan-2 (U/mL)	<150	63
S-pancreas-1 antigen (U/mL)	<30	25
Erastase-1 (ng/dL)	100–400	170
IgG4 (mg/dL)	4.8–105.0	39.9

The average period between PSC and ICC diagnoses are reported to be 2.3 years in Sweden.[7] Similarly, a Japanese national survey for PSC conducted in 2003 reported that a relatively short period between PSC and ICC diagnoses is a characteristic of PSC-associated ICC (average period, 2.6 ± 3.5 years).[5] However, the period between PSC and ICC diagnoses in our case was 14 years, which is more than five times longer than the average period in Japan. Although the reason for this discrepancy remains unclear, a possible reason is that the national survey was performed in hospitals specializing in gastroenterology. In the Japanese survey, 50% of ICC cases were diagnosed within a month after diagnosis of PSC, suggesting that about a half of the PSC patients were referred to medical specialists for examination of suspected ICC, and ICC might be already developed when these patients visited the hospitals. Another possible reason is UDCA administration. UDCA is known to inhibit taurocholate and taurolithocholate-induced growth of human cholangiocytes.[8] In addition, the incidence of ICC in PSC patients treated with UDCA is reported to be lower than that in PSC patients not treated with UDCA.[9] In our case, administration of UDCA from the early stage of PSC may have contributed to late onset of ICC.

Another feature of ICC in Japanese PSC patients is that the complication of IBD is a negative factor for the development of ICC. Although our patient had UC, the impact of IBD on the development of ICC is unclear. Recently, Melum *et al.* reported that the natural killer cell receptor G2D, which plays a crucial role in tumor surveillance by NK cells,[10] is involved in preventing development of ICC in patients with PSC.[11] On the other hand, steroids inhibit natural killer cell receptor G2D-mediated NK cell activity.[12] Since our patient had an allergic reaction to 5-aminosalicylic acid, the cumulative dose of steroids administration is more than 25 000 mg. Thus, IBD might have had an indirect effect on the development of ICC in our patient.

Even in transplanted patients with PSC-associated ICC, average tumor-free survival rate is only 30–35% in 3 years,[4] therefore, data on risk factors and effect of chemotherapy for ICC may provide important information on the clinical management of PSC patients. ICC is generally considered a late complication of advanced PSC-related liver cirrhosis.[13] However, histological examination in non-cancerous lesions showed mild inflammation and fibrous expansion of the portal area in our patient. Likewise, the prevalence of esophageal varices is low in PSC patients with ICC,[14] suggesting that ICC may not inevitably be a late complication of PSC; therefore, it may be necessary to be alert to the development of ICC in any stage of PSC.

Intrahepatic cholangiocarcinoma shows a variable cholangiocytic differentiation[15] and ICC with HPC phenotypes has been proposed recently.[16–19] In our case, some of the ICC cells were weak immunoreactive for CD133 and NCAM, and most of the ICC cells were strong immunoreactive for K7 and K19, suggesting that the origin of ICC is derived from HPCs. Even though curative partial hepatectomy was performed, intra- and extra-hepatic metastases and poor prognosis were seen in our case. HPC phenotype is reported to be an independent factor for worse prognosis of ICC patients.[20] Thus, poor prognosis could be related to the HPC phenotype in our case and immunohistochemistry for HPC markers may be important for selecting therapeutic strategy and predicting prognosis for ICC patients.

Concerning chemotherapy, gemcitabine was administered as adjuvant chemotherapy in our patient.

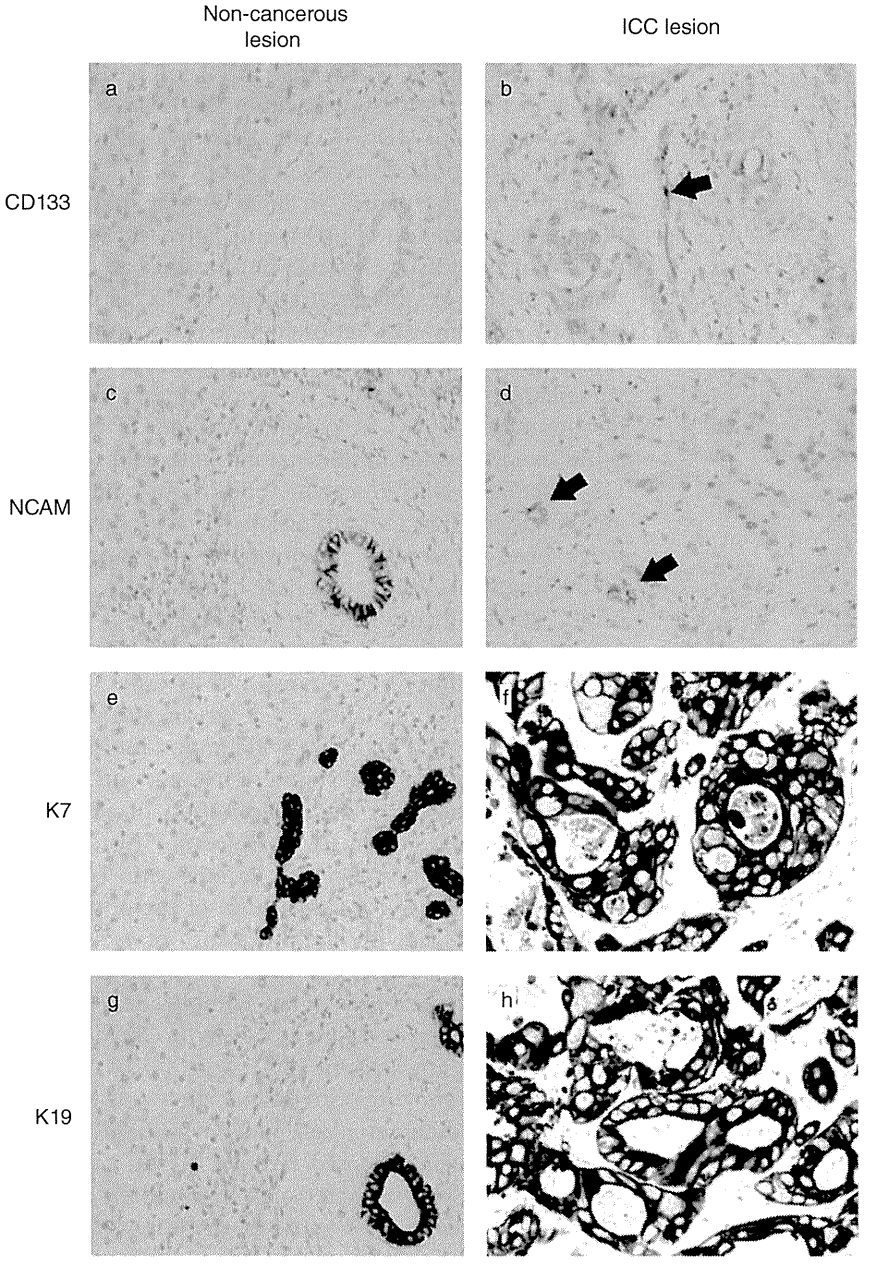

Figure 5 Immunostainig for CD133 (a and b), neural cell adhesion molecule (NCAM) (c and d), K7 (e and f), and K19 (g and h) of non-cancerous and Intrahepatic cholangiocarcinoma (ICC) lesions. Some ICC cells are weak immunoreactive for CD133 (b; arrow) and NCAM (d; arrow), and most of the ICC cells are strong immunoreactive for K7 (f) and K19 (g). Original magnification × 400. K, keratin.

However, multiple metastases occurred in the patient and he died 21 months after the onset of the ICC, suggesting that gemcitabine may not have had significant beneficial effects on the prognosis of our patient. Since there is no specific data on chemotherapy for PSC-associated ICC, it is hoped that ongoing study of molecular targeted therapy for epidermal growth factor receptors will result in a better prognosis for patients with PSC-associated ICC.[4] Thus, future studies will be focused on examining risk factors and chemotherapy for ICC in patients with PSC.

Here, we report a case of ICC that developed after a 14-year follow-up of a patient with PSC and UC in Japan. This report provides novel information on the association of development of ICC with morbidity duration of PSC and complication of IBD in Japan.

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ORIGINAL ARTICLE

Safety and tolerance of sorafenib in Japanese patients with advanced hepatocellular carcinoma

Sadahisa Ogasawara · Fumihiko Kanai · Shuntaro Obi · Shinpei Sato · Taketo Yamaguchi · Ryosaku Azemoto · Hideaki Mizumoto · Youhei Koushima · Naoki Morimoto · Nobuto Hirata · Takeshi Toriyabe · Yusuke Shinozaki · Yoshihiko Ooka · Rintaro Mikata · Tetsuhiro Chiba · Shinichiro Okabe · Fumio Imazeki · Masaharu Yoshikawa · Osamu Yokosuka

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Abstract

Purpose Sorafenib provides a survival benefit for patients with advanced hepatocellular carcinoma (HCC). However, there has been little experience with it in Japan. This study evaluated the safety and tolerance of sorafenib in Japanese patients with HCC.

Methods Clinical data for patients given sorafenib for advanced HCC were captured from eight institutions. All patients were classified as Child-Pugh A and the treatment was started at 400 mg twice daily. We recorded adverse events, treatment duration, and survival retrospectively. Adverse events were graded using Common Terminology Criteria, version 3.0; tumor response was assessed according to Response Evaluation Criteria in Solid Tumor, version 1.1.

Results Of the 54 patients treated, their median age was 69 years (range 48–82), 91% were males, 52% had HCV infection, and 22% had HBV infection. The most common drug-related adverse events were hand–foot skin reactions (HFSR) (72%), aspartate transaminase elevation (55%), alanine aminotransferase elevation (52%), rash (50%), fatigue (41%), and diarrhea (32%). Liver failure occurred in 19%. The median time to treatment failure was 2 months. Dose reduction was required in 83% of the patients, and this occurred within 2 weeks in 44%. The median overall survival was 6.9 months.

Conclusions These data suggest that sorafenib is generally tolerated in Japanese patients with HCC. Nevertheless, the majority needed a dose reduction. Adverse events including HFSR, rash, and liver failure occurred more frequently in our patients than those reported elsewhere. Careful attention must be paid to these adverse events during sorafenib administration.

S. Ogasawara · F. Kanai (✉) · T. Toriyabe · Y. Shinozaki · Y. Ooka · R. Mikata · T. Chiba · S. Okabe · F. Imazeki · M. Yoshikawa · O. Yokosuka
Department of Medicine and Clinical Oncology, Graduate School of Medicine, University of Chiba, 1-8-1 Inohana, Chuo-ku, 260-8670 Chiba, Japan
e-mail: kanaif@faculty.chiba-u.jp

S. Obi · S. Sato
Department of Gastroenterology and Hepatology, Kyoundo Hospital, 1-8 Kandasurugadai, Chiyoda-ku, 101-0062 Tokyo, Japan

T. Yamaguchi
Department of Gastroenterology, Chiba Cancer Centre, 666-2 Nitonacho, Chuo-ku, 260-8717 Chiba, Japan

R. Azemoto
Department of Gastroenterology, Kimitsu-Chuo Hospital, 1010 Sakurai, 292-8535 Kisarazu, Japan

H. Mizumoto
Department of Gastroenterology, Funabashi Municipal Medical Centre, 1-21-1 Kanasugi, 273-8588 Funabashi, Japan

Y. Koushima
Department of Gastroenterology, Saitama Red Cross Hospital, 8-3-33 Kamiochiai, Chuo-Ku, 333-8533 Saitama, Japan

N. Morimoto
Department of Gastroenterology, Shimotsuga-Sogo Hospital, 5-32 Fujimi, 328-8505 Tochigi, Japan

N. Hirata
Department of Gastroenterology, Kameda Medical Centre, 929 Higashicho, 296-0042 Kamogawa, Japan

Keywords Hepatocellular carcinoma · Sorafenib · Safety · Tolerance · Japanese

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide [1]. HCC develops mostly in patients with liver cirrhosis, which is typically caused by hepatitis C virus (HCV) infection, hepatitis B virus (HBV) infection, or alcohol [2]. The annual incidence of HCC in HCV-positive liver cirrhosis and chronic hepatitis is 6–7% and 1–2%, respectively [2]. The risk of cancer developing from chronic hepatitis or cirrhosis depends on the degree of fibrosis [3]. The hepatocarcinogenesis in the patients with hepatitis viruses differs between HCV and HBV. HCC occurs frequently in the cirrhotic livers of patients with HCV-positive liver disease. By contrast, HCC often develops in chronic HBV infection in the absence of cirrhosis. HCC developing from HBV infection has a lower cirrhosis complication rate than does HCC developing from HCV infection.

The etiology of HCC varies regionally [4]. In the Asia-Pacific region, except Japan, 70% of HCC is HBV-related and 20% is HCV-related [5]. In contrast, in Japan, 71–75% of HCC is HCV-related [2, 6]. The incidence of HCV infection is also increasing in the USA and Europe, as is the incidence of HCC [7].

Both surgical resection and local ablation therapy, including radiofrequency ablation, are considered curative for HCC [8–10]. Transarterial chemoembolization (TACE) has been applied to patients with advanced incurable HCC [11, 12]. However, the majority of patients experience recurrence or metastasis after these treatments. Although systemic therapy is available for advanced HCC, the prognosis remains poor. No standard systemic therapy that prolongs survival had been indentified before sorafenib was approved.

Sorafenib, an oral multikinase inhibitor, blocks tumor cell proliferation by targeting Raf/MEK/ERK signaling at the level of Raf kinase, and exerts an antiangiogenic effect by targeting vascular endothelial growth factor receptor-beta (VEGFR-β, PDGF-β) tyrosine kinases [13]. The Sorafenib HCC Assessment Randomized Protocol (SHARP) and Asia-Pacific studies demonstrated a significant survival benefit and good tolerance in patients with advanced HCC, making sorafenib the new reference standard for systemic therapy of patients with advanced HCC [14, 15]. In the SHARP study, approximately 90% of the patients were enrolled from Europe [14], and the Asia-Pacific study was conducted in China, Taiwan, and South Korea [15], but not Japan. The sorafenib groups in the SHARP and Asia-Pacific studies reflected the geographic patient pools, including HCV infection (29 vs. 10.7%) and HBV infection (19 vs. 70.7%) [14, 15]. In both studies, baseline disease characters differed from those of Japanese HCC patients. HCV-related HCC is most common in Japan, as mentioned above, and most of these patients have hepatitis or cirrhosis due to HCV.

In Japan, a phase I study evaluated the pharmacokinetics, safety, and preliminary efficacy of sorafenib in HCC patients [16]. Then, based on the results of the SHARP and Asia-Pacific studies, together with the phase I study in Japanese HCC, the use of sorafenib to treat HCC patients was approved by the Japanese Ministry of Health, Labour, and Welfare in May 2009 [14–16]. However, the phase I study included few patients (six Child-Pugh A patients and eight Child-Pugh B patients receiving 400 mg twice daily) [16]. Thus, little is, in fact, known about the safety and tolerance profile of sorafenib in Japanese HCC patients. In this study, we evaluated the safety and tolerance of sorafenib in Japanese HCC patients.

Materials and methods

HCC patients treated with sorafenib between May 2009 and December 2009 at eight medical centers in Japan were analyzed retrospectively. Patients were required to meet the following criteria at baseline: (1) diagnosis of HCC based on the European Association for the Study of Liver Disease/American Association for Liver Disease criteria or liver histology [8]; (2) Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 0, 1, or 2; (3) classified as Child-Pugh A; (4) required to have adequate renal, hematological, and hepatic function (platelet count $\geq 50 \times 10^9$/L, hemoglobin concentration $\geq$8.5 g/L, albumin concentration $\geq$2.8 g/L, total bilirubin concentration $\leq$3.0 mg/dL, alanine aminotransferase (ALT) concentration $\leq$5 times the upper limit of normal (ULN), serum creatinine concentration $\leq$1.5 times the ULN, and prothrombin time-international normalized rate (INR) $\leq$2.3. Patients who received 400 mg sorafenib twice daily as an initial dose were selected, and treatment interruptions and dose reductions (first to 400 mg once daily, and then to 400 mg once every other day) were allowed for the toxicity study. Dose reduction and treatment discontinuation were based on the package insert and were required for drug-related toxicities. For grade 3/4 toxicities, patients received a lower dose when the toxicity improved to grade 2 or better, but therapy was discontinued if the recovery time was 30 days or longer. Dose reduction was introduced for grade 3 non-hematologic toxicities until the toxicity was grade 2 or better; patients were then treated at one dose

level lower, and therapy was discontinued if the recovery time was 30 days or longer. Treatment was discontinued for patients with drug-related grade 4 non-hematologic toxicities. However, a modified scale resulting from a phase II trial was used for skin toxicity [17].

We recorded demographics, prior therapy, plasma α-fetoprotein (AFP) level, existence of microvascular invasion, or extrahepatic spread of HCC, Barcelona Clinic Liver Cancer (BCLC) score, tumor response, survival data, and relevant toxicities.

Adverse events were recorded according to the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0). Based on contrast-enhanced computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI), performed at baseline and 1–3 months after treatment, the tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors criteria version 1.1 (RECIST v1.1). The duration of treatment and survival were estimated using the Kaplan–Meier method.

Results

Patient baseline characteristics

In total, 54 patients were included in this retrospective study. Their median age was 69 years (range 48–82), and 49 patients (91%) were males. Most had good performance status (ECOG-PS was 0 in 81% and 1 in 15% of patients). At baseline, 28 patients (52%) had HCV infection and 12 patients (22%) had HBV infection. Of the patients, 38 (70%) were classified as BCLC stage C and 28 patients (52%) had extrahepatic metastases. Before receiving sorafenib therapy, 50 patients (93%) had been treated with surgery, local ablation, or TACE (Table 1).

Table 1 Baseline demographics and disease characteristics of the enrolled patients

Number of patients	54
Sex, no. (%)	
Male	49 (91)
Female	5 (9)
Age (years)	
Median (range)	69 (48–82)
Body weight (kg)	
Median (range)	60.8 (43.6–81.3)
Body surface area ($m^{2)}$	
Median (range)	1.66 (1.32–1.93)
ECOG PS, no. (%)	
0	44 (81)
1	8 (15)
2	2 (4)
Child-Pugh score, no. (%)	
5	36 (67)
6	18 (33)
Hepatitis virus status, no. (%)	
HCV infection	28 (52)
HBV infection	12 (22)
Alcohol	8 (15)
Other	6 (11)
BCLC stage, no. (%)	
B (intermediate)	16 (30)
C (advanced)	38 (70)
Macroscopic vascular invasion, no. (%)	12 (22)
Extrahepatic spread, no. (%)	
Any	28 (52)
Lymph nodes	8 (15)
Lung	14 (26)
Bone	6 (11)
Prior treatment, no. (%)	
Any	50 (93)
Surgery	27 (50)
Local ablation	25 (46)
Transarterial chemoembolization	43 (80)
Biochemical analysis, median (range)	
Platelets/mm^3	133,500 (50,000–296,000)
Albumin (g/dL)	3.7 (2.8–4.9)
Total bilirubin (mg/dL)	0.8 (0.2–1.9)
Aspartate aminotransferase (AST) (IU/L)	51 (18–176)
Alanine aminotransferase (ALT) (IU/L)	40 (11–162)
Alpha fetoprotein (AFP) (ng/mL)	246.6 (2.8–184,100.0)

Safety and tolerability

The overall incidence of drug-related adverse events of any grade was 98% and 36 patients (68%) experienced grade 3/4 adverse events (Table 2). HFSR occurred in 39 patients (72%) and was grade 3/4 in 14 patients (26%). Rash occurred in 27 patients (50%) and was grade 3/4 in 7 patients (13%). Fatigue, diarrhea, and hypertension occurred in 22 (41%), 17 (32%), and 14 patients (26%), respectively; none of these toxicities was grade 3/4. Liver failure under treatment, defined as encephalopathy, massive ascites, or jaundice, occurred in ten patients (19%). The median average daily dose was 450 mg (range 182–800 mg). Dose reduction was required in 45 patients (83%) (Table 3). The most common adverse events leading to dose reduction were HFSR ($n = 21$, 38%), aspartate transaminase (AST)/ALT elevation ($n = 8$, 15%), rash ($n = 7$, 13%), and liver failure ($n = 4$, 7%). Treatment was discontinued in 17 patients (31%) for sorafenib intolerance (Table 4). The most frequent adverse events leading to