Table 4. Results of univariate and multiple analysis for prognostic factors in patients treated with sorafenib

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age, years (≤65/>65)	1.1 (0.6–2.1)	0.86		
Gender (M/F)	1.2 (0.49–3.3)	0.5		
Etiology (HBV/HCV/nonHBVnonHCV)	1.3 (0.7–2.5)	0.33		
Platelet count, $\times 10^4/\mu l$ (≤15/>15)	1.9 (0.9–3.7)	0.38		
Child-Pugh (A/B)	5 (1.7–11.1)	0.001	3.7 (1.3–10.0)	0.012
Tumor volume (≤50%/>50%)	1.6 (1.0–3.0)	0.13		
Metastasis (absent/present)	1.6 (0.8–3.2)	0.059		
Tumor thrombosis (absent/present)	1.6 (0.9–3.3)	0.88		
AFP ratio (≤1.0/>1.0) at 4 weeks from start of treatment	1.6 (0.7–3.1)	0.052		
DCP ratio (≤3.0/>3.0) at 4 weeks from start of treatment	1.1 (0.5–2.5)	0.5		
AFP ratio (≤1.0/>1.0) at 8 weeks from start of treatment	3.0 (1.6–6.2)	0.002	3.3 (7.4–10.0)	0.011
DCP ratio (≤3.0/>3.0) at 8 weeks from start of treatment	1.1(0.5–2.5)	0.33		
PS (0/1–3)	2.3 (1.2–4.5)	0.008	1.7 (0.8–3.7)	0.14
Response (CR + PR + SD/PD + not evaluated)	5 (2.5–10)	0.001	2.5 (1.61–7.14)	0.029
Continuation of sorafenib treatment, weeks (>8/<8)	13 (5.8–29.2)	<0.001	10.9 (4.1–29.3)	<0.001

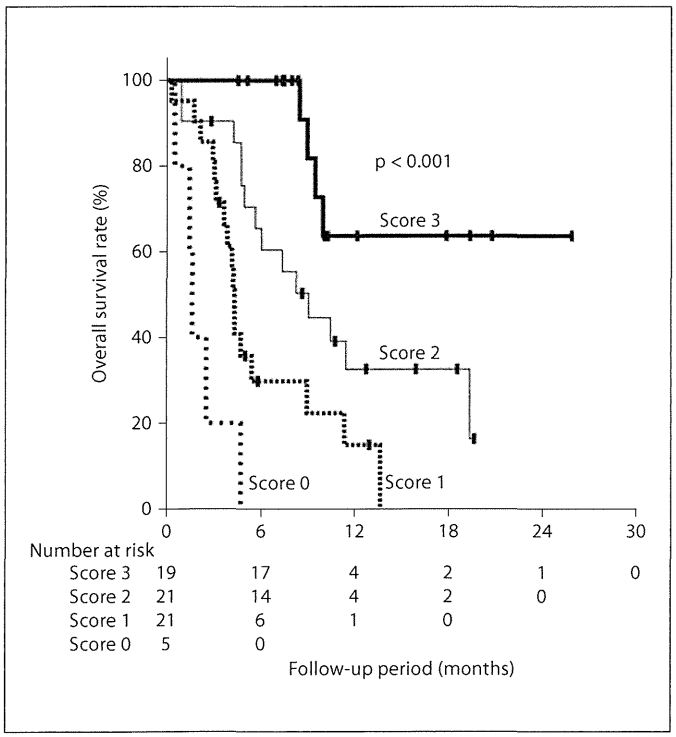

Fig. 5. Stratification of the response to sorafenib treatment by the combination of mRECIST, Child-Pugh and AFP ratio.

Stratification of Prognosis following Sorafenib Treatment with the Combination mRECIST, AFP Ratio and Child-Pugh

A sum score of the response by mRECIST (PD: 0, CR or PR of SD: 1), Child-Pugh score (Child-Pugh B: 0, Child-Pugh A: 1) and AFP ratio at 8 weeks from the start of treatment (>1:0, ≤1:1) was calculated. The patients were divided into 4 groups based on the number of positive factors, CR + PR + SD, Child-Pugh A and AFP ratio at 8 weeks from the start of treatment (≤1), and this positive number was used as a new prognostic score for evaluation of the outcome of sorafenib-treated patients with advanced HCC. The median survival time for a prediction score of 0 (n = 5) was 3 months, while that for a score of 1 was 5 months (n = 21) and 9 months for a score of 2 (n = 21). The survival rate for a score of 3 was 62% at 24 months. The difference in the percentages of patients among the 4 groups was statistically significant ($p < 0.001$; fig. 5).

Discussion

In this study, 1 patient evaluated as PR by RECIST was evaluated as CR by mRECIST. Four patients evaluated as SD by RECIST were evaluated as PR by mRECIST. Therefore, the response rate by mRECIST was 9% compared to only 3% by RECIST. Furthermore, patients assessed as CR or PR by mRECIST had a good prognosis. Although

the disease control rate was the same in mRECIST and RECIST, overall survival was better stratified for response assessment by mRECIST ($p = 0.009$) than by RECIST ($p = 0.09$). However, the proportion of patients assessed as CR and PR by mRECIST was less than 10%. Therefore, assessment by mRECIST seems to be of only limited value because most patients showed SD and PD in sorafenib treatment.

AFP and DCP are serological tumor markers used in the screening and diagnosis of HCC [12–14]. They are also useful as indicators of the therapeutic effect upon examination before and after tumor resection or local ablation therapy [17–19]. Two reports analyzed the relation between AFP and response and prognosis to sorafenib treatment. Kuzuya et al. [23] concluded that evaluation of the AFP ratio at 2 and 4 weeks after starting sorafenib therapy was useful for the prediction of the response to treatment. Yau et al. [24] reported that a fall in AFP at 6 weeks after starting sorafenib therapy is a useful predictor of the treatment outcome. In this study, the AFP ratio at 8 weeks – but not that at 4 weeks – correlated significantly with the mRECIST response at 8 weeks. The reason for the unsuitability of the AFP ratio at 4 weeks could be due to the finding that the proportion of patients with an AFP ratio of ≤ 1 at 4 weeks (53%) was more than that at 8 weeks (29%) in PD patients. Furthermore, sorafenib is a cytostatic agent, and the aim of sorafenib treatment is to obtain long SD. In other words, it is impossible to achieve the goal without long-term administration even if a patient is assessed as a good responder at 4 weeks after starting sorafenib therapy. Indeed, the median overall survival was 2.1 months in 17 patients who stopped the treatment within 8 weeks, whereas it was 10.1 months in 49 patients who continued the treatment for more than 8 weeks. These data suggest that it is probably inappropriate to assess the response to sorafenib treatment by AFP at 4 weeks, and that such assessment must be conducted at least at 8 weeks after starting the therapy.

On the other hand, no significant difference in overall survival was seen using the DCP ratio, although one clinical report described serial changes in DCP following sorafenib treatment [25]. In this regard, Murata et al. [26] reported that liver cancer cells cultured under hypoxic conditions produce high levels of DCP. One possible mechanism for the high DCP levels following sorafenib treatment is that sorafenib-mediated inhibition of angiogenesis renders the tumor cells hypoxic, subsequently leading to increased DCP production. These results suggest that the high levels of DCP noted after sorafenib treatment may reflect HCC cell ischemia.

We speculated that an elevation of AFP would indicate tumor progression and no response of sorafenib. Elevation of DCP would not indicate tumor progression.

In conclusion, our study demonstrated that mRECIST assessed at 8 weeks and measurement of the AFP at 8 weeks after starting treatment and of Child-Pugh before treatment are significant and independent determinants of survival, and also that the assessment of AFP value should be conducted after at least 8 weeks of continuous sorafenib treatment. In addition, in patients who continue sorafenib treatment for at least 8 weeks, the combination mRECIST assessed at 8 weeks, AFP ratio measured after 8 weeks of treatment and Child-Pugh score are significant predictors of the prognosis of sorafenib treatment.

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In daily practice, the concept of fiberoptic intubation in the awake patient is not clearly defined. In most cases, the choice of technique is dependent on institutional and personal preferences. Ultimately, such a choice is a compromise between safety, practicability, and acceptance. The technique as shown in the video is a thoroughly documented, well-tested method that has not been changed for many years.[5]

Thomas Heidegger, M.D.

Spitalregion Rheintal Werdenberg Sarganserland
Walenstadt, Switzerland
thomas.heidegger@srrws.ch

Since publication of his article, the author reports no further potential conflict of interest.

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Deferoxamine for Advanced Hepatocellular Carcinoma

TO THE EDITOR: We have previously reported that the iron chelator deferoxamine can prevent liver injury as well as the development of preneoplastic lesions in rats,[1,2] and we have proposed the use of deferoxamine as an anticancer drug. The antiproliferative effect of deferoxamine arrests the cell cycle and induces apoptosis.[3] To our knowledge, no clinical study has been performed to evaluate deferoxamine therapy in patients with hepatocellular carcinoma.[4]

Our study involved 10 patients (6 men and 4 women) who had advanced hepatocellular carcinoma and did not have a response to hepatic arterial infusion chemotherapy with anticancer drugs. The average age of the patients was 64 years (range, 43 to 77). Written informed consent was obtained before the study, which was approved by the institutional review board of Yamaguchi University Hospital. Seven patients had hepatitis C virus infection, 2 patients had hepatitis B virus infection, and 1 patient did not have either type of infection. The tumor stages were classified as II, IVA, and IVB (according to the Liver Cancer Study Group of Japan criteria) for 1, 2, and 7 patients, respectively. The Child–Pugh class was A, B, and C for 3, 5, and 2 patients, respectively. (In the Child–Pugh classification of liver disease, class A indicates the least severe disease, class B moderately severe disease, and class C the most severe disease.) The patients received an arterial infusion of deferoxamine (at a dose of 10 to 80 mg per kilogram of body weight) over 24 hours on alternate days, through the injection port.

Deferoxamine was administered an average of 27 times (range, 9 to 78). Two, three, and five patients had a partial response, stable disease, and progressive disease, respectively (according to the Eastern Cooperative Oncology Group criteria). The overall response rate was 20%.

Tumor-marker levels (alpha-fetoprotein, des-γ-carboxyprothrombin, alpha-fetoprotein L3, or all of these levels) decreased in patients with a partial response. In one patient, a massive hepatocellular tumor with lung metastases disappeared with deferoxamine treatment (Fig. 1). The 1-year cumulative survival rate was 20%. Four patients had grade 2 or 3 interstitial pneumonia (according to the Common Terminology Criteria for Adverse Events, version 4.0), and one patient had grade 2 renal dysfunction. However, no grade 4 adverse events were observed.

Sorafenib, a multikinase inhibitor, has recently been established as the standard of care for patients with advanced hepatocellular carcinoma and preserved liver function (Child–Pugh class A) because it increases survival.[5] However, its safety and efficacy for patients with Child–Pugh class B or C disease is still unknown. Deferoxamine may warrant testing in patients with Child–Pugh class B or C hepatocellular carcinoma.

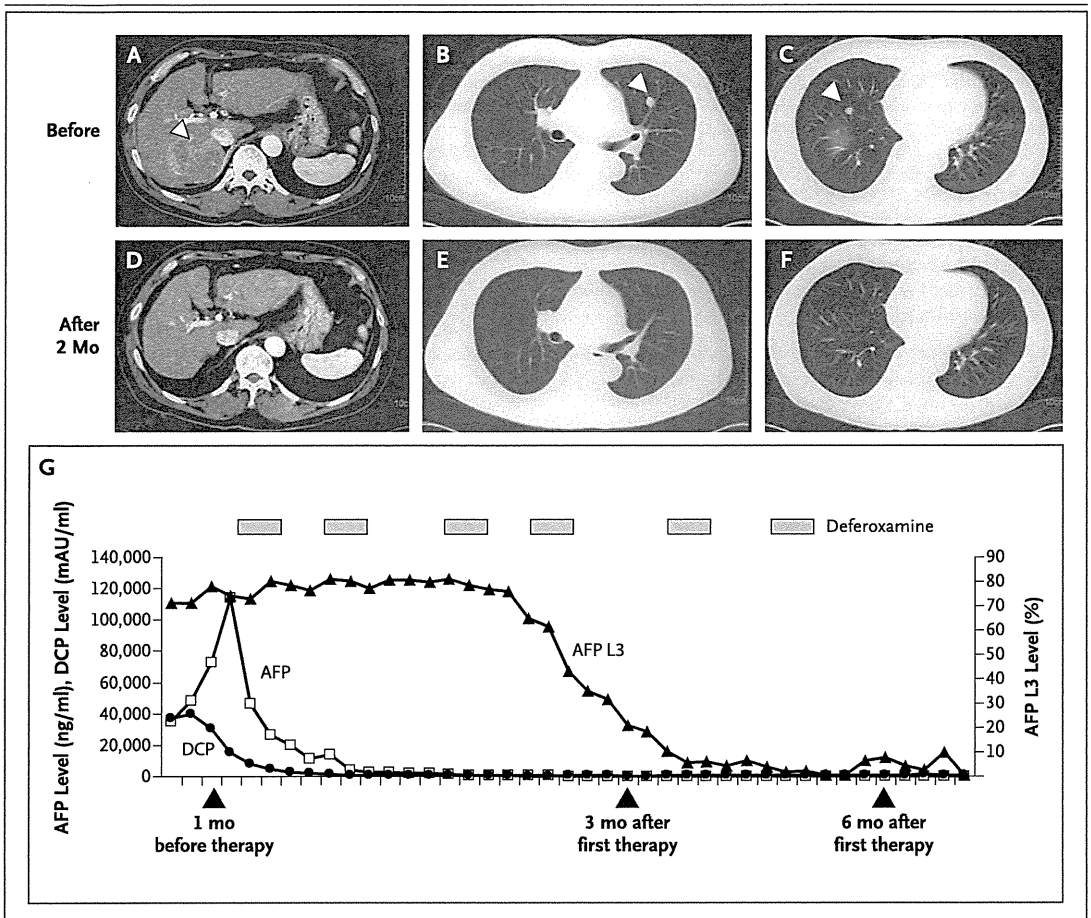

Figure 1. Deferoxamine Treatment in One Patient.

A 62-year-old man presented with a massive hepatocellular tumor with multiple small lung metastases (stage IVB). The hepatic reserve function was Child–Pugh class B (a score of 8) before treatment (in the Child–Pugh classification of liver disease, class A [a score of 5 or 6] indicates the least severe disease, class B [7 to 9] moderately severe disease, and class C [10 to 15] the most severe disease). In Panel A, abdominal dynamic computed tomography (CT) before treatment shows a tumor (arrowhead). In Panels B and C, plain chest CT scans obtained before treatment show multiple lung metastases (arrowheads). Two months after arterial infusion of deferoxamine (at a dose of 50 mg per kilogram of body weight per day), the liver tumor and multiple lung metastases were not observed on abdominal dynamic CT (Panel D) and plain chest CT (Panels E and F). As shown in Panel G, after arterial infusion of deferoxamine, the levels of three tumor markers (alpha-fetoprotein [AFP], des-γ-carboxyprothrombin [DCP], and AFP L3) decreased. The patient was considered to have a partial response according to the Eastern Cooperative Oncology Group criteria. The patient survived 20.9 months with deferoxamine treatment.

Takahiro Yamasaki, M.D., Ph.D.
Shuji Terai, M.D., Ph.D.
Isao Sakaida, M.D., Ph.D.

Yamaguchi University Graduate School of Medicine
Ube, Japan
t.yama@yamaguchi-u.ac.jp

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Contact Tamara Rios, Rios Associates, 3729 N. Bay Horse Loop, Tucson, AZ 85719; or call (520) 907-3318; or see http://www.medspanish.org.

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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

Table 2 Drug-related adverse events

	Any	Grade 3/4
Overall incidence	53 (98)	36 (68)
Hematological		
Hemoglobin	1 (2)	0
Leukocytes	4 (8)	0
Platelets	14 (26)	3 (6)
Dermatologic events		
Hand–foot skin reaction	39 (72)	14 (26)
Rash	27 (50)	7 (13)
Alopecia	9 (17)	
Gastrointestinal events		
Anorexia	12 (22)	4 (7)
Diarrhea	17 (32)	0
Vomiting	3 (6)	1 (2)
Fatigue	22 (41)	0
Voice changes	2 (4)	0
Hypertension	14 (26)	0
Abdominal pain not otherwise specified	5 (9)	0
Bleeding	4 (8)	2 (4)
Laboratory		
AST	30 (55)	13 (24)
ALT	28 (52)	8 (15)
Bilirubin	15 (28)	6 (11)
Amylase	15 (28)	3 (6)
Liver failure	10 (19)	

Liver failure is defined as encephalopathy, massive ascites, or jaundice

Table 3 Adverse events causing dose reduction

	Number of patients (%)
Patients requiring dose reduction	45 (83)
Hand–foot skin reaction	21 (38)
AST/ALT	8 (15)
Rash	7 (13)
Liver failure	4 (7)
Anorexia	2 (4)
Bleeding	2 (4)
Vomiting	1 (2)
Time to dose reduction	
<2 weeks	24 (44)
≥2 weeks to <4 weeks	12 (22)
≥4 weeks	9 (17)

treatment discontinuation were liver failure ($n = 4$, 7%), HFSR ($n = 4$, 6%), fatigue ($n = 3$, 6%), and abdominal pain not otherwise specified ($n = 3$, 6%). The median time to treatment failure (TTF; defined as the period from first treatment to discontinuation of sorafenib treatment, progression, or death) was 2 months (Fig. 1).

Table 4 Adverse events leading to treatment discontinuation

	Number of patients (%)
Any adverse events	17 (31)
Liver failure	4 (7)
Hand–foot skin reaction	3 (6)
Fatigue	3 (6)
Abdominal pain not otherwise specified	3 (6)
Anorexia	2 (4)
Rash	2 (4)

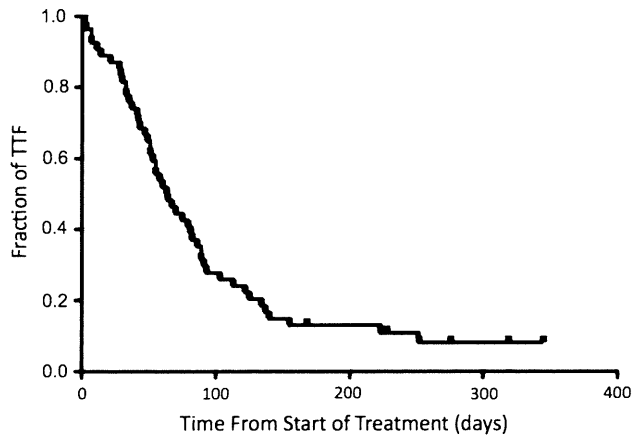

Fig. 1 Kaplan–Meier analysis of time to treatment failure (TTF). The median TTF was 2 months

Efficacy

According to RECIST version 1.1, one patient (2%) had a partial response, 25 patients had stable disease (57%), and the disease control rate (DCR; defined as no disease progression for ≥4 weeks) was 34% (Table 5).

At the time of analysis, with a median follow-up of 5.7 months (range 0.5–13.3), 49 patients had discontinued treatment (92%) and 28 patients were dead (52%). The overall median survival was 6.9 months (Fig. 2)

Discussion

The SHARP and Asia-Pacific studies, large, multicentre, phase III, randomized, double-blind, placebo-controlled trials of sorafenib, revealed a survival benefit and the tolerability of sorafenib in advanced HCC patients. However, considering the varying etiologies and treatment strategies for HCC in different regions [4], it is unclear whether these results apply to Japanese HCC patients. In Japan, high-risk groups for HCC, such as cirrhosis or hepatitis patients, undergo ultrasonography every 3–4 months and CT or MRI every 6–12 months for the early detection of HCC. Because we find HCC when it is earlier, Japanese HCC

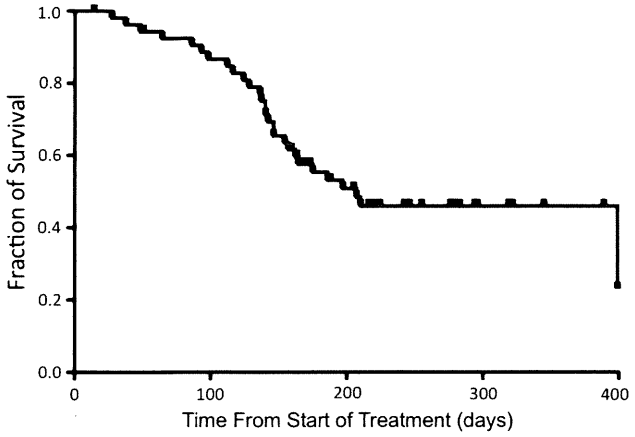

Fig. 2 Kaplan-Meier analysis of overall survival (OS). The median OS was 6.9 months

Table 5 Response rates using the response evaluation criteria in solid tumors

Response ($n = 44$)	Number of patients (%)
Complete response	0
Partial response	1 (2)
Stable disease	25 (57)
Progressive disease	18 (41)
DCR	15 (34)

DCR is the disease control rate, defined as the proportion of patients who had a best response rating of a complete response, partial response, or stable disease that was maintained for ≥4 weeks from the first manifestation of the rating

patients are often able to undergo surgery, local ablation, and TACE. Despite the efficacy of these procedures, patients frequently develop recurrence or disease progression after these treatments. In contrast, in much of the rest of Asia, the majority of patients are present with advanced disease, with large tumors, multiple tumors, and portal tumor thrombosis. These patients are less likely to receive curative treatment [18]. Furthermore, the liver function of HBV-related HCC patients tends to be better than that of HCV-related HCC patients. Shiratori et al. [2] reported that 38.6, 39.3, and 22.1% of cases presented as Child-Pugh A, B, and C when the severity of cirrhosis was classified in Japanese HCV-related HCC patients. By contrast, among the HBV-related HCC patients, 65.2, 26.1, and 8.7% cases presented as Child-Pugh A, B, and C. Additionally, liver function might worsen with the repetition of local therapies because sorafenib was only given to Child-Pugh A patients. Fewer HCV-related HCC patients (52%) were included in the present analysis compared with the general HCC prevalence in Japan (71–75%) [2, 6].

In the SHARP study, common drug-related adverse events were diarrhea (39%), fatigue (22%), HFSR (21%), rash (16%), alopecia (14%), anorexia (14%), and nausea (11%) [14]. Dose reduction due to adverse events was needed in 26% of subjects. The most common adverse events leading to dose reduction were diarrhea (8%), HFSR (5%), and rash (3%) [14]. Treatment was discontinued because of adverse events in 38%. The most frequent adverse events leading to sorafenib discontinuation were gastrointestinal events (6%), fatigue (5%), and liver dysfunction (5%) [14]. In comparison, in the Asia-Pacific study, the common drug-related adverse events were HFSR (45.0%), diarrhea (25.5%), alopecia (24.8%), fatigue (20.1%), rash (18.8%), hypertension (18.8%), and anorexia (12.8%) [15]. Dose reduction due to adverse events was needed in 30.9%, and treatment was discontinued due to adverse events in 19.5% [15]. The most common drug-related adverse events resulting in dose reduction were HFSR (11.4%) and diarrhea (7.4%) [15]. Compared with these studies, we observed a higher incidence of adverse events, especially HFSR, rash, hypertension, and liver failure.

The incidence of HFSR and rash in the Asia-Pacific study was higher than in the SHARP study [14, 15]. In a phase I study of a small population of Japanese patients with HCC, five of the six patients experienced HFSR and four experienced rash; these patients were Child-Pugh A receiving 400 mg twice daily [16]. In a phase II study of Japanese patients with advanced renal cell carcinoma [19], HFSR occurred in 55% and rash occurred in 37.4%. Asian patients, particularly Japanese, frequently develop HFSR. Although it is possible that the physiological difference is partly associated with race, prevention and management of HFSR are required in Japanese patients.

Regarding hypertension, Wu et al. [20] reported a 23.4% (95% CI 16.0–32.9%) overall incidence from a systemic review and meta-analysis of nine studies of renal cell cancer or other solid tumor. Hypertension was experienced by 14 patients (26%) in our study; no case was grade 3/4. Varying rates of hypertension have been reported, with a 5% incidence in the SHARP study and an 18.8% incidence in the Asia-Pacific study. In our study, the incidence of hypertension was comparable with that reported by Wu et al., although it was slightly higher compared with that reported in the SHARP and Asia-Pacific studies.

Liver failure occurred in ten patients (19%), while it was uncommon in the SHARP and Asia-Pacific studies. Nevertheless, Ozenne et al. [21] reported that seven (21%) French patients with Child-Pugh A experienced liver failure. The SHARP and Asia-Pacific studies showed the efficacy of sorafenib in carefully selected patients with advanced HCC. Liver failure may occur with the use of sorafenib in an unselected cirrhotic population. In our study, the median time to experience liver failure was 33 days (range 7–115); liver failure can happen in the

early days of treatment. Furthermore, a common adverse event leading to treatment discontinuation was liver failure (7%).

In our study, 43 patients required dose reduction due to adverse events (83%). This was more frequent than in either the SHARP or Asia-Pacific studies. The most common adverse event leading to dose reduction was HFSR (43%) [12, 13]. Our patients suffered more HFSR than those in the SHARP and Asia-Pacific studies [12, 13]. The cause may be differences, such as age or race. Nevertheless, treatment discontinuation due to HFSR was required in only 6% of the patients; in the majority of the patients, it could be controlled by dose reduction. This concurred with the finding that two of seven patients with Child-Pugh A experienced HFSR when they took 400 mg daily in the Japanese phase I study [16].

In our series, 44% of the patients required dose reduction within 2 weeks and the median daily dose was 450 mg (range 182–800), demonstrating that it is difficult for Japanese patients to continue sorafenib treatment at 400 mg twice daily. Treatment was discontinued because of adverse events in 31% of our patients, which was similar to the rate in the SHARP study, but higher than in the Asia-Pacific study. Adverse events could be managed by dose reduction in the majority of patients. Therefore, careful follow-up is recommended.

The median overall survival was 10.7 months in the SHARP trial and 6.5 months in the Asia-Pacific trial. The differences in survival time might have been caused by differences in patient background. Patients in the Asia-Pacific study displayed more extrahepatic spread, more hepatic tumors, a worse ECOG-PS, and increased concentrations of AFP compared with patients in the SHARP study [14, 15]. The median survival time was 9.2 months in a phase II study [17] and 15.6 months in a Japanese phase I study [16], although Child-Pugh B patients were included in both of these studies. More recently, two retrospective studies from Europe showed that the median survival times for Child-Pugh A patients were 8.9 [21] and 8.3 months [22]. The median overall survival in our series was 6.9 months, although the survival benefits cannot be directly compared, as this was a retrospective study. Our study included many patients with higher serum AFP levels, suggesting the inclusion of highly advanced cases in the present study.

In summary, the present study demonstrated that sorafenib was generally tolerated in Japanese HCC patients because the probability of treatment discontinuation due to adverse events was acceptable, although most patients needed dose reduction. The overall safety profile of sorafenib was similar to that seen in previous studies in patients with HCC, except for the higher rates of HFSR, rash, and liver failure.

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Effect of Aging on Risk for Hepatocellular Carcinoma in Chronic Hepatitis C Virus Infection

Yasuhiro Asahina,[1] Kaoru Tsuchiya,[1] Nobuharu Tamaki,[1] Itsuko Hirayama,[1] Tomohiro Tanaka,[1] Mitsuaki Sato,[1,2] Yutaka Yasui,[1] Takanori Hosokawa,[1] Ken Ueda,[1] Teiji Kuzuya,[1] Hiroyuki Nakanishi,[1] Jun Itakura,[1] Yuka Takahashi,[1] Masayuki Kurosaki,[1] Nobuyuki Enomoto,[2] and Namiki Izumi[1]

An increase in the aging population is an impending problem. A large cohort study was carried out to determine the influence of aging and other factors on hepatocarcinogenesis in patients treated with interferon. Biopsy-proven 2547 chronic hepatitis C patients registered at our referral center since 1992 were included. Of these, 2166 were treated with interferon-based therapy. Incidences of hepatocellular carcinoma (HCC) associated with interferon were analyzed by Kaplan-Meier and person-years methods for an average follow-up of 7.5 years. Factors associated with HCC risk were determined by Cox proportional hazard analysis. HCC developed in 177 interferon-treated patients. The risk for HCC depended on age at primary biopsy and increased more than 15-fold after 65 years of age. Even when stratified by stage of fibrosis, the cumulative and annual incidences of HCC were significantly higher in older patients than in younger patients ($P < 0.001$) at the same stage of fibrosis, except for cirrhosis. Progression of fibrosis over time was significantly accelerated in older patients. The impact of viral eradication on HCC prevention was less significant in older patients than in younger patients. Multivariate analysis confirmed that age, gender, liver fibrosis, liver steatosis, total cholesterol level, fasting blood sugar level, baseline and postinterferon alpha-fetoprotein level, and virological response to interferon were independent risk factors associated with HCC. Aging was the strongest risk factor for a nonvirological response to interferon-based antiviral therapy. *Conclusion:* Elderly patients are at a higher risk for HCC. Hepatitis C viral eradication had a smaller effect on hepatocarcinogenesis in older patients. Patients should therefore be identified at an earlier age and treatment should be initiated. (HEPATOLOGY 2010;52:518-527)

Primary liver cancer is the third most common cause of cancer mortality worldwide,[1] and hepatocellular carcinoma (HCC) is one of the most frequent primary liver cancers.[2,3] Infection with hepatitis C virus (HCV) is a common cause of chronic hepatitis, which progresses to HCC in many patients.[4] The prevalence of older patients has been increasing in Japan, and this is an impending problem in other countries where viral spread has occurred more recently.[5] The number of Americans older than 65 years is expected to double by the year 2030.[6] In Western Europe, people older than 65 years already constitute 15%-18% of the population[7]; thus, aging patient who is chronically infected with HCV is

Abbreviations: AFP, alpha-fetoprotein; HBc, hepatitis B core; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; SVR, sustained virological response.

From the [1]Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Tokyo, Japan; and [2]First Department of Internal Medicine, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan.

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Address reprint requests to: Namiki Izumi, M.D., Ph.D., Chief, Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, 1-26-1 Kyonan-cho, Musashino-shi, Tokyo 180-8610, Japan. E-mail: nizumi@musashino.jrc.or.jp; fax: +81-422-32-9551.

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one of the most important issues confronted by physicians.

Viral eradication with interferon-based therapy for chronic hepatitis C has been shown to prevent HCC by studies conducted in Japan and Italy.[8-11] However, this finding is controversial according to another study conducted in Europe and Canada,[12] in which viral eradication did not significantly reduce the risk for HCC in 479 consecutively treated patients. The likelihood of development of HCC among interferon-treated patients is difficult to determine because of the paucity of adequate long-term cohort studies. Moreover, in patients who are treated with interferon the effect of certain factors, including aging, on the risk for HCC remains unclear. Furthermore, the benefit of viral eradication with interferon-based therapy, including pegylated interferon and ribavirin combination therapy, in older patients remains unknown. To further clarify this, we conducted a large-scale, long-term cohort study and analyzed the influence of aging and other host and virological factors in patients treated with interferon.

Patients and Methods

Patients. Consecutive patients (n = 2547) chronically infected with HCV who underwent liver biopsy between 1992 and January 2008 at our referral center were enrolled. Of these, 2166 patients were treated with interferon-based antiviral therapy, whereas 381 patients did not receive interferon treatment (Fig. 1). All patients had histologically proven chronic hepatitis or cirrhosis. HCV infection was proven in all patients by identification of HCV RNA. Patients with a history of HCC, autoimmune hepatitis, or primary biliary cirrhosis were excluded. We also excluded patients who had a history of excessive alcohol consumption (50 g/day) and confirmed alcohol abstinence during follow-up. No patient was positive for hepatitis B surface antigen or antihuman immunodeficiency virus antibody. Written informed consent was obtained from all patients. The study was approved by the Ethical Committee of Musashino Red Cross Hospital in accordance with the Declaration of Helsinki.

Histological Evaluation. A liver biopsy specimen was obtained laparoscopically using 13G needles. When laparoscopy was impossible, ultrasound-guided liver biopsy was performed with 15G needles (n = 254). The mean length of the specimen was 18 mm (range 12-40 mm), and the mean number of portal tracts was 17 (range 8-34). Liver biopsy specimens

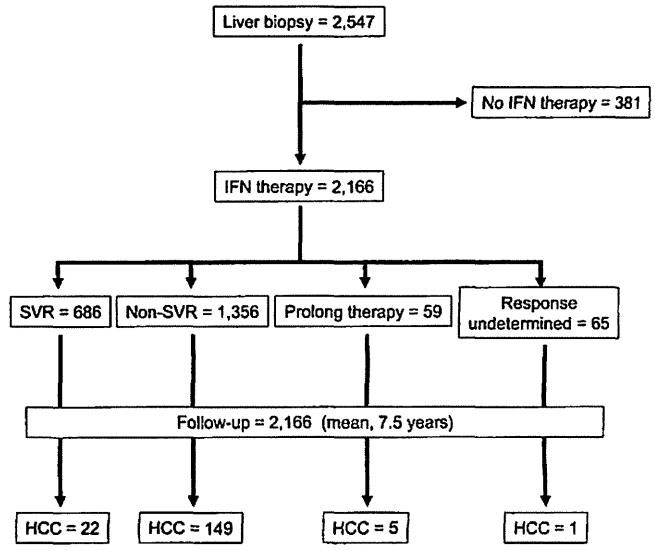


Fig. 1. Clinical outcomes of the patients enrolled in the present study. HCC, hepatocellular carcinoma; SVR, sustained virological response.

were scored by board-certified pathologists for stage of fibrosis and grade of inflammatory activity according to the classification of Desmet et al.[13] Additional macroscopic pathological information was obtained from laparoscopic findings. The percentage of steatosis was quantified by determining the average proportion of hepatocytes affected by steatosis. In this study, superimposed nonalcoholic steatohepatitis (NASH) was defined as a central pattern of colocalization of hepatic steatosis and hepatocyte ballooning with pericellular/perisinusoidal fibrosis or Mallory hyaline.

Interferon Treatment. Among the 2166 patients treated with interferon-based antiviral therapy, 1062 patients received interferon-alpha or beta monotherapy either for 24 weeks (n = 1003) or for 2 to 5 years (n = 59); 386 patients received interferon-alpha and ribavirin combination therapy for 24 weeks; 306 received pegylated interferon-alpha monotherapy for 48 weeks; and 412 received pegylated interferon-alpha and ribavirin combination therapy for 48 weeks. All interferon treatment was initiated within 48 weeks after liver biopsy.

Definitions of Response to Interferon Therapy. A patient negative for serum HCV RNA after the first 6 months of completion of interferon-based therapy was defined as a sustained viral responder. HCV RNA was determined by the qualitative Amplicor or TaqMan HCV assay (Roche Molecular Diagnostics, Tokyo, Japan).

Data Collection and Patient Follow-up. Data on patient characteristics, biochemical data, hematological

data, virological data, histological data, and treatment details were collected at enrollment. Age was determined at primary liver biopsy. Patients were examined for HCC with abdominal ultrasonography, dynamic computed tomography, and/or magnetic resonance imaging every 3-6 months. Serum alpha-fetoprotein (AFP) levels were measured every 1-2 months. This screening program constitutes the standard of care in Japan. To evaluate the effect of interferon-induced AFP reduction on hepatocarcinogenesis, the average AFP level after interferon treatment was calculated in each patient. HCC diagnosis was confirmed with needle biopsy, surgically resected specimens, or typical radiological findings diagnosed by board-certified radiologists. Figure 1 shows the schema for patient follow-up and clinical outcomes.

The start date of follow-up was the date of primary liver biopsy and the endpoint of follow-up was the development of HCC or the latest medical attendance until January 2009. The mean follow-up period was 7.5 years (range 0.5-17 years). The factors associated with development of HCC were retrospectively analyzed.

Change in Fibrosis Staging Over Time. To evaluate change in fibrosis staging over time, 271 patients who had not achieved a sustained virological response (SVR) with interferon therapy underwent a sequential biopsy after the initial biopsy. The interval between the paired biopsies was on average 4.8 years (range 0.7-14 years). The yearly rate of progression of fibrosis was calculated as the change in fibrosis staging divided by the time between paired biopsies.

Statistical Analysis. Categorical data were compared by the chi-square test and Fisher's exact test. Distributions of continuous variables were analyzed with Student's t test or the Mann-Whitney U test for two groups. All tests of significance were two-tailed and a P value of <0.05 was considered statistically significant. The cumulative incidence curve was determined with the Kaplan-Meier method and differences among groups were assessed using the log-rank test. Factors associated with HCC risk and virological response to interferon therapy were determined by the Cox proportional hazard model and logistic regression analysis, respectively. To depict the role of aging in developing risk for HCC, the multivariate Cox proportional hazard model was used after adjusting for stage of liver fibrosis, steatosis, and virological response to interferon. A polynomial regression was used to fit risk ratios for segments of the age distribution. Statistical analyses were performed using the Statistical Package for the Social Sciences software version 11.0 (SPSS, Chicago, IL).

Results

Patient Characteristics. Patient characteristics at the time of enrollment are shown in Table 1. The distribution of stages of liver fibrosis differed between younger and older patients, indicating the need to adjust for stage of liver fibrosis when comparing the two subgroups.

Response to Interferon Therapy. The response to interferon therapy was determined in 2042 (97.2%) of the interferon-treated patients, excluding those who received prolonged interferon treatment at the endpoint. SVR rates are shown in Table 1. The percentage of patients showing SVR was significantly lower in older patients (≥65 years) than in younger patients (<65 years) ($P < 0.001$). Overall response rates to the different types of interferon therapy were as follows: interferon monotherapy, 31.5% (312/992); interferon-alpha and ribavirin combination therapy, 28.6% (108/378); pegylated interferon-alpha monotherapy, 37.9% (108/285); and pegylated interferon-alpha and ribavirin combination therapy, 41.1% (159/387). Response rates in genotype-1 patients (n = 1347) were 20.6% (114/554), 17.9% (29/162), 18.9% (56/297), and 36.8% (123/334), and those in nongenotype-1 patients (n = 565) were 52.2% (163/312), 63.1% (77/122), 65.0% (52/80), and 70.6% (36/51). Overall response rates of interferon and pegylated interferon monotherapy seem to be high because of the high response rates in the nongenotype-1 patients treated with these regimens.

Overall Cumulative Incidence of HCC. During follow-up, HCC developed in 177 interferon-treated patients (Fig. 1). The cumulative incidence of HCC 5, 10, and 15 years after interferon therapy was 4.7%, 11.6%, and 15.5%, respectively. The cumulative incidence in SVR patients was 2.1%, 4.3%, and 4.3%, respectively, which was significantly lower than that in non-SVR patients (5.8%, 14.9%, and 20.2%, respectively; log-rank test, $P < 0.001$).

Effect of Aging on Risk for HCC. The risk ratio determined by multivariate Cox proportional hazards analysis after adjustment for stage of liver fibrosis, degree of liver steatosis, and virological response to interferon demonstrated that the risk for HCC after interferon treatment was age-dependent and increased predominantly when the age at primary liver biopsy was >65 years (Fig. 2A). Hence, we defined older patients as those ≥65 years of age at primary liver biopsy and younger patients as those aged <65 years. As shown in Fig. 2B, the cumulative incidence of HCC was significantly higher in older patients than in younger patients (log-rank test, $P < 0.001$).

Table 1. Characteristics of Patients Enrolled in the Present Study

Characteristics	Total	<65 year	≥65 year	P Value*
Patients, n	2166	1614	552	
Sex, n (%)				<0.001†
Male	1080 (49.9)	840 (52.0)	240 (43.6)	
Female	1086 (50.1)	774 (48.0)	312 (56.4)	
Age (SD), year	55.4 (12.1)	51.1 (10.8)	68.4 (2.9)	<0.001‡
BMI (SD), kg/m^2	23.3 (3.1)	23.4 (3.0)	23.3 (3.1)	0.9‡
Fibrosis stage, n (%)				<0.001†
F0	27 (1.3)	24 (1.5)	3 (0.5)	
F1	860 (39.7)	704 (43.6)	156 (28.2)	
F2	733 (33.8)	515 (31.9)	218 (39.5)	
F3	444 (20.5)	301 (18.6)	143 (25.9)	
F4	102 (4.7)	70 (4.3)	32 (5.8)	
%Severe steatosis (≥10%)	27.6	27.1	29.3	0.4†
ALT level (SD), IU/L	95 (18)	101 (119)	76 (58)	<0.001‡
HCV load (SD), KIU/mL	880 (1046)	861 (1016)	924 (1116)	0.2‡
HCV genotype, n (%)				<0.001†
1a	7 (0.3)	5 (0.3)	2 (0.4)	
1b	1414 (69.6)	1036 (68.9)	378 (71.3)	
2a	373 (18.3)	273 (18.2)	100 (18.9)	
2b	211 (10.4)	164 (10.9)	47 (8.9)	
Others	28 (1.4)	25 (1.7)	3 (0.6)	
Duration (SD), year	7.5 (4.4)	8.1 (4.4)	5.8 (3.7)	<0.001‡
IFN regimen, n (%)				<0.001†
IFN mono	1062 (49.0)	833 (51.6)	229 (41.5)	
PEG-IFN mono	306 (14.1)	200 (12.4)	106 (19.2)	
IFN + RBV	386 (17.8)	291 (18.0)	95 (17.2)	
PEG-IFN + RBV	412 (19.0)	290 (18.0)	122 (22.1)	
SVR, n (%)	686 (33.6)§	565 (36.6)‖	121 (24.3)¶	<0.001‡

Unless otherwise indicated, data are given as the mean (SD).

ALT, alanine aminotransferase; BMI, body mass index; HCV, hepatitis C virus; IFN, interferon; N/A, not applicable; PEG, pegylated; RBV, ribavirin; SVR, sustained virological response.

*Comparison between <65 years and ≥65 years.

†Chi-squared test.

‡Student *t* test.

§Virological responses were determined in 2042 patients.

‖Virological responses were determined in 1545 patients.

¶Virological responses were determined in 497 patients.

As shown in Fig. 2C-E, even when stratified by stage of fibrosis the cumulative incidences among patients at stages F0/F1, F2, and F3 were significantly greater in older patients than in younger patients (log-rank test, $P < 0.001$). These differences were not significant among patients with cirrhosis (Fig. 2F, log-rank test, $P = 0.7$).

The annual incidence of HCC after interferon treatment was calculated by the person-years method (Table 2); it increased with the degree of liver fibrosis from 0.2% (F0 or F1) to 4.6% (F4) and was higher among older patients at the same stage of liver fibrosis.

Among the 177 patients with HCC, 92 showed evidence of a single blood transfusion. We analyzed the relationship between duration of infection and age in these 92 patients. A significant and strong negative correlation was found between the interval from blood transfusion to development of HCC and the age of the patients at the time of blood transfusion ($r = -0.74$, $P < 0.001$) (Fig. 3A). The mean duration of chronic infection was 22.0 years in patients who had received blood transfusion at >40 years of age, which was significantly shorter than that in patients who received it at ≤40 years of age (40.6 years, $P < 0.001$).

The presence of cirrhosis at the time of development of HCC, which was defined as having any of the following criteria, was evaluated: (1) histological evidence for cirrhosis, (2) findings of cirrhosis in any radiological study, or (3) presence of marked portal hypertension (i.e., presence of esophagogastric varices). Following this, 142 of the 177 with HCC (80.2%) were diagnosed as having cirrhosis, of which 42 were diagnosed histologically, 69 radiologically, and 31 based on the presence of marked portal hypertension. No significant difference was found in the proportion of patients with cirrhosis between older and younger patients, at the rate of 78.3% (94/120) in older

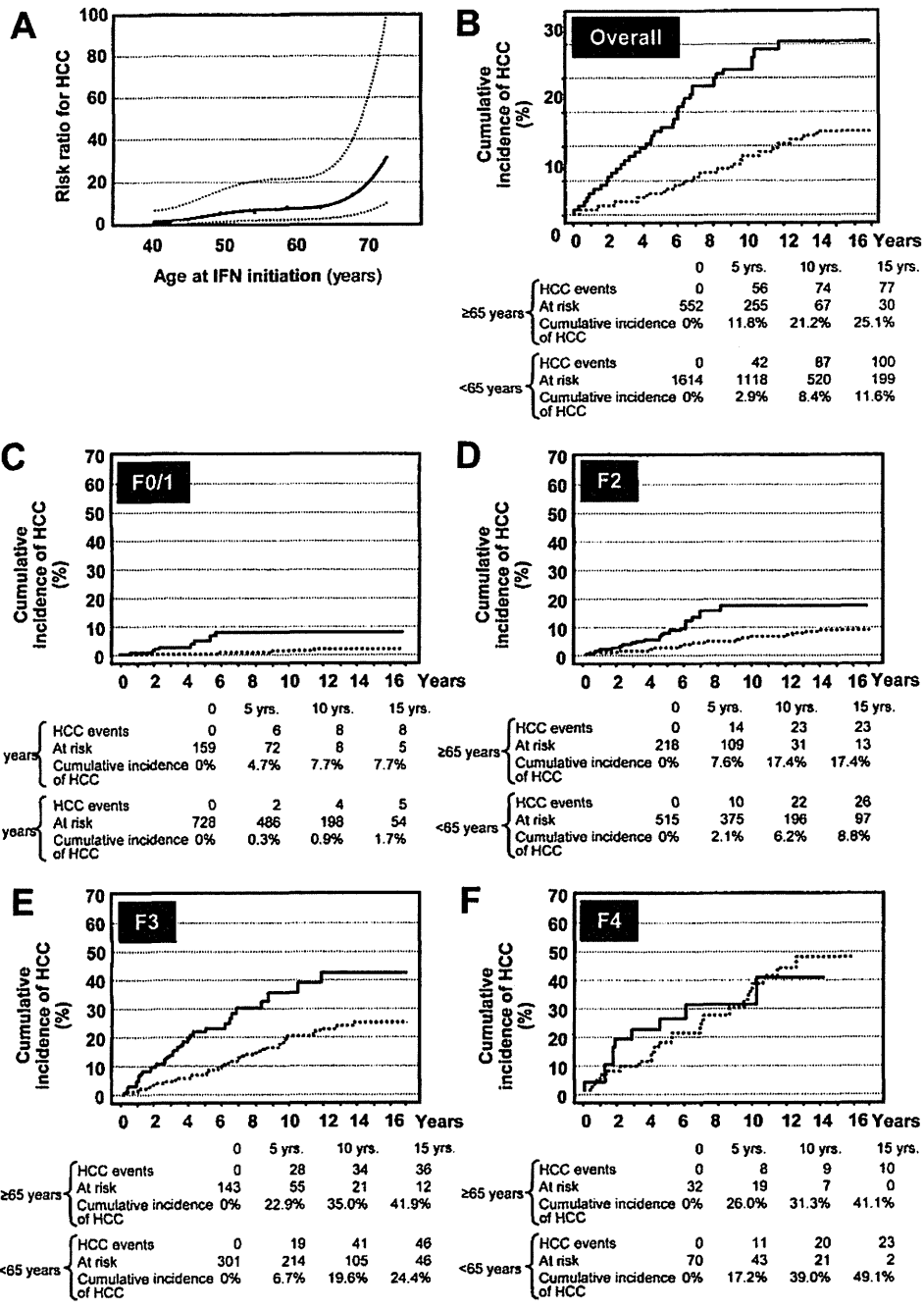


Fig. 2. Effect of aging on the risk for HCC. (A) Risk ratio (solid line) and 95% CI (dotted lines) for the risk of HCC according to age. To show the age-dependent relationship, a multivariate Cox proportional hazard model was used after adjustment for gender, stage of liver fibrosis, body mass index, and virological response to interferon therapy. Curves were fitted using polynomial regression. (B-F) Cumulative incidence of HCC after interferon therapy among younger (<65 years, n = 552, dotted line) and older patients (≥65 years, n = 1614, solid line). (B) Overall data, $P < 0.001$. (C) Patients with stage F0 or F1 liver fibrosis (no or mild fibrosis with portal expansion), $P < 0.001$. (D) Patients with stage F2 liver fibrosis (bridging fibrosis without architectural distortion), $P < 0.001$. (E) Patients with stage F3 liver fibrosis (bridging fibrosis with architectural distortion), $P < 0.001$. (F) Patients with stage F4 liver fibrosis (cirrhosis), $P = 0.7$. All P values were obtained by the log-rank test. The numbers of HCC events and patients at risk at each timepoint are shown below the graphs.

patients and 84.2% (48/57) in younger patients ($P = 0.36$, comparison at the age of HCC development).

Influence of Aging on Progression in Fibrosis Staging Over Time. In 271 patients who underwent paired biopsies, fibrosis staging progressed in 69 patients (25.5%), remained unchanged in 154 (56.8%), and regressed in 48 patients (17.7%). The overall rate of progression of fibrosis in these patients was 0.06 ± 0.02 fibrosis stages per year. Progression of fibrosis over time was significantly accelerated in older patients than in younger patients (0.21 ± 0.10 versus 0.03 ± 0.21 fibrosis stages per year, $P = 0.03$, Mann-Whitney U test) (Fig. 3B).

Effect of Viral Eradication on Risk for HCC in Older Patients. As shown in Fig. 4, the effect of viral eradication on the prevention of HCC was less significant in older patients than in younger patients. The annual incidence was higher among older patients than among younger patients with the same virological response (Table 2).

Influence of Liver Steatosis on Risk for HCC. The cumulative incidence of HCC after interferon therapy was significantly higher in patients with severe steatosis (≥10%) than in those with milder steatosis (at 5, 10, and 15 years: 8.6%, 19.1%, 32.0% versus 1.8%, 4.8%, 7.0%, respectively, log-rank test, $P < 0.001$).

Table 2. Annual Incidence of HCC After IFN Treatment

Factors	Total	<65 Years	≥65 Years
Fibrosis stage			
F0/F1	0.2%	0.1%	0.9%
F2	0.8%	0.6%	1.7%
F3	2.5%	1.8%	4.6%
F4	4.6%	4.4%	5.1%
Total	1.1%	0.8%	2.4%
Degree of liver steatosis			
<10%	0.5%	0.2%	1.4%
≥10%	2.0%	1.8%	3.0%
Virological response			
SVR	0.4%	0.2%	1.3%
Non-SVR	1.4%	1.0%	2.9%

Data were calculated by the person-years method. IFN, interferon; SVR, sustained virological response.

The annual incidence was higher in older patients than in younger patients with the same degree of liver steatosis (Table 2). In patients with severe steatosis (≥10%), superimposed NASH was diagnosed in 6.0% (26/435). Overall, superimposed NASH was significantly associated with hepatocarcinogenesis on univariate analysis (risk ratio, 4.1; 95% confidence interval [CI], 1.8-9.4; $P < 0.001$), but not on multivariate analysis. Superimposed NASH was significantly associated with high body mass index (27.2 ± 4.6 kg/m^2 versus 23.0 ± 3.1 kg/m^2, $P < 0.001$), hyperglycemia (186 ± 67 mg/dL versus 115 ± 39 mg/dL, $P < 0.001$), and advanced fibrosis (F3) (risk ratio, 2.9; 95% CI, 1.4-6.0; $P = 0.005$).

Factors Associated with Hepatocarcinogenesis After Interferon Therapy. Univariate analysis demonstrated factors that increase the risk ratio for the development of HCC (Table 3). Multivariate analysis using Cox proportional hazards regression confirmed that aging was one of the most significant independent factors associated with the development of HCC after interferon therapy. In this analysis, advanced fibrosis, presence of steatosis, male gender, lower total cholesterol level, higher fasting blood sugar level, higher baseline AFP level, insignificant improvement of mean AFP level after interferon therapy, and nonresponse to interferon therapy were also significantly associated with risk for HCC (Table 3).

We identified 22 patients in whom HCC developed even after achieving SVR. Univariate and multivariate logistic regression analyses indicated that both liver steatosis and aging were independently associated with the development of HCC among patients who achieved SVR (n = 686) (Table 4). Anti-HBc was detected in only 4 out of 22 patients and the age distribution was similar among anti-HBc-positive and anti-HBc-negative patients.

Response to Interferon Therapy in Older Patients. Multivariate logistic regression analysis confirmed that aging, female gender, severe liver fibrosis, extremely severe liver steatosis, genotype-1, high HCV load, and nonuse of pegylated interferon and ribavirin were independent risk factors for non-SVR (Supporting Table 1). The odds ratio, determined by multivariate logistic regression analysis after adjustment for these factors, demonstrated that the risk for non-SVR was age-dependent (Supporting Fig. 1). It was also ≈2.5 times higher in patients aged ≥65 years than in those aged <35 years.

In patients with genotype-1b and a high viral load who were treated with pegylated interferon and ribavirin combination therapy, the SVR rate was significantly lower in older patients than in younger patients (<49 years, 59.3%; 50-59 years, 50.5%; 60-65 years, 27.3%; ≥65 years, 25.2%; intention-to-treat analysis). Multivariate logistic regression analysis showed that

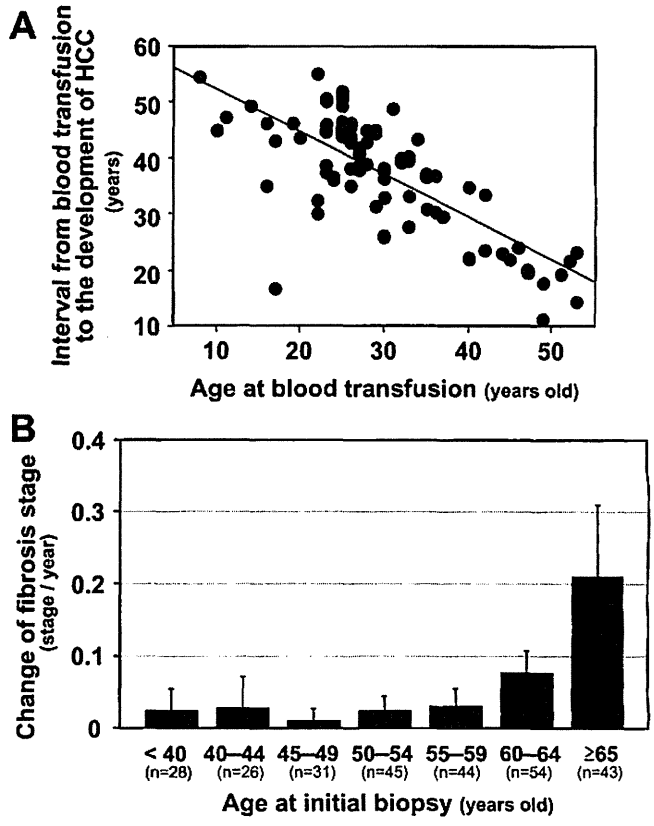
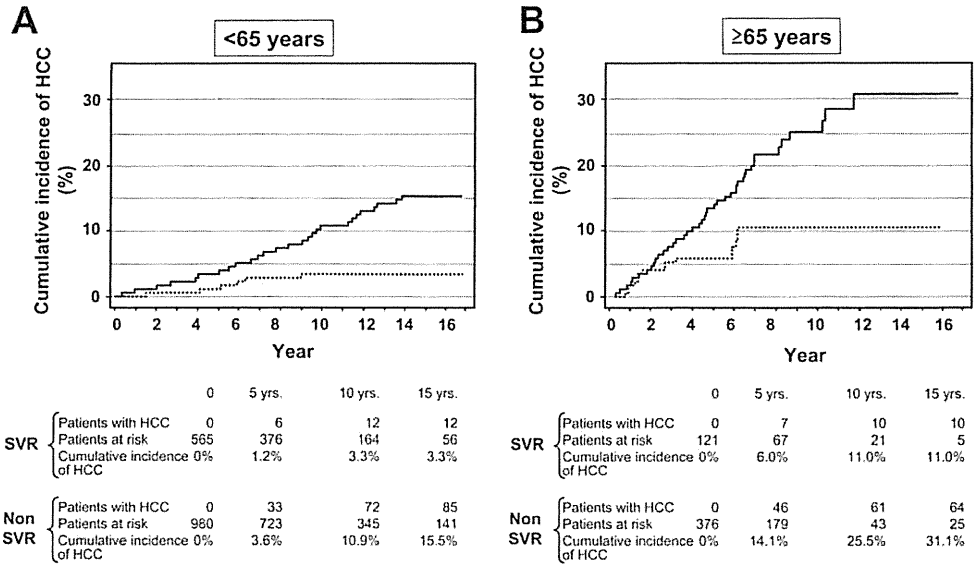


Fig. 3. (A) Relationship between the interval from blood transfusion to development of HCC and the age at blood transfusion (n = 92). A significant and strong negative correlation was observed ($r = -0.74$, $P < 0.001$). (B) Change in fibrosis staging over time. A total of 271 patients who had not achieved SVR by interferon therapy underwent a sequential biopsy after the initial biopsy. The yearly rate of progression of fibrosis was calculated as the change in fibrosis stage divided by the time between the paired biopsies. The yearly rate of progression of fibrosis was significantly higher in older patients (≥65 years) than in younger patients (<65 years) ($P = 0.03$, Mann-Whitney U test).



		0	5 yrs.	10 yrs.	15 yrs.
SVR	Patients with HCC	0	6	12	12
	Patients at risk	565	376	164	56
	Cumulative incidence of HCC	0%	1.2%	3.3%	3.3%
Non SVR	Patients with HCC	0	33	72	85
	Patients at risk	980	723	345	141
	Cumulative incidence of HCC	0%	3.6%	10.9%	15.5%

		0	5 yrs.	10 yrs.	15 yrs.
SVR	Patients with HCC	0	7	10	10
	Patients at risk	121	67	21	5
	Cumulative incidence of HCC	0%	6.0%	11.0%	11.0%
Non SVR	Patients with HCC	0	46	61	64
	Patients at risk	376	179	43	25
	Cumulative incidence of HCC	0%	14.1%	25.5%	31.1%

Fig. 4. Cumulative incidence of HCC after interferon therapy among SVRs (dotted lines) and non-SVRs (solid lines) according to age. (A) Younger patients (<65 years). The cumulative incidence of HCC was significantly higher in SVR than in non-SVR (log-rank test, $P < 0.001$). (B) Older patients (≥65 years). The cumulative incidence of HCC was significantly higher in SVR than in non-SVR (log-rank test, $P = 0.02$). However, the difference between SVR and non-SVR was less in older patients than in younger patients. The number of HCC events and patients at risk at each timepoint are shown below the graphs.

aging was the strongest independent factor contributing to SVR in these patients (data not shown). The odds ratio for the risk of non-SVR was 1.8 for each additional 10 years of age (95% CI, 1.5-2.3, $P < 0.001$).

Discussion

In this large cohort study we demonstrated that aging is significantly associated with the development of HCC in patients treated with interferon. The risk ratio increased predominantly in patients older than 65 years, which was more than 15 times that in patients in their 20s. Aging is becoming the most critical risk factor for the development of HCC. Although liver fibrosis was also an important risk factor, we clearly demonstrated that the risk for hepatocarcinogenesis after interferon treatment was significantly higher in older patients at each stage of liver fibrosis except for cirrhosis. Hence, physicians should be aware that older patients can develop HCC regardless of the stage of fibrosis.

Because the present study included a large cohort, it was difficult to determine the duration of infection in all patients, and this might have affected the risk determination for HCC development. Therefore, we analyzed the relationship between duration of chronic infection and HCC development in patients who underwent a single blood transfusion. We found a significant and strong negative correlation between the interval from blood transfusion to development of HCC and the age of the patients at the time of blood transfusion. Consistent with our results, a previous report with posttransfusion HCV demonstrated that the age of patients, rather than the duration of HCV infection, was more significant for HCC development.[14-16] Therefore, older age and not duration of infection is more likely to influence hepatocarcinogenesis. Moreover, our analysis of sequential biopsy specimens demonstrated that the progression rate of liver fibrosis significantly accelerated in patients aged >65 years. Hence, the progression of fibrosis along with aging may also contribute to the increased risk for hepatocarcinogenesis in older patients.

We further demonstrated that liver steatosis was an independent risk factor for the development of HCC, which was not mentioned in previous reports.[8-11] The presence of steatosis is related to both viral (genotype-3 or HCV core protein) and host metabolic factors.[17,18] In our cohort, most superimposed NASH was associated with host metabolic factors such as high body mass index and hyperglycemia, whereas infection of genotype-3 was only noted in two patients. In vitro experiments have suggested an association between liver steatosis induced by HCV core protein and hepatocarcinogenesis,[19] and have proposed virus-associated steatohepatitis as a new aspect of chronic hepatitis C.[20,21] Because steatosis was likely to be related to hepatocarcinogenesis, patients with chronic hepatitis C, whose liver histology shows superimposed NASH,