RNA in B cells achieved either RVR or SVR; 12 of these 14 patients (86%) had a NVR. These results suggest that the absence of HCV RNA in B cells is a useful predictor of the response to IFN-based therapy. The ability to predict the response is defined based on sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) (Table 4). In genotype 1-infected patients, sensitivity, specificity, PPV and NPV for NVR according to genetic variation near IL28B were 100%, 87.7%, 65.0% and 100%, respectively. When both IL28B SNP variants and the presence of HCV RNA in B cells were combined, specificity and PPV were higher (specificity 98.2% and PPV 92.3%). In HCV genotype 2-infected patients possessing a major allele of the IL28B SNP, two of four patients (50%) with HCV RNA-positive B cells failed to achieve SVR. In contrast, all 15 patients with HCV RNA-negative B cells achieved SVR. Even in patients with minor alleles of the IL28B SNPs, both of two patients with HCV RNA-negative B cells achieved SVR. In genotype 2-infected patients, sensitivity, specificity, PPV and NPV for SVR according to the presence of HCV RNA in B cells were 90.0%, 100%, 100% and 60.0%, respectively.

These combined results indicate that the minor alleles of IL28B SNPs plus the presence of HCV RNA in B cells are useful predictors for NVR in genotype 1-infected patients, and the presence of HCV RNA in B cells is a predictor for non-SVR in genotype 2-infected patients.

Lymphotropic HCV has an IFN-resistant phenotype

We further characterized the viral phenotype of IFN resistance for B cell-tropic HCV and the effects of IL28B genotype on HCV RNA titre in B cells. Figure 2a shows that HCV RNA titres in B cells were significantly higher in genotype 1-infected s than in genotype 2-infected patients. The positive rates of HCV RNA in B cells were 68.8% (53/77) and 24.0% (6/25), respectively ($P = 0.0001$). These results suggest that genotype 1 HCV can infect and/or associate with B cells more efficiently than genotype 2. However, HCV RNA titres in B cells did not differ between patients bearing the major allele (T/T) of the IL28B SNP and those with the minor alleles (G/G or T/G) (data not shown), indicating that the IL28B genotype does not affect HCV infection of (or

Table 4 Predictive factors for outcomes of the IFN-based therapy in patients infected with HCV genotypes 1 and 2

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Genotype 1: Predictive factor for NVR				
IL28B T/G,G/G	100	87.7	65.0	100
IL28B T/G, G/G and HCV RNA in B cells (+)	92.3	98.2	92.3	98.2
Genotype 2: Predictive factor for SVR				
IL28B T/T	85.7	33.3	90.0	25.0
HCV RNA in B cells (−)	90.0	100	100	60.0

HCV, hepatitis C virus; NVR, null viral responder; PPV, positive predictive value; SVR, sustained viral responder.

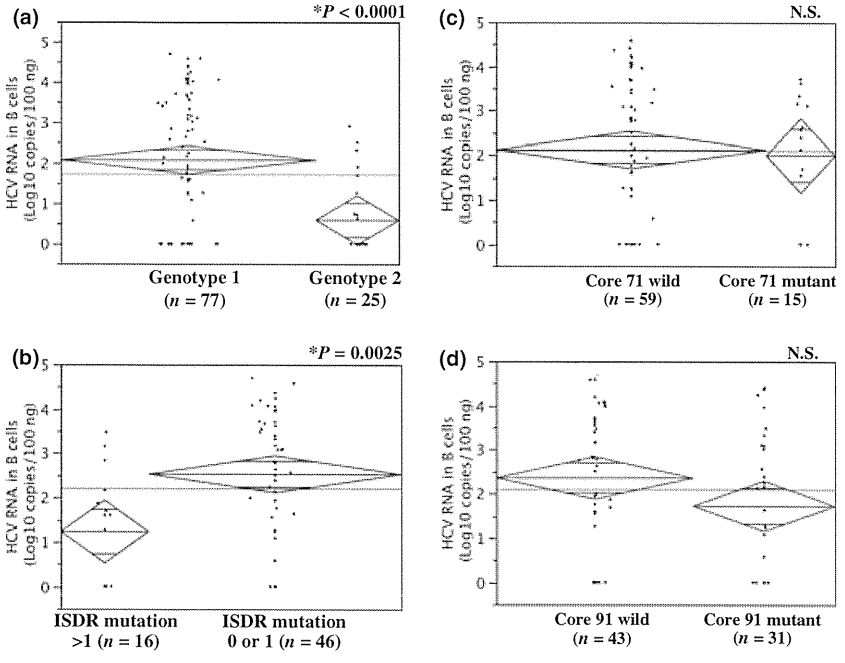

Fig. 2 Comparison of hepatitis C virus (HCV) RNA titres in B cells of (a) patients infected with HCV genotypes 1 and 2; (b) patients infected with HCV with 0-1 interferon sensitivity determining region amino acid mutations *vs* those with >1 mutations; (c) patients infected with HCV with codon 70 amino acid mutation of the core region *vs* those with wild type; and (d) patients infected with HCV with codon 91 amino acid mutation of the core region *vs* those with wild type. A horizontal grey line shows mean of all samples. Two grey diamonds indicate the averages and 95% confidence interval of each group. Statistical significance was determined by Student's *t* test. N.S.: not significant.

association with) B cells. We next analysed the effects of viral sequence and quasispecies diversity, which are known to affect the outcome of the IFN-based therapy, on HCV RNA titres in B cells. The number of nucleotide mutations in the ISDR of the NS5A region and missense mutations at codons 70 and 91 of the core region were determined in samples from patients infected with HCV genotype 1. Figure 2b shows that the HCV RNA levels in B cells were higher in patients infected with HCV with 0 or 1 mutation in the ISDR (ISDR 0-1) than in those harbouring HCV with more than one ISDR mutations (ISDR > 1). Additionally, the fraction of patients with HCV RNA in B cells was higher among those infected with ISDR 0-1 HCV [ISDR 0-1: 38/46 (82.6%) *vs* >1: 9/16 (56.3%), $P = 0.0463$]. However, substitutions at core positions 70 or 91 did not associate with HCV RNA titre in B cells (Fig. 2c,d). These results suggest that the number of mutations in ISDR, but not core mutations, affect the persistence of HCV in B cells.

DISCUSSION

While the human hepatocyte is the primary target for HCV infection, HCV also has lymphotropism, especially toward B cells [7,23]. Previous reports demonstrated the *in vitro* and *in vivo* association of HCV with B cells [7,24,25]. In our earlier report, we detected the replication of HCV in B cells in about 5% of HCV-infected patients and the presence of HCV RNA in about 64% of these patients [7]. Stamataki *et al.* [25] also demonstrated that HCV JFH1 bound (but did not replicate in) B cells in the cell culture system and that the virion binding B cells became more stable than free virions. These results suggest that the HCV isolates can be classified into three subgroups. The first subgroup consists of HCV isolates that neither infect nor adhere to B cells. A second subgroup (which encompasses most HCV isolates) can associate with B-cell surface receptors, but do not replicate efficiently in these cells. Such binding may induce activation and signalling, contributing to prolonged B-cell survival. The third subgroup (detected in only 5% of patients) consists of HCV isolates capable of infecting B cells and replicating efficiently in these cells.

The present study showed that HCV isolates that have infected and/or associated with B cells had an IFN-resistant phenotype. HCV RNA titres in B cells were significantly higher in patients with poor responses to IFN-based therapy (Fig. 1). Furthermore, the presence of HCV RNA in B cells was one of the factors determining the outcome of IFN-based therapy (Table 2). The precise mechanism of these clinical effects remains unknown; B-cell-associated viruses may be more stable than free virions [25]. Although current antiviral therapies can eliminate free HCV virions from sera, HCV is thought to survive in lymphocytes [19,20]. Peripheral blood memory B cells infected with HCV may be recruited to the liver of patients with CH-C [26]. Lymphotropic HCV may survive even after the IFN-based therapy and re-infect hepatocytes through the infiltration of HCV-infected B cells to the liver.

Another important issue is that HCV infection of and/or association with B cells may also contribute to IFN resistance by inducing dysfunction in B cells. The patients with HCV-positive B cells had at least one abnormality of LPD markers, indicating that HCV infection of and/or association with B cells reflected the presence of B cell-disorders [7]. In fact, HCV has been reported to bind naïve B cells through CD81, leading to the abnormal activation of B cells in the absence of ligation with the B cell receptor [24].

Many predictive markers (both viral and host factors) are associated with IFN-based treatment outcomes. Prediction of NVR and/or non-SVR status might allow hepatologists to pay closer attentions to poorly responding patients while minimizing unnecessary therapy. Recently, the genotypes of IL28B SNPs have been reported to be a valuable predictor for the outcome of IFN-based therapy [17,27,28]. In the present study, multivariable analyses showed that the genotypes of IL28B SNPs and the presence of HCV RNA in B cells were independent predictive markers for NVR in genotype 1-infected patients (Table 2c). (No genotype 2-infected NVR patients were detected in this study.) The combination of IL28B minor alleles and the presence of HCV RNA in B cells are especially valuable for predicting the NVR *vs* VR (viral responder) distinction in patients infected with HCV genotype 1 and for predicting the SVR *vs* non-SVR distinction in patients infected with HCV genotype 2. In patients infected with HCV genotype 1, the PPV for NVR in individuals with the IL28B minor allele was significantly elevated from 65.3% to 92.3% by the addition of HCV RNA in B cells as a predictive marker (Table 4). Similarly, increases in sensitivity, specificity, PPV and NPV for SVR were all higher in HCV genotype 2-infected patients when the presence of HCV RNA in B cells was used as a marker. The detection of HCV RNA in B cells may serve as a useful parameter for predicting the outcome of IFN-based therapy in patients infected with HCV genotype 2 although further studies with an increased population size are warranted.

Multiple host and viral factors are proposed as predictors of outcomes for IFN-based therapy. Host genotype (IL28B SNP alleles) and mutations in the virus (including the ISDR and the HCV core region) have been reported as significant pretreatment predictors of response to PEG-IFN and ribavirin combination therapy [29,30]. The present study shows that patients with B-cell-associated HCV RNA typically are infected with genotype 1, and their HCV has fewer mutations in the ISDR. Lerat *et al.* [8] have shown that PBMCs from patients infected with genotype 1 exhibit a higher detection rate of positive- and negative-strand HCV RNA, and their results are consistent with our observations: HCV ISDR mutations, but not substitutions of the core region, affect HCV RNA titres in B cells. HCV ISDR mutations may affect HCV infection of B cells through the effects on IFN signalling [31]. Neither viral titres nor the detection of HCV

RNA in B cells was associated with the genotypes of IL28B SNPs, which are thought to be the strongest genetic factor predicting the outcome of IFN-based therapy. Detail mechanisms underlying the association of the genotype of IL28B SNPs with the outcome of the IFN-based therapy, remain unknown. Expression levels of interferon λ mRNA and/or *in situ* cytokine levels in liver may differ between patients with the major or minor alleles of IL28B SNPs. It is possible that the circumstance of the innate immunity against HCV in liver is different from that in B cells. It is speculated that the presence of HCV RNA in B cells is linked to the interferon-resistance phenotype of the virus itself and/or the host immune-disorders triggered by the abnormal activation of B cells in patients. In conclusion, HCV that infects or associates with B cells appears to present an IFN-resistant phenotype, and the presence of HCV RNA in B cells is a useful predictive marker for resistance to IFN-based therapy.

ACKNOWLEDGEMENTS

The authors thank to Hidekazu Tsukamoto for critical reading of the manuscript. This work was supported by the Research Grant-in-Aid from Miyakawa Memorial Research Foundation to M.I., Research Grant-in-Aid from Viral Hepatitis Research Foundation of Japan to M.I., KAKENHI [22590745] to T.I., and Grants-in-Aid for Research on Publicly Essential Drugs and Medical Devices [KHC1012] to T.I.

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Hepatology Research

Hepatology Research 2012 doi: 10.1111/j.1872-034X.2011.00936.x

Original Article

Cost-effectiveness analysis on the surveillance for hepatocellular carcinoma in liver cirrhosis patients using contrast-enhanced ultrasonography

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Aim: Sonazoid is a new contrast agent for ultrasonography (US). Contrast-enhanced ultrasonography (CEUS) using Sonazoid enables Kupffer imaging, which improves the sensitivity of hepatocellular carcinoma (HCC) detection. However, there are no studies on the cost-effectiveness of HCC surveillance using Sonazoid.

Methods: We constructed a Markov model simulating the natural history of HCV-related liver cirrhosis (LC) patients, and compared three strategies (no surveillance, US surveillance and CEUS surveillance). The transition probability and cost data were obtained from published data. The simulation and analysis were performed using TreeAge pro 2009 software.

Results: When compared to the no surveillance group, the US and CEUS surveillance groups increased the life expectancy by 1.67 and 1.99 quality-adjusted life-years (QALY), respectively, and the incremental cost effectiveness ratio (ICER) were 17 296 $US/QALY and 18 384 $US/QALY, respectively. These results were both less than the commonly-accepted threshold of $US 50 000/QALY. Even if the CEUS surveillance group was compared with the US surveillance group, the ICER was $US 24 250 and thus cost-effective. Sensitivity analysis showed that the annual incidence of HCC and CEUS sensitivity were two critical parameters. However, when the annual incidence of HCC is more than 2% and/or the CEUS sensitivity is more than 80%, the ICER was also cost-effective.

Conclusions: Contrast-enhanced ultrasonography surveillance for HCC is a cost-effective strategy for LC patients and gains their longest additional life years, with similar degree of ICER in the US surveillance group. CEUS surveillance using Sonazoid is expected to be used not only in Japan, but also world-wide.

Key words: contrast-enhanced ultrasonography, cost-effective analysis, hepatocellular carcinoma, Sonazoid, surveillance

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is the fifth most common neoplasm in the world.[1] Although many environmental factors, including aflatoxins and alcohol,[2,3] have been implicated in the development of HCC, hepatitis B virus and hepatitis C virus (HCV) are the most important factors associated with the progression from chronic hepatitis to cirrhosis, and eventually to HCC.[4] Surveillance for HCC is recommended in patients with chronic liver injury to detect small-sized HCCs, which can be efficiently treated.[5] Ultrasonography (US) is a major surveillance method, because it provides low cost, real-time and non-invasive detection. However, there are some problems associated with this surveillance approach. It is known that the annual incidence of HCC increases with the degree of fibrosis.[6] Unfortunately, an increase in fibrosis makes US surveillance substantially more difficult, because the

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Received 10 July 2011; revision 28 September 2011; accepted 24 October 2011.

intrahepatic echo patterns in US become rough with advanced fibrosis.

Recently, a novel intravenous contrast medium for US, "Sonazoid", has become available in Japan. This strategy of using US with Sonazoid dramatically improves the sensitivity in the diagnosis of hepatic malignancy.[7] Thus, contrast-enhanced ultrasonography (CEUS) using Sonazoid can effectively detect HCCs that are usually overlooked by B-mode, which is currently used for observation. Therefore, this new contrast medium would be desirable for use in HCC surveillance. However, it is almost five times more expensive than the conventional observational approach in Japan. Until now, the surveillance for HCC using this novel agent has not been evaluated with regard to its cost-effectiveness, and this is the focus of the current study.

METHODS

WE USED TREE Age Pro 2009 (Tree Age Software Inc., William-stown, MA, USA) software to construct a Markov model, and estimated the cost-effectiveness of a surveillance program for HCC. The transition probabilities used in the analysis are listed in Table 1. The age specific mortality rate was obtained

Table 1 Values used in the analyses

Variable	Base value	Range	References
Excess annual mortality			
Child A Cirrhosis	0.02	0.00–0.08	8–11
Child B/C Cirrhosis	0.13	0.07–0.40	
Large HCC	0.90	0.50–1.00	12–14
Annual transition rate			
Child A to Child B/C	0.04	0.02–0.08	8,10,15,16
Small HCC to Large HCC (Undetected)*	0.30	0.10–0.60	17–19
Small HCC to large HCC (TAE treated)*	0.10	0.02–0.20	20–22
Annual incidence of HCC			
Incidence of new HCC	0.07	0.01–0.08	6,8,23–27
Incidence of HCC after curative treatment	0.20	0.10–0.37	13,25,28
Probability of small HCC at diagnosis	0.90	0.66–1.00	23,29
Test characteristics			
US			
Sensitivity	0.70	0.40–0.80	30–32
Specificity	0.90	0.70–0.90	
CEUS			
Sensitivity	0.90	0.80–0.95	7
Specificity	0.95	0.80–0.95	
Cost data			20,23,31,33–37
US	61		
CEUS	248		
Confirmation test	862	170–1 100	
LC	587	300–1 200	38
Decompensated LC	6 422	6 422–23 000	38
Terminal care	5 556	5 000–42 000	38
Resection	19 390	12 000–40 000	39
RFA	10 333	35 000–11 000	39
TAE	7 778	35 000–12 000	
Health-related QOL			40
Child A	0.75	0.66–0.83	
Child B/C	0.66	0.46–0.86	
HCC	0.64	0.44–0.86	

*Per 6 months. The costs were $US/6 months, and the baseline cost has been adjusted to US dollars (Currency rate: $1.00 = \90.00).
CEUS, contrast-enhanced ultrasonography; HCC, hepatocellular carcinoma; LC, liver cirrhosis; QOL, quality of life; RFA, radio-frequency ablation; TAE, transcatheter arterial embolization; US, ultrasonography.

from the homepage of the Japanese Ministry of Health, Labour, and Welfare.

Decision model

We estimated the long-term outcomes of different treatments by modifying a previously published computer simulation model[41] using current data on the natural history of chronic hepatitis C in Japan (Fig. 1). Each cycle consisted of 6 months. During each cycle, patients died according to the population-based mortality.

The decision tree for our analysis was composed of three arms: (i) the no surveillance group or "no surveillance" (ii) the B-mode US surveillance group or "US group", and (iii) the CEUS surveillance group or "CEUS group".

Assumptions 1 (program)

Based on the limited information available in the literature, the following assumptions were made:

1 the transition data from liver cirrhosis (LC) to decompensated LC are constant regardless of the patient's age and prior history of HCC;
2 the progression from compensated to decompensated cirrhosis is irreversible;
3 the incidence of HCC is the same in compensated versus decompensated cirrhosis.
4 the probabilities of HCC recurrence and growth remain constant over time;
5 surgery is not performed in patients with a background of decompensated cirrhosis or HCC recurrence; and
6 liver transplantation is not the first-choice for HCC therapy because it is still very rare in Japan.

Assumptions 2 (surveillance)

With regard to surveillance, the following assumptions were made:

1 HCC can be divided into two categories: "small" and "large". Small tumors (1–5 cm in diameter, and no

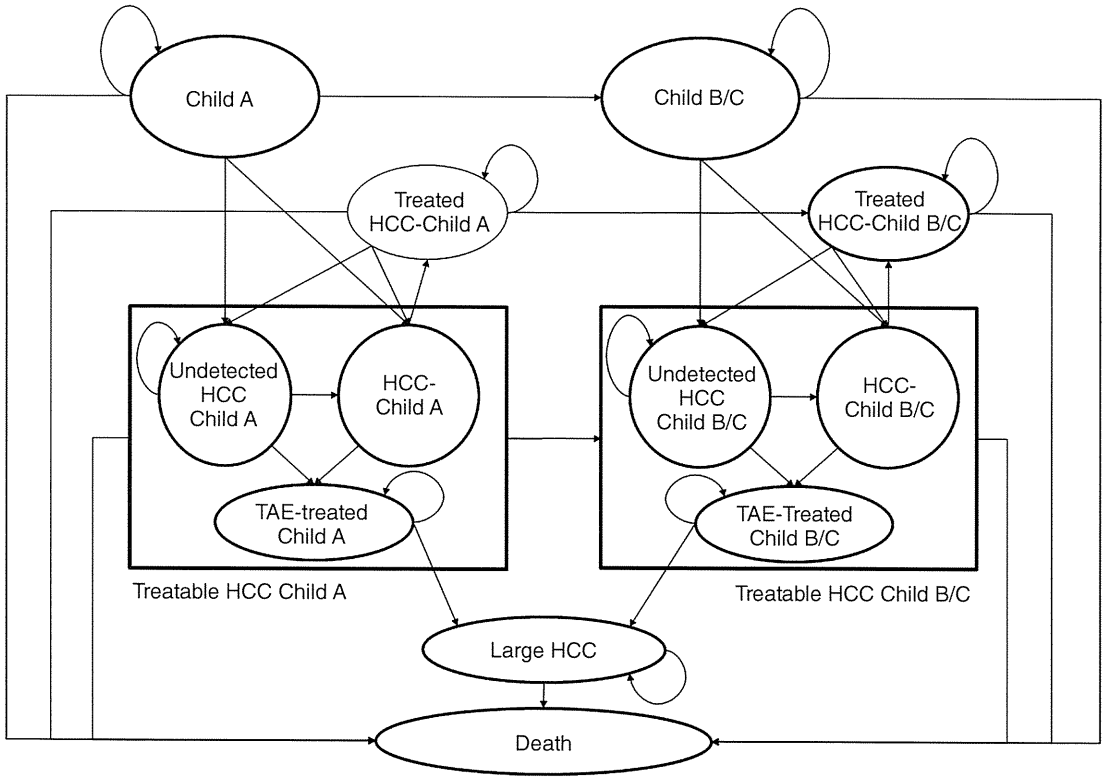

Figure 1 Natural history model. The arrows represent possible transitions during each 6 month cycle. Patients enter this model with Child A cirrhosis, and might develop Child B/C cirrhosis, hepatocellular carcinoma (HCC), both Child B/C and HCC, or death. If the health status does not change, then the patients remain in the same state of health. Surveillance and treatment strategies were superimposed on this model. TAE, transcatheter arterial embolization.

more than three in number) are asymptomatic, and remain undetected until the surveillance is performed. Large tumors are symptomatic, and the patient can receive palliative treatment only;
2 there are no small HCCs that can be detected incidentally in the no surveillance group;
3 patients with positive surveillance tests undergo a confirmatory test. [CT and either MRI (70%) or liver biopsy (30%)];
4 the test performance is independent of previous test results;
5 compliance with the program is 100%; and
6 there is a small rate of false-positive diagnoses, which will be discovered before any treatment.

The tumor growth rate was calculated with the assumption of a doubling time of 120 days.[17,18,42]

Since one year's worth is different in the health status, health-states utility should be taken into account for cost effectiveness analysis. Thus, we obtained the health-state utility information from meta-analysis.[40] The survival and costs were also discounted at the commonly accepted annual rate of 3%, because time and cost of distant future are generally thought to be of less value than those of present time.

Cost

The cost data shown in Table 1 are from data published in Japan, because Sonazoid is currently available only in Japan.

The data were converted to US currency at the exchange rate of US$1.00 = JP\90.00. The cost of transcatheter arterial embolization (TAE) was estimated by including health insurance reimbursement using the reimbursement data in our hospital, because there were no available national data.

Sensitivity analysis

The results obtained from this model depended on the values that were used in the study; therefore a one-way sensitivity analysis was performed on all variables.

RESULTS

Accuracy of our model

TO VALIDATE THE model's accuracy, we compared this model's survival rate with the cumulative survival rates of 417 compensated cirrhosis patients obtained from a large European cohort clinical study under surveillance.[43] When we set the annual incidence rate of HCC as 4% to fit the European model, these two survival curves were very similar, and the accuracy of our model was validated (Fig. 2).

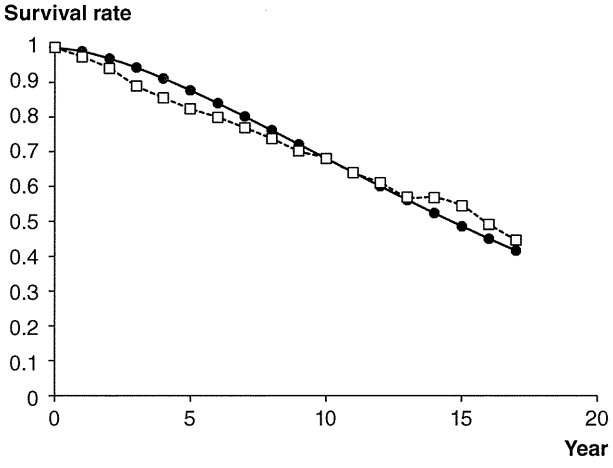

Figure 2 Comparison of the survival curves for compensated cirrhosis states between the one predicted by the current model and published data from a large cohort study.[43] Both data sources yielded similar curves. —●—, our model; -□-, Sangiovanni *et al.* 2004[43].

Baseline analysis

The expected life years of each group according to the starting age of the surveillance are shown in Figure 3.

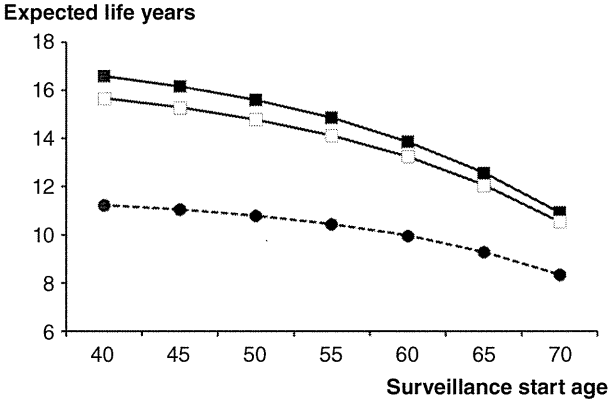

Figure 3 Expected life years according to surveillance at a starting age before it was discounted, and adjusted by health-state utilities. Although the expected life years decreased with age, both the ultrasonography (US) and contrast-enhanced ultrasonography (CEUS) surveillance groups increased the life expectancy even in 70-year-old patients. CEUS surveillance achieved the greatest gain in life expectancy in all analyzed age groups. —■—, CEUS Surveillance; —□—, US Surveillance; -●-, No Surveillance.

Table 2 Baseline analysis

Strategy	Total cost (US$)	Incremental cost (US$)	Expected life years (year)	QALY	Incremental QALY	IECR (US$/QALY)
No surveillance	29 142	–	10.45	6.18	–	–
US surveillance	58 064	28 922	14.13	7.85	1.67	17 296†
CEUS surveillance	65 726	36 584	14.86	8.17	1.99	18 384† (24 250‡)

†Compared with the no surveillance group.
‡Compared with the US surveillance group.
CEUS, contrast-enhanced ultrasonography; ICER, incremental cost effective rate; QALY, quality-adjusted life-year.

Both the US group and the CEUS group could extend their additional life years as compared with the no US group, regardless of age. The CEUS group could also extend their additional life years as compared with the US group. The biggest difference in expected life years between the US and CEUS groups was 0.93 at an age of 40 years. The superiority of surveillance with CEUS over US was also seen in the 70 year-old patients group. If the sensitivity of US was lower than 50%, then CEUS could extend their additional life years by 2 years and more as compared with the US group.

In the no surveillance group, 55 year-old patients (base value) with compensated HCV-related cirrhosis are expected to live 10.45 life years. When surveillance for HCC with conventional US or CEUS was used in these patients, their expected life years increased by 3.68 years and 4.41 years, respectively. Since the discount rate and health-related utility should be considered in cost-effective analysis, we showed the results of the baseline cost-effectiveness analysis in Table 2. Even though the additional expected life years became small when the program was analyzed while considering the discount rate and health-related utility, in comparison to having no surveillance, the US and CEUS groups still showed an increase in QALYs, 1.67 and 1.99 QALYs, respectively.

Next, the incremental cost-effectiveness ratio (ICER) was estimated, which is a measure of the extra cost incurred to save one year of life. The ICER of the US and CEUS groups, as compared to the no surveillance group, were $US 17 296/QALY and $US 18 384/QALY, respectively. These values were well below $US 50 000/QALY, which is commonly considered to be the cost-effective threshold. Even when the CEUS group was compared with the US group, the ICER of the CEUS group was $US 24 250/QALY, and was also cost-effective.

Sensitivity analysis

The above results depended largely on the baseline values used in this model, but the estimates of these parameters vary in the published literature. We therefore examined the effects of changing the value of each parameter through sensitivity analysis (Fig. 4). After performing the sensitivity analysis on all parameters in this model, three important parameters emerged in CEUS surveillance compared with US surveillance: the annual HCC incidence rates, and the CEUS sensitivity, and the US sensitivity.

Figure 5a shows the differences of ICERs in varying the US sensitivity. The ICERs of the US and CEUS groups were also less than US$ 20 000, and cost-effective when compared with the no surveillance group. On the other hand, when the CEUS group was compared with the US group, the ICER of the CEUS group increased as the US sensitivity increased up to almost the CEUS sensitivity. However, if the US sensitivity was 80%, then the ICER was $US 34 143, and still less than the threshold of $US 50 000/QALY. If the US sensitivity was lower than 60%, then the ICER of the CEUS group was almost $US 20 000, and thus was more cost-effective. On the other hand, CEUS sensitivity was especially affected when the CEUS group was compared with the US group, and the ICER rose sharply when the CEUS sensitivity was lower than 80% (Fig. 5b).

DISCUSSION

IN THE PRESENT study, we analyzed the cost-effectiveness of CEUS for HCC surveillance using Sonazoid in liver cirrhosis patients, and demonstrated that CEUS surveillance could cost effectively extend the expected life years, even compared with the US surveillance.

Currently, there are only two US contrast agents, Sonazoid and Levovist, which can be used for Kupffer imaging in the post-vascular phase. However, Levovist bubbles are very fragile, and are collapsed by US emissions easily. Therefore, Kupffer imaging in the post-vascular phase using Levovist needs to be performed by a single sweep scan of the liver, which is insufficient for surveillance.

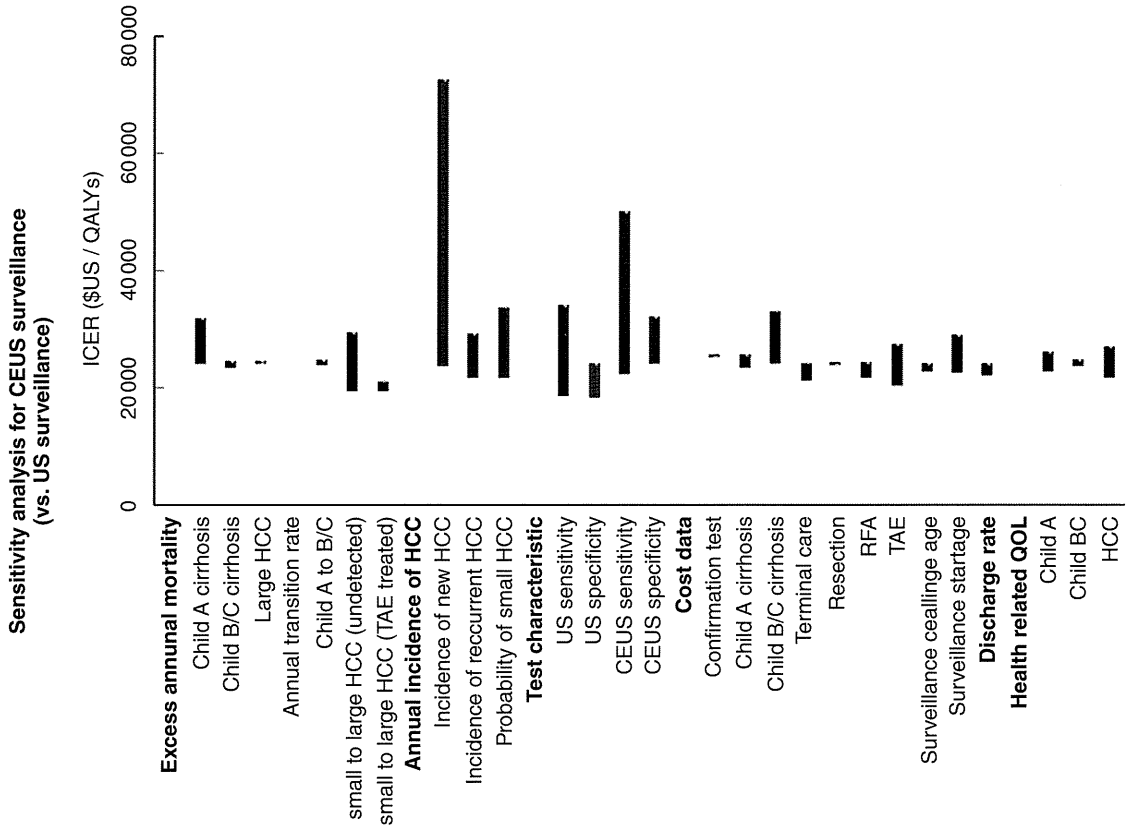

Figure 4 One way sensitivity analysis of the incremental cost-effectiveness ratio (ICER) for the contrast-enhanced ultrasonography (CEUS) surveillance group. When the ICER of the CEUS group was compared with the ultrasonography (US) group, the annual incidence rate of hepatocellular carcinoma (HCC) and CEUS sensitivity were critical parameters in this model. QALY, quality adjusted life year; RFA, radio-frequency ablation; TAE, transcatheter arterial embolization.

Sonazoid is composed of a hard shell containing bubbles, and produces stable, non-linear oscillations in the low-power acoustic field. Because of this feature, Sonazoid provides detailed perfusion features during vascular imaging in the vascular phase, and Kupffer imaging in the post-vascular phase at least 10 min after injection, without collapsing the bubbles. Specifically, Sonazoid CEUS is stable for at least 3 h after injection and allows for multiple and real time scans, because the Sonazoid microbubbles are phagocytosed by Kupffer cells.[44] In contrast, malignant hepatic tumors including HCC contain few or no Kupffer cells, which lead to clear negative contrast as a perfusion defect in Kupffer imaging.[45,46] Thus, surveillance for HCC using Sonazoid is especially useful for LC patients whose liver parenchyma have become roughened by fibrosis. For these reasons, the trend towards the use of US contrast agents in Japan has changed dramatically from Levovist to Sonazoid after it became commercially-available in 2007.

A recent study on the cost-effectiveness of surveillance for HCC reported the sensitivity of US at only 28.6% for detecting middle-sized HCC (between 2 and 5 cm in diameter).[47] The sensitivity of US depends on the skill of the operator, especially in LC patients, in which the intrahepatic echo patterns become roughened with advanced fibrosis. In sensitivity analysis, the US sensitivity was an important factor. When the US sensitivity is expected to be low due to patient physiologic factors such as obesity, CEUS surveillance is recommended. US technicians whose skill may not achieve the average level are also advised to perform additional CEUS using Sonazoid.

Contrast-enhanced ultrasonography sensitivity was a critical factor for cost-effectiveness. When the CEUS group was compared with the US group, and CEUS surveillance was not cost-effective if CEUS sensitivity was lower than 75% (Fig. 5b). As noted earlier, CEUS using Sonazoid is effective for Kupffer imaging, and it

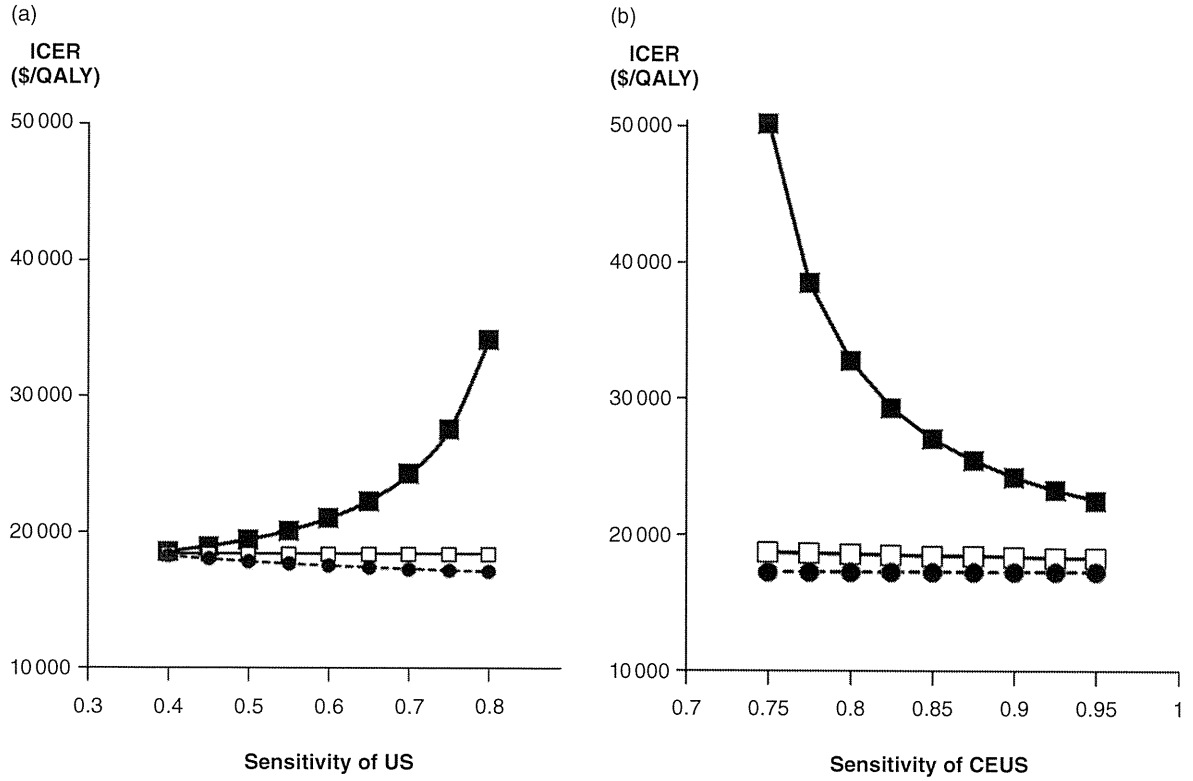

Figure 5 Effects of the sensitivity of ultrasonography (US) (A) and contrast-enhanced ultrasonography (CEUS) (B). When the incremental cost-effectiveness ratio (ICER) was compared with the no surveillance group, both US and CEUS surveillance groups were less than $US 20 000/quality adjusted life year (QALY) in all ranges. The ICER of the CEUS surveillance group achieved $US 50 000/QALY when the sensitivity of CEUS was lower than 0.75. –■–, CEUS (vs US surveillance); –□–, CEUS (vs no surveillance); -●-, US (vs no surveillance).

has been reported to have high sensitivity.[7] This helps technicians to detect the HCC more easily. Thus, a greater than 75% sensitivity represents a reasonable value for Sonazoid CEUS.

The incidence of HCC is the most critical parameter in decision-making for the surveillance of patients with cirrhosis. In our baseline analysis, we selected 7% as a baseline value because most studies in Japan reported 5–8% as the incidence of HCC.[6,26,48,49] This rate is slightly higher than the one in the United States and Europe, where incidence rates are reported from 1.5 to 4%.[8,27] Figure 6 shows how the incidence rate affects the ICER. When the ICER of the CEUS group was compared with the US group, it increased as the rate decreased. However, when the rate was 2%, the ICER of the CEUS group was still less than $50 000/QALY.

Although our results enable us to evaluate the effectiveness of CEUS surveillance, the study has some limitations. First, Sonazoid is available only in Japan. Thus, there are only Japanese published reports for analysis. On the other hand, our baseline data of US sensitivity 70% could be affected by the regional difference, and might be estimated lower than in the Japanese one. However, even if the US sensitivity was as high as 80%, ICER was still lower than $US 40 000 when CEUS surveillance was compared with US surveillance (Fig. 5a).

Similarly, our results were analyzed based on some hypothesis. Thus, the validation is desirable but is difficult because there are also ethical issues. For the solution of the problems, we performed the sensitivity analysis with the widest possible range using many representative reports. As the results of our analysis, we could indicate that the parameters except the HCC incidence rate, US sensitivity and CEUS sensitivity have little impact on cost-effectiveness.

In summary, our analysis suggests that surveillance for HCC in patients with compensated HCV-related cirrhosis by CEUS using Sonazoid was a cost-effective strategy. Since this cost-effectiveness decreased when the HCC incidence rate was low, this strategy should be selected

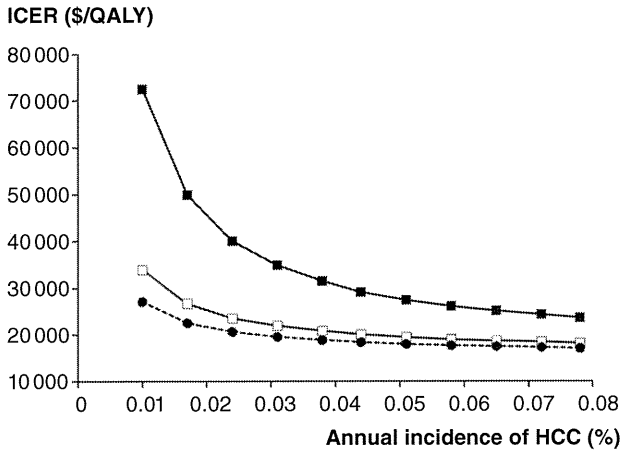

Figure 6 Effects of the annual incidence of hepatocellular carcinoma (HCC). The incremental cost-effectiveness ratio (ICER) values of the ultrasonography (US) and contrast-enhanced ultrasonography (CEUS) surveillance groups were less than $US 35 000/ quality adjusted life year (QALY) in all ranges as compared with the no surveillance group. However, the ICER of the CEUS surveillance group achieved $US 50 000/QALY as compared with the US surveillance group when the incidence was lower than 0.016. -■-, CEUS (vs no surveillance); -□-, CEUS (vs US surveillance); -●-, US (vs no surveillance).

considering of the influence of patient factors such as age, gender and fibrosis grade.

ACKNOWLEDGMENTS

THIS WORK WAS supported by Grant-in-aid for Researchers, Hyogo College of Medicine, 2009.

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Hepatology Research

Hepatology Research 2012; **42**: 22–32 doi: 10.1111/j.1872-034X.2011.00889.x

Review Article

Anticarcinogenic impact of interferon therapy on the progression of hepatocellular carcinoma in patients with chronic viral infection

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Hepatocellular carcinoma (HCC) is mainly caused by a persistent infection due to the hepatitis B or hepatitis C virus. The number of HCC cases is increasing in Asian and African countries, as well as in European and American countries. Interferon (IFN) therapy, used for type B chronic liver diseases, inhibits hepatic carcinogenesis in patients with compensated cirrhosis. However, there is insufficient evidence that IFN therapy inhibits hepatic carcinogenesis in patients with chronic hepatitis B. There are few cases of HCC due to chronic hepatitis B, and long-term follow-up periods verifying the inhibitory effect of IFN on hepatic carcinogenesis have not been obtained. To improve the prognosis of type B chronic liver diseases, it is important that hepatitis treatment follows guidelines in which a patient's age and the extent of hepatic fibrosis are taken into account. As for chronic hepatitis C, since a sustained virological response (SVR) in IFN therapy inhibits hepatic carcinogenesis and improves prognosis, treatment that aims for an SVR while taking into consideration host-sided and virus-sided factors is recommended for patients with type C chronic liver diseases. In areas with low incidence of HCC (e.g. USA), a large number of cases and a long-term follow-up period are needed before it can be accepted that IFN therapy inhibits hepatic carcinogenesis. After locally curative treatment of HCC, IFN therapy suppresses recurrence and improves survival rates.

Key words: chronic hepatitis, hepatitis B virus, hepatitis C virus, hepatocellular carcinoma, interferon, prevention

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) ranks fifth in the number of patients worldwide who are diagnosed with cancer; its death toll ranks third.[1] Approximately 600 000 to 700 000 patients worldwide die of HCC each year; the number of HCC cases is increasing in Asian and African countries, as well as in European and American countries.[2,3] HCC is mainly derived from a persistent infection due to the hepatitis B virus (HBV) or hepatitis C virus (HCV); thus, treating viral hepatitis inhibits hepatic carcinogenesis. In clinical and epidemiological studies of patients with chronic hepatitis B, active replication of HBV is linked to progression to cirrhosis and HCC.[4] Cessation of HBV replication reduces complications and improves prognosis. If, as a result of interferon (IFN) therapy, seroclearance of hepatitis B e antigen (HBeAg) can be achieved and the patient is negative for HBV DNA, then this might reduce the chances of HCC developing.[5] IFN therapy for chronic hepatitis C helps to reduce the risk of HCC developing in patients in whom a sustained virological response (SVR) has been achieved and that therapy also helps to reduce the risk of HCC developing in patients in whom viral clearance has proven difficult.[6,7] This paper reviews clinical research studies that have focused on the inhibitory effect of IFN therapy on hepatic carcinogenesis.

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Received 27 March 2011; revision 11 August 2011; accepted 11 August 2011.

THE ANTITUMOR ACTION OF IFN

INTERFERON IS A cytokine with varied forms of bioactivity including antiviral action as well as action to inhibit cell growth, angiogenetic activity, action to regulate the immune response, and action to inhibit

telomerase activity. IFNs are generally grouped into type I IFNs, which include IFN-α, -β, and -ω, and type II IFN, which consists solely of IFN–γ.[8–10] IFN-α and -β are widely used clinically to treat viral diseases such as chronic hepatitis B and C and neoplastic diseases such as renal cell carcinoma and glioblastoma. Evidence of IFN's direct antitumor action has been reported, i.e. IFN-α and -β have been found to inhibit growth of a hepatoma cell line in a concentration-dependent manner.[11] In addition, IFN has been found to exhibit antitumor action by inducing apoptosis of tumor cells via p53 and by stopping the progression of the cell cycle.[12] Similarly, an *in vivo* study noted that an IFN dose similar to that used clinically suppressed the growth of hepatic carcinoma cells.[13] Moreover, alpha fetoprotein (AFP) levels decreased after administration of IFN to patients with chronic hepatitis C and consistently elevated AFP levels; the mechanism for this phenomenon may be antitumor action.[14] In addition, IFN is also assumed to have indirect antitumor action by immunopotentiation via natural killer cells.[15] Nevertheless, the current reality is that the mechanism of IFN's antitumor action has yet to be fully elucidated.

HBV-RELATED HCC

THERE ARE AN estimated 300 million or more HBV carriers in the world; many of them are concentrated in Asian and African areas.[1] About 15% of HCC cases in Japan are HBV-related.[16] The annual incidence of HCC in patients with type B chronic hepatitis is 0.1% to 1.0% and in patients with type B cirrhosis, 2.2% to 4.3%; the incidence of HCC is higher in Asia than elsewhere in the world.[17] A study of the natural history of HCC has reported that factors for a high risk of developing the condition are cirrhosis, being an elderly male, having genotype C or F1, having a double substitution (A1762T and G1764A) in the core promoter region, and high HBV DNA levels.[4] Since it is difficult to completely eliminate HBV, the primary goals of treatment are to eliminate or reduce HBV DNA in the blood and to normalize the levels of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT).[18]

We searched the medical published reports and found that the inhibitory effect of IFN therapy on hepatic carcinogenesis in patients with type B chronic hepatitis and cirrhosis was first reported in 1996; we also found four randomized controlled trials (RCT) – three from Europe and one from Asia (Table 1).[19–22] The paper from Asia indicated that IFN therapy inhibits hepatic carcinogenesis, but the papers from Europe did not have this

Table 1 Baseline characteristics of randomized control trials assessing effect of interferon (IFN) on hepatocellular carcinoma (HCC) development in hepatitis B virus (HBV)-infected patients

Study [reference]	Year	Sample size (*n*)	Male (%)	Mean age (years)	HBeAg positive (%)	Pre-existing cirrhosis (%)	IFN regimen	Mean follow-up (years)	VR (%)	Incidence of HCC (%)
Lampertico P *et al.*[21]	1997	T21	T80	T44	T0	T19	α-2b: 6 MU 3 times a week for 24 months	3.8	T28	T5
		C21	C90	C47	C0	C14			C0	C0
Krogsgaard K *et al.*[19]	1998	T210	81	36	T100	19	α-2a: 2.5–18 MU 3 times a week for 12–24 weeks	4.7	T24	T1
		C98			C100				C20	C1
Mazzella G *et al.*[20]	1999	T33	T76	T36	T100	T0	α: 5 MU/m^2 3 times a week for 24 weeks	7.1	T36	T3
		C31	C80	C40	C100	C0		6.6	C0	C6
Lin SM *et al.*[22]	1999	T67	T100	T32	T100	T10	α: 4–6 MU/m^2 3 times a week for 12 weeks	7.4	T42	T1.5
		C34	C100	C32	C100	C14		6.5	C24	C11.8

C, control group (no treatment); HBeAg, hepatitis B e antigen; MU, million units; T, IFN treated group; VR, virological response.

finding. In a study involving 308 patients with HBe antigen (HBeAg)-positive chronic hepatitis and cirrhosis, Krogsgaard *et al.*[19] administered a 2.5 to 10 million unit (MU)/m^2 dose of IFN-α2a three times weekly for 12 to 24 weeks to 210 patients (i.e. the treatment group). During a mean follow-up period of 4.7 years, HCC occurred in two patients in the treatment group and in one patient in the control group. In a study involving 64 patients with HBeAg-positive chronic hepatitis, Mazzella *et al.*[20] administered a 5 MU/m^2 dose of IFN-α three times weekly for 24 weeks to 33 patients (i.e. the treatment group). During a mean follow-up period of 7.1 years, HCC occurred in three patients whose chronic hepatitis had progressed to cirrhosis (one patient in the treatment group and two patients in the control group). In a study involving 42 patients with HBeAg-negative chronic hepatitis, Lampertico *et al.*[21] administered a 6 MU dose of IFN-α2b three times weekly for 96 weeks to 21 patients (i.e. the treatment group). During the mean follow-up period of 3.8 years, HCC occurred in one patient in the treatment group. In a study involving 101 patients with HBeAg-positive chronic hepatitis, Lin *et al.*[22] administered a 4–6 MU dose of IFN-α three times weekly for 12 weeks to 67 patients (i.e. the treatment group). During a mean follow-up period of 7 years, HCC occurred in one patient in the treatment group and in four patients in the control group ($P = 0.043$). They believed that IFN therapy had an inhibitory effect on hepatic carcinogenesis.

On the other hand, reports from a study involving patients with HBeAg-positive cirrhosis[23] and several studies involving patients with HBeAg-positive chronic hepatitis and HBeAg-negative chronic hepatitis[19,20,24,25] deny that IFN therapy inhibits hepatic carcinogenesis. Based on their meta-analysis of seven non-randomized controlled trial (NRCT) studies involving patients with cirrhosis,[20,23,26–30] Cammà *et al.*[31] believe that IFN therapy inhibits hepatic carcinogenesis (risk difference [RD], −6.4%; confidence interval [CI], −2.8 to −10; $P < 0.001$). However, their analyses of subgroups with small variations showed no significant differences and they found that IFN therapy did not inhibit hepatic carcinogenesis. Sung *et al.*[32] in a meta-analysis of 12 papers (which included an RCT study)[5,19,20,23–26,28–30,33,34] concluded that, compared with patients in the control group, patients in the IFN therapy group had a 34% reduced risk of developing HCC. This effect was especially beneficial for patients with cirrhosis. However, in a recent meta-analysis based on two RCT studies,[20,22] Zhang *et al.*[35] concluded that IFN therapy does not necessarily reduce the development of HCC.

At the current point in time, previous reports offer conflicting results with regard to whether or not IFN therapy suppresses hepatocarcinogenesis when used to treat hepatitis B virus-related chronic liver disease. Reasons for this conflict are presumably related to discrepancies in IFN's suppression of carcinogenesis brought about by differences in the clinical characteristics of the patients studied. In other words, numerous factors, such as: (i) patient age; (ii) sex; (iii) liver function tests; (iv) differences in the mode of infection (vertical or horizontal infection); (v) stage of liver fibrosis and grade of necroinflammatory activity; (vi) positivity or negativity for HBeAg; (vii) HBV genotype; (viii) levels of HBV DNA; (ix) treatment protocol; (x) therapeutic efficacy; and (xi) follow-up period, may affect study results. In a NRCT involving 313 patients with cirrhosis due to hepatitis B, Ikeda *et al.*[26] administered 6 MU IFN-α three times a week for 40 weeks to 94 patients in a treatment group (including 61 patients who were positive for HBeAg). A follow-up lasting an average of 7 years revealed 10 patients in the treatment group and 51 of 219 patients in an untreated group developed HCC; this finding indicated that use of IFN decreased the rate of carcinogenesis. In addition, Lin *et al.*[5] reported a case-control study matching for age, sex, HBeAg, ALT, and levels of HBV DNA. Their results revealed that five patients in a group receiving IFN therapy and 16 in an untreated group developed HCC ($P = 0.025$) in a mean follow-up of 6.8 years. A follow-up of 15 years indicated that the cumulative rate of hepatocarcinogenesis was significantly lower for patients who had cirrhosis and were receiving IFN therapy in comparison to the control group, but differences between the control group and patients who did not have cirrhosis and were receiving IFN therapy were not noted. Multivariate analysis indicated that independent risk factors for the progression of HCC were age, not having undergone IFN therapy, pre-existing cirrhosis, carrying HBeAg, and having the HBV genotype C (in comparison to genotype B). Based on previous studies, IFN therapy for patients with compensated cirrhosis B should be able to suppress hepatocarcinogenesis.[5,22,23,26,31,32,36] However, the inhibitory effect of IFN therapy on hepatic carcinogenesis for patients with type B chronic hepatitis has not yet gained a sufficient consensus. One reason is that there are few cases of hepatic carcinogenesis that develop from type B chronic hepatitis; thus, researchers cannot obtain either a sufficient number of cases or long-term follow-up periods to verify that IFN therapy inhibits hepatic carcinogenesis. An HBV carrier who has a high level of HBV DNA

rapidly progresses to cirrhosis, which is associated with a high rate of HCC.[37] In patients with HBeAg seroconversion and reduced levels of HBV DNA due to IFN therapy, the progression of cirrhosis slows and development of HCC is inhibited.[5] When serum transaminase returns to normal and HBV DNA falls below detection limits due to IFN therapy given to HBeAg-negative European patients, an improved prognosis is noted but IFN therapy has not been found to suppress hepatocarcinogenesis.[38] Miyake *et al.* reported that IFN therapy has been found to suppress hepatocarcinogenesis in Asians; they also reported that IFN has an effect in populations with a 10% or greater incidence of HCC that have not undergone IFN therapy and study populations with 70% or more subjects that are positive for HBeAg.[39]

Compared with the standard IFN, pegylated-IFN (PEG-IFN) has been reported as more effective in the elimination of HBeAg, reducing HBV DNA, and normalizing the serum ALT level.[36] However, there is no report on whether PEG-IFN (in comparison with the standard IFN and nucleos(t)ide analogs such as lamivudine) more greatly reduces the risk of developing HCC. Future research is needed.

In addition, IFN for type B cirrhosis is not price-listed in Japan, and the IFN administration period for type B chronic hepatitis is 6 months. Price-listing of IFN for type B cirrhosis, the extension of the administration period, and the approval of using PEG-IFN are pending.

HCV-RELATED HCC

THE HCV WOULD not be naturally eliminated when an infection is passed to humans. About 70% of persistently infected people become carriers and necroinflammatory reactions continue; as a result, hepatic fibrosis progresses to cirrhosis.[40] However, hepatic fibrosis progression rates in persistently HCV-infected people differ significantly among individuals and are influenced by the person's age when infected, the amount of alcohol intake, gender, and the extent of liver function abnormality. It has been demonstrated that, in people who have insulin resistance and fatty livers, the hepatic fibrosis progression rate is rapid and the sustained virological response (SVR) ratio in IFN therapy is reduced.[41,42] HCC incidence rates increase in relation to the progression of hepatic fibrosis.[43] The annual incidence of HCC from type C compensated cirrhosis is reportedly 7.1% in Japan and 3.7% in both Europe and America; and the annual incidence of HCC from chronic hepatitis is 1.8% in Japan and 0% in both Europe and America.[17] When such natural courses are taken into account, the treatment goals for type C chronic hepatitis are to prevent the progression to cirrhosis and to inhibit hepatic carcinogenesis.

In 1995, we examined (using an RCT) the inhibitory effect of IFN therapy on hepatic carcinogenesis for type C cirrhosis.[44,45] Ninety patients with type C cirrhosis were divided into two groups: the IFN treatment group and the untreated group. We examined the long-term clinical effects of IFN therapy. In the IFN treatment group, an SVR occurred in seven patients and a biological response (BR) occurred in six patients. In the untreated group, the spontaneous disappearance of the HCV and sustained normalization of ALT level did not occur. During the mean follow-up period of 8.2 years, the cumulative incidence rate of HCC was significantly lower in the IFN treatment group than in the untreated group (27% vs. 73%, respectively) ($P = 0.001$). The relative risk (RR) was 0.256. A multicenter Japanese study – the Inhibition of Hepatocarcinogenesis by Interferon Therapy (IHIT) study – showed that, compared with the untreated group, the risk of hepatic carcinogenesis was inhibited by 0.51-fold in the IFN treatment group; the RR of hepatic carcinogenesis was 0.197 in patients who achieved SVR with IFN therapy.[46] To our knowledge, seven RCT papers have been published since 1995 that investigated the inhibitory effect of IFN therapy on hepatic carcinogenesis (Table 2).[44,47–52] In a study involving 99 patients with compensated cirrhosis, Valla *et al.*[47] administered a 3 MU dose of IFN-α2b three times weekly for 48 weeks to 52 patients (i.e. the treatment group). A mean follow-up period of 3.3 years showed that HCC occurred in five patients in the treatment group and in nine patients in the control group; however, there was no statistically significant difference between the groups. On the other hand, the results of a meta-analysis by Cammà *et al.*[31] confirmed that IFN therapy inhibits hepatic carcinogenesis in patients with type C cirrhosis. Their investigation of 3109 patients in three RCT studies[44,47,53] and 11 NRCT studies[28,30,46,54–61] showed that the risk of developing HCC in the IFN treatment group was reduced by 12.8% (95% CI, −8.3% to −17.2%), compared with the risk in the untreated group. They reported that, especially in patients who obtained a SVR, there was a marked inhibition of hepatic carcinogenesis (as indicated by an RD of −19.1%). Even in people who did not have a SVR, the RD was significantly reduced (at −11.8%). Miyake *et al.*[62] reported that hepatic carcinogenesis was inhibited in the IFN-treated group, compared with the untreated group (RR, 0.45; 95% CI, 0.31–0.65), based on their meta-analysis of three RCT studies[47–49] and six

Table 2 Baseline characteristics of randomized control trials assessing effect of interferon (IFN) on hepatocellular carcinoma (HCC) development in hepatitis C virus (HCV)-infected patients

Study [reference]	Year	Sample size (*n*)	Male (%)	Mean age (years)	Pre-existing cirrhosis (%)	IFN regimen	Mean follow-up (years)	SVR (%)	Incidence of HCC (%)
Nishiguchi S *et al.*[44]	1995	T45	T62	T55	T100	α: 6 MU 3 times a week for 24 weeks	T4.4	T16	T4
		C45	C51	C57	C100		C5.5	C0	C38
Valla DC *et al.*[47]	1999	T45	T73	T57	T100	α-2b: 3 MU 3 times a week for 48 weeks	3.3	NA	T11
		C49	C65	C56	C100				C18
Bernardinello E *et al.*[48]	1999	T38	T50	T56	T100	β: 6 MU 3 times a week for 24 weeks followed by 3 MIU for another 24 weeks	5	T3	T5
		C23	C61	C58	C100			C0	C4
Francesco A *et al.*[50]	2004	T30	T57	T55	T100	α-2b: 6 MU daily for 1 month followed by 3 MIU daily for 11 months plus ribavirin 1 g daily for 12 months	5	T43	T0
		C30	C60	C57	C100			C0	C30
Soga K *et al.*[49]	2005	T103	T49	T52	T0	α, α-2a or α-2b: 3–10 MU daily for 2–4 weeks and 3 times a week for total of 14–28 weeks or β; 3–6 MU daily for 6–8 weeks	7.8	T32	T5
		C30	C43	C54	C0			C0	C23
Fartoux L *et al.*[51]	2007	T51	T45	T60.5	T100	α-2a: 3 MU 3 times a week for 2 years	2	T0	T12
		C51	C45	C60.5	C100			C0	C12
Lok AS *et al.*[52]	2009	T495	T71	T50	T40	PEG-IFN α-2a: 90 μg weekly for 3.5 years	T4.6	T0	T4.6
		C510	T79	C53	C41		C4.9	C0	T4.9

C, control group (no treatment); MU, million units; NA, not available; PEG-IFN, pegylated interferon; SVR, sustained virological response; T, IFN treated group.

NRCT studies[50,55,58,63–65] published between 1989 and 2009.

The inhibitory effect of IFN is furthermore demonstrated in non-responders (NRs) to IFN therapy (RR, 0.48; 95% CI, 0.26–0.66). Zhang *et al.*[35] recently performed a meta-analysis on the effect of non-maintenance IFN therapy on hepatic carcinogenesis. They used only four RCT papers (in three papers, the subjects were patients with type C cirrhosis).[45,47–49] The results indicated that IFN therapy inhibited hepatic carcinogenesis in the IFN treatment group, compared with the untreated group (RR, 0.39; 95% CI, 0.26–0.59). The results of IFN therapy, when focusing only on patients with cirrhosis, also showed the same inhibitory effect (RR, 0.44; 95% CI, 0.28–0.68). In one study, patients who were initially NR to IFN therapy were divided into two groups: a maintenance IFN treatment group and an untreated group.[51,52] An analysis of the results showed that IFN therapy has no inhibitory effect on hepatic carcinogenesis.

In the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial,[52] 1005 patients had cirrhosis and had chronic hepatitis that progressed to fibrosis (i.e. bridging fibrosis). Of these, patients who were unresponsive to a combination therapy with PEG-IFN and ribavirin (RBV) were divided into two groups – the maintenance treatment group (PEG-IFN α-2a, 90 μg) and the untreated group. The incidence of HCC in each group was investigated. During a mean follow-up period of 4.6 years, there was no difference between the two groups in the incidence of HCC. In a continuation of the HALT-C report,[7] the mean follow-up period was extended to 6.1 years. The results showed that IFN therapy inhibited hepatic carcinogenesis in patients with cirrhosis in the maintenance IFN treatment group, compared with its inhibitory effect in the untreated group (HR, 0.45; 95% CI, 0.24–0.83). On the negative side, maintenance IFN therapy insufficiently inhibited hepatic carcinogenesis in patients with chronic hepatitis that had progressed to fibrosis. However, the incidence of HCC was reduced in these patients if their liver had a histological improvement with IFN therapy.

One report shows that maintenance IFN therapy reduces the incidence of HCC in elderly patients with chronic hepatitis, compared with patients in the untreated group.[66] Kumada *et al.* state that the administration of IFN therapy is important in normalizing serum ALT level or reducing the AFP level, even if HCV does not disappear.[6] For non-SVR patients receiving IFN therapy, a patient's age is an important risk factor for hepatic carcinogenesis, and the annual incidence of HCC in patients with chronic hepatitis and hepatic fibrosis is significantly higher in aged people than in young people.[67] It can be accordingly conjectured that the reason for a higher complication rate of HCC among HCV carriers in Japan than among HCV carriers in the USA is that Japanese carriers have a higher mean age and a higher extent of hepatic fibrosis.[68] These factors may be responsible for the difference in the inhibitory effect of IFN therapy on hepatic carcinogenesis noted between patients in Japan and patients in the USA.

Based on past studies investigating the inhibitory effect of IFN therapy on hepatic carcinogenesis in patients with type C chronic liver diseases, a consensus has been reached concerning the following three points:

- Point 1: Patients achieving SVR with IFN therapy have a reduced HCC incidence rate and an improved HCC prognosis.[46,69,70]
- Point 2: Because of the use of combination therapy (e.g. PEG-IFN and RBV) in recent years, the treatment outcome has improved and the SVR ratio is about 50% to 80%.[71] However, for patients with chronic hepatitis that has progressed to fibrosis and for patients with compensated cirrhosis, IFN therapy alone reduces the SVR ratio and reduces the incidence of complications associated with the liver (including hepatic carcinogenesis).[69]
- Point 3: IFN therapy reduces the incidence rate of HCC when a BR is achieved or when there is a histological improvement.[66,72]

Further examinations are needed to determine whether maintenance IFN therapy inhibits hepatic carcinogenesis and whether there is any difference between IFN therapy NR patients and IFN-untreated patients in the rate of hepatic carcinogenesis. Studies are needed that take into account the amount of IFN administered, the administration period, and the use of RBV and novel concurrent drugs. In addition, we expect that combination therapy with PEG-IFN and RBV for patients with compensated cirrhosis will be promptly price-listed in Japan.

RECURRENCE INHIBITION AFTER LOCALLY CURATIVE TREATMENT FOR HCC

EVEN IF LOCALLY curative treatment for HCC is performed, HCC relapses occur at an annual rate of 15% to 20%. This high rate is not caused by any other malignant neoplasms, and it results in a high mortality.[73] To improve the prognosis of patients with HCC, measures are needed that advance HCC treatment and inhibit recurrence.

Basic investigations reveal that IFN has anti-viral activity and it inhibits the growth of HCC.[74,75] In a retrospective examination, Someya *et al.* reported that singlevariate and multivariate analyses showed that IFN therapy inhibits recurrence in patients with HCC-complicated type B cirrhosis after locally curative treatment.[76] Lo *et al.*[77] performed an RCT, using as subjects 40 patients who had undergone a radical hepatic resection because of HBV-related HCC. On examining the IFN treatment group (in which patients were administered 10 MU/m^2 of IFN-α2b three times weekly for 12 weeks) and the untreated group, they found that the one-year and 5-year survival rates were 97% and 79%, respectively, in the IFN treatment group and 85% and 61%, respectively, in the untreated group. Therefore, the IFN treatment group had a better prognosis ($P = 0.137$). A multivariate analysis demonstrated that IFN therapy may reduce the risk of death (HR, 0.42; 95% CI, 0.17–1.05; $P = 0.063$). In the examination of subgroups, there was no difference between the IFN treatment group and the untreated group in the 5-year survival rate in patients at stage I/II; however, in patients at stage III/IV A, IFN therapy inhibited the early recurrence of HCC and improved the 5-year survival rate from 24% to 68% ($P = 0.038$). Sun *et al.*[78] in their RCT also reported that IFN therapy was useful after an operation for HCC and that the median overall survival time and median disease-free time were significantly longer in treated patients, compared with the untreated patients.

We found six RCT studies that examined the inhibitory effect of IFN therapy on recurrence after locally curative treatment for HCV-related HCC.[79–84] Ikeda *et al.*[79] and Kubo *et al.*[80] showed that IFN therapy significantly inhibits the recurrence of HCC. Shiratori *et al.*[81] reported no difference between the IFN-treated group and the control group with the first relapse of HCC, but noted that IFN therapy inhibits a second or later recurrence of HCC. Only Mazzaferro *et al.*[83] reported that IFN therapy shows no significant difference between the IFN treatment group and the control group; however, at the first relapse of HCC, IFN therapy inhibits recurrence in patients having a single tumor that is free from vascular invasion and has a diameter of less than 3 cm. An examination of NRCT, which were performed in Japan, also showed that IFN therapy significantly inhibits the relapse of HCC (especially in patients who receive IFN treatment aimed at eliminating HCV), achieves an SVR,[85–87] and improves survival rates.[88] Maintenance IFN therapy after the locally curative treatment of HCC reportedly inhibits recurrence.[85,89,90] Kudo *et al.*[89] reported that IFN therapy inhibits the first relapse (as well as a second or third relapse) and improves the prognosis. We also demonstrated that long-term maintenance IFN therapy, given after the combination therapy with PEG-IFN and RBV, effectively inhibits HCC recurrence and improves prognosis.[91] Singal *et al.*[92] performed a meta-analysis of five RCT papers[79,81–83,93] and five NRCT papers.[87,89,94–96] They reported that IFN therapy inhibits HCC recurrence (odds ratio [OR], 0.31; 95% CI, 0.26; $P < 0.0001$) and significantly extends the overall survival time. Furthermore, Zhang *et al.*[97] conducted a meta-analysis of six RCT papers (Two papers focused on HBV-related HCC and four papers focused on HCV-related HCC).[77,78,80–83,93] Their meta-analysis showed that IFN therapy inhibits early recurrence (OR, 0.62; 95% CI, 0.42–0.93; $P = 0.02$) and improves the one-year survival rate (OR = 3.14; 95% CI = 1.79–5.52; P (00.0001). Shen *et al.*[98] similarly performed a meta-analysis of 13 papers on HBV-related and HCV-related HCC (nine papers involved RCT[77–84,93], and four papers involved NRCT[87,89,94,99]). From this, they concluded that IFN therapy improved the one-year, 2-year, and 3-year recurrence-free survival rates in the IFN treatment group, compared with the control group.

Based on past studies investigating the inhibitory effect of IFN therapy on HCC recurrence after locally curative treatment, HCC recurrence is reduced through HCV clearance. Thus, IFN therapy for viral eradication is recommended for patients with hepatitis C if possible. Meanwhile, in patients with hepatitis B, IFN therapy after locally curative treatment may improve their prognosis. Further examinations are needed to determine whether IFN therapy after locally curative treatment reduces HCC recurrence in patients with hepatitis B.

FINAL COMMENTS

FOR PATIENTS WITH chronic hepatitis B, IFN therapy reduces the risk of hepatic events (including the inhibitory effect for developing HCC) particularly among responders to treatment in Asian, but not in European patients. The progression to cirrhosis and a high level of HBV DNA (greater than 10^5 copies/mL) are strong risk factors for hepatic carcinogenesis from type B chronic liver diseases.[37] Liaw *et al.*[100] reported that therapy with lamivudine, a nucleos(t)ide analog, significantly reduces the progression to non-compensated cirrhosis and inhibits the development of HCC. Matsumoto *et al.*[101] also had similar results in a multicenter study of Japanese patients with type B chronic hepatitis. As for inhibition of hepatic carcinogenesis from type B chronic liver diseases, measures for hepatitis