Table 3. Causes of death in the interferon and control groups

	Interferon group						
	Virological response		Biochemical response				
	Sustained response (n = 161)	Non-response (n = 484)	Sustained response (n = 206)	Transient response (n = 144)	Non-response (n = 299)	Total (n = 649)	Control group (n = 58)
All deaths (n)	4	38	6	6	30	42	13
Liver-related deaths (n)	1	28	1	4	24	29	7
Hepatocellular carcinoma	1	25	1	3	22	26	5
Other causes	0	3	0	1	2	3	2
Liver-unrelated deaths (n)	3	10	5	2	6	13	6

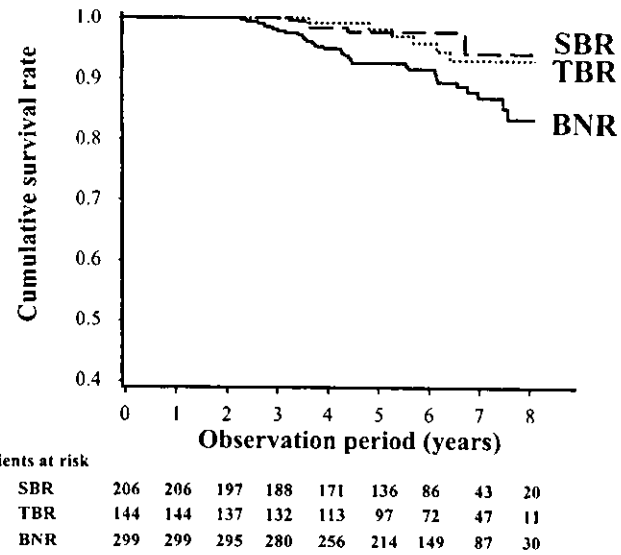

Fig. 2. Cumulative survival rates in the IFN-treated patients, categorized by sustained biochemical response (*SBR*; *dashed line*), transient biochemical response (*TBR*; *dotted line*), and biochemical non-response (*BNR*; *solid line*). Log-rank test showed significant differences between SBR and BNR (P = 0.007) and between TBR and BNR (P = 0.049)

ers. In the control group, 6 patients died of causes other than liver disease; 2 patients died of stomach cancer; 1 patient each died of lung cancer, colon cancer, and cerebral infarction; and in 1 patient, the cause of death was a traffic accident. In the IFN group, we identified 13 liver-unrelated deaths; 4 patients died of stomach cancer; 3 died of lung cancer; and 1 each died of breast cancer, colon cancer, esophageal cancer, pneumonia, chronic renal failure, and multiple myeloma.

Cox proportional hazard regression analysis

Cox proportional hazard regression analysis revealed that the risk of overall death in the IFN group was lower than that in the control group, with a marginally significant difference (risk ratio, 0.37; 95% CI, 0.13–1.05; Table 4). The patients with a sustained virological response had a low risk of overall death (risk ratio, 0.15; 95% CI, 0.04–0.59) compared with the control group. Sustained and transient biochemical responders also showed low risks of overall death (risk ratio, 0.18; 95% CI, 0.05–0.65; and risk ratio, 0.24; 95% CI, 0.07–0.87). The risk of liver-related death in the IFN group was similar to that in the control group (Table 4). However, the patients with sustained virological and biochemical response had a low risk of liver-related death compared to the control group (risk ratio, 0.12; 95% CI 0.01–1.16 and risk ratio, 0.10; 95% CI, 0.01–0.95, respectively). In transient biochemical responders, the risk ratio for liver-related deaths was 0.50 (95% CI, 0.11–2.21).

Table 4. Risk ratios for death in interferon and control groups

	All deaths			Liver-related deaths		
	Risk ratio	95% CI	*P* value	Risk ratio	95% CI	*P* value
Control group	1.00			1.00		
IFN group	0.37	0.13–1.05	0.06	0.80	0.25–2.53	0.71
Sustained virological response	0.15	0.04–0.59	0.01	0.12	0.01–1.16	0.07
Virological non-response	0.44	0.16–1.23	0.12	0.97	0.31–3.05	0.96
Sustained biochemical response	0.18	0.05–0.65	0.01	0.10	0.01–0.95	0.05
Transient biochemical response	0.24	0.07–0.87	0.03	0.50	0.11–2.21	0.36
Biochemical non-response	0.54	0.19–1.53	0.24	1.26	0.40–4.03	0.69

Age, sex, time of liver biopsy (until 1992/after 1993) and histologic staging score were adjusted in the Cox proportional hazard analysis

SMR

The SMRs in the IFN and control groups are shown in Table 5 and Fig. 3. In the control group, overall mortality was slightly higher than that in the sex- and age-matched general population (SMR, 1.40; 95% CI, 0.76–2.45). On the other hand, overall mortality in the IFN group was significantly lower compared with that of the general population (SMR, 0.73; 95% CI, 0.52–0.98). Liver-related mortality was high in the control group (SMR, 10.70; 95% CI, 4.29–22.05), and it was also high in the IFN group (SMR, 5.05; 95% CI, 3.38–7.26), although it was half of that in the control group. In the patients with sustained virological response, liver-related mortality (SMR, 0.65; 95% CI, 0.01–3.61) was very low compared with that in the control group, and it was similar to that for the general population. On the contrary, liver-related mortality was high in virological non-responders (SMR, 6.71; 95% CI, 4.46–9.70).

In terms of biochemical response, the SMRs for liver-related death of sustained and transient biochemical responders in the IFN groups were low compared with that in the control group (SMR, 0.53; 95% CI, 0.01–2.97 and SMR, 3.25; 95% CI, 0.87–8.32, respectively). In the patients with biochemical non-response, liver-related mortality was high, and was equal to that in the control group (SMR, 9.12; 95% CI, 5.84–13.57).

The IFN group showed lower liver-unrelated mortality than the general population (SMR, 0.25; 95% CI, 0.13–0.43), whereas the control group had liver-unrelated mortality similar to the general population (SMR, 0.71; 95% CI, 0.26–1.55).

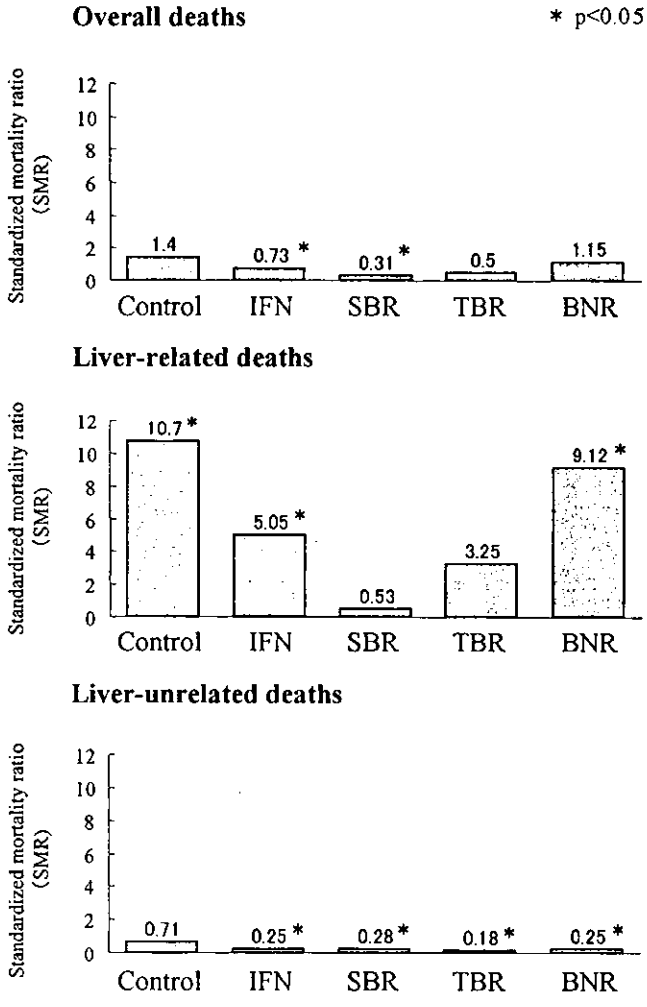

Fig. 3. Standardized mortality ratios (*SMR*s) for overall, liver-related, and liver-unrelated deaths. *SBR*, sustained biochemical response; *TBR*, transient biochemical response; *BNR*, biochemical non-response. When the SMR did not include unity, we considered the difference from the expected number of deaths to be significant

Discussion

There have been a few reports regarding the effect of IFN therapy on survival in chronic hepatitis C patients.[10,16–19] Yoshida et al.[17] reported that IFN therapy had a preventive effect on liver-related death, bringing

Table 5. Standardized mortality ratios (SMRs) in interferon and control groups

	All deaths			Liver-related deaths			Liver-unrelated deaths		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
Control group	13	9.1	1.40 (0.76–2.45)	7	0.7	10.70 (4.29–22.05)	6	8.4	0.71 (0.26–1.55)
Interferon group	42	57.8	0.73 (0.52–0.98)	29	5.7	5.05 (3.38–7.26)	13	52.0	0.25 (0.13–0.43)
Sustained virological response	4	15.8	0.25 (0.07–0.65)	1	1.5	0.65 (0.01–3.61)	3	14.3	0.21 (0.04–0.61)
Virological non-response	38	41.7	0.91 (0.64–1.25)	28	4.2	6.71 (4.46–9.70)	10	37.6	0.27 (0.13–0.49)
Sustained biochemical response	6	19.5	0.31 (0.11–0.67)	1	1.9	0.53 (0.01–2.97)	5	17.6	0.28 (0.09–0.66)
Transient biochemical response	6	12.1	0.50 (0.18–1.08)	4	1.2	3.25 (0.87–8.32)	2	10.9	0.18 (0.02–0.66)
Biochemical non-response	30	26.2	1.15 (0.77–1.64)	24	2.6	9.12 (5.84–13.57)	6	23.5	0.25 (0.09–0.55)

A difference from the expected number of deaths was considered significant when the 95% confidence interval (CI) of SMR did not include unity

about improved survival of chronic hepatitis C patients, as assessed by multivariate analysis and SMR. Recently, we also reported that IFN therapy improved survival by preventing liver-related deaths in patients with chronic hepatitis C, in a multicenter, large-scale, retrospective cohort study.[20] In that study, we showed that liver-related mortality, as well as overall mortality, was much higher in untreated patients than in IFN-treated patients, as assessed by SMR. Furthermore, we found that patients showing sustained and transient biochemical responses to IFN therapy had a very low risk of death compared with untreated patients.

In this study, we evaluated the effect of IFN therapy on survival in patients over 60 years of age with histologically proven chronic hepatitis C, by SMR and by risk ratio calculated by Cox proportional hazard regression analysis. Compared with the general population, liver-related mortality was high in the IFN-treated patients (SMR, 5.05), but it was much lower than that in the control group (SMR, 10.70). Yoshida et al.[17] also examined the effect of IFN therapy on liver-related mortality in chronic hepatitis C patients over 60 years of age in their large-scale retrospective cohort study, and reported that the SMR for liver-related death in IFN-treated patients was much lower than that in the untreated patients, which was consistent with our result. In our IFN group, sustained virological responders and sustained biochemical responders had very low liver-related mortality (SMR, 0.65 and 0.53, respectively), which was equal to that in the sex- and age-matched general population. Multivariate regression analysis also showed that IFN therapy reduced the risk of liver-related death in sustained virological responders by 88% and in sustained biochemical responders by 90%. The overall mortality in the control group was not high (SMR, 1.40), whereas that in the IFN group was significantly lower in comparison with the sex- and age-matched general population (SMR, 0.73). These results may reflect a selection bias due to the nature of the liver biopsy procedure, which was undergone by all of the patients in our study. This kind of selection bias may occur, as aged patients sometimes have illnesses other than liver disease, which make a liver biopsy difficult. Furthermore, IFN-treated patients had a significantly lower risk of liver-unrelated mortality compared with the untreated patients. It seems likely that this may be attributed not to the beneficial effect of IFN therapy on liver-unrelated mortality but to a selection bias in using IFN; only the patients who had no serious diseases, such as cardiovascular disease, received IFN therapy. However, our study indicated that IFN therapy could reduce liver-related mortality, particularly in patients with sustained virological or biochemical response.

In the patients with a transient biochemical response, liver-related mortality was low when compared with the

control group, as assessed by SMR. The SMR of the transient biochemical responders (3.25; 95% CI, 0.87–8.32), which included unity, was lower than that in the control patients (10.70; 95% CI, 4.29–22.05). Similarly, the risk ratio for liver-related death in transient biochemical responders was 0.50, although this was not significant. On the other hand, SMR, as well as the risk of liver-related death estimated by multivariate analysis in the biochemical non-responders (SMR, 9.12; adjusted risk ratio, 1.26), was similar to that in the control patients. These data suggest that a reduction in liver-related mortality by IFN therapy can be expected in patients showing a transient biochemical response. Retreatment or long-term treatment with IFN might lead to an improved survival rate in transient biochemical responders, although such treatment may not be easy with some aged patients.

There was no difference between the baseline characteristics of the IFN and control groups, except for the age distribution. However, because our study was a retrospective cohort study, it had some limitations. Because the time at liver biopsy in the control group was earlier than that in the IFN group, lead-time bias may have existed. The survival of the IFN group could be higher than that of the control group. To minimize this bias, 5-year time-specific mortality rates for the general population were prepared in the SMR analysis. Furthermore, the time at liver biopsy was included as a variable for the multivariate analysis. Another limitation of our study is the small number of patients in the control group compared with the IFN group. This limitation may also be overcome by calculating the SMRs of the IFN and control groups, representing the ratio of the observed number of deaths to the expected number of deaths, calculated after taking sex-, calendar time-, and cause-specific mortality rates for the general population into consideration. The beneficial effect of IFN therapy on survival in the aged patients with chronic hepatitis C resulting from the SMR analysis was consistent with that of the Cox proportional hazard regression analysis.

In conclusion, we showed in this study that IFN therapy reduced liver-related mortality in aged patients with chronic hepatitis C, especially in those exhibiting a biochemical response and in those showing a sustained virological response. IFN therapy is recommended for aged patients with chronic hepatitis C in whom a biochemical response or a sustained virological response can be expected, after screening for diseases other than chronic hepatitis C.

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Cost-effectiveness of ribavirin plus interferon alpha-2b for either interferon relapsers or non-responders in chronic hepatitis C: a Japanese trial

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Abstract

The aim of this study was to examine the cost-effectiveness of combination therapy with ribavirin plus interferon alpha-2b compared with interferon monotherapy for hepatitis C-infected Japanese patients who had either temporarily responded or not responded to initial interferon treatment. Data from a recent randomized clinical trial among relapsed or non-responding patients comparing combination therapy to interferon alone were applied to a computer cohort simulation Markov process model to project lifelong clinical and economic outcomes. Combination therapy for 24 weeks should increase life expectancy by 1.6 quality-adjusted life years and should reduce discounted (3% per year) lifetime costs by ¥121,000 when compared to retreatment with interferon alone. For the subgroup of patients with genotype 1b and high viral load, combination therapy should be cost-effective (¥187,000 per QALY gained with a 3% annual discount rate) by well-accepted international standards. These results were robust with combination therapy remaining cost-effective or cost saving in sensitivity analysis involving reasonable variation in all parameters.

For patients similar to those enrolled in the interferon alpha-2b and ribavirin trials in Japan, combination therapy should be considered cost-effective with the higher drug treatment costs nearly completely offset by future savings through reductions in future liver complications from hepatitis C.

Keywords: Chronic hepatitis C; Interferon; Ribavirin; Cost-effective analysis

1. Introduction

Hepatitis C virus (HCV) affects 170 million individuals worldwide and more than 2 million in Japan. Hepatitis C can lead to cirrhosis and hepatocellular carcinoma (HCC). In Japan, it results in more than 30,000 deaths annually [1], and 84% of Japanese HCC patients were reported to be seropositive for anti-HCV antibody [2]. Interferon treatment of hepatitis C-infected patients has been found to reduce substantially the incidence of HCC in those who respond completely or partially to interferon [3–7].

Interferon monotherapy for chronic hepatitis C infection in Japan leads to complete remission with viral eradication in 30–40% and to normalization of liver tests without eradication in 10–20%. The majority of patients however relapse once treatment is stopped with only 15–20% of interferon treated patients demonstrating a durable effect 6–12 months after therapy. More than one-half of patients are non-responders or relapsers and usually receive another course of interferon with a higher dose or for a longer duration [8,9].

Because the Japanese Ministry of Health, Labor and Welfare has recently launched an HCV screening program in the general population, many previously unidentified individuals and their physicians will be facing antiviral treatment decisions in the near future. It will be critical to determine how such HCV-infected patients should be treated clinically and to assess the social and monetary implications for Japan.

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A randomized controlled study to determine the effectiveness of the combination of interferon alpha-2b plus ribavirin, an oral nucleoside analogue, was conducted in Japan recently. Combination therapy was found to significantly increase sustained response rates compared with interferon monotherapy in patients in whom prior interferon monotherapy had failed to eradicate HCV [10].

A prior study has shown that treating Japanese patients who have hepatitis C with interferon is "cost-effective" with an incremental or marginal cost-effectiveness ratio that is within the range of other well-accepted medical interventions. Combination therapy, however, is more expensive than interferon alone, raising questions about its economic value or cost efficiency.

The aim of this study was to estimate the incremental cost-effectiveness of the combination of ribavirin plus interferon compared with interferon alone for patients with hepatitis C who have relapsed (relapsers) or who did not respond to interferon at all (non-responders). We used data from a randomized clinical trial to estimate short-term events such as viral eradication and then projected long-term outcomes using a published Markov model that simulates the natural history of chronic hepatitis C.

2. Methods

We performed a cost-effectiveness analysis for the clinical trial of ribavirin and interferon alpha-2b in treating chronic hepatitis C patients who have relapsed or who were non-responders to prior interferon monotherapy in Japan. Summary data (age, gender, initial histology, genotype and virological response) from the clinical trial were then applied to a previously published and validated computer cohort simulation. The model was originally adapted to reflect the natural history and the clinical management of hepatitis C in Japan [11,12] and was further updated to reflect more recent studies [13].

We used actual data for 126 patients (mean age 49.5 years and 31% women) from a clinical trial in Japan [10]. Briefly, the study was a double-blind randomized placebo-controlled trial, comparing 24 weeks of interferon alpha-2b plus a placebo with the combination of ribavirin and interferon alpha-2b. Our analysis used the following data from the trial: age, gender, pretreatment histology, viral response after 24 weeks of treatment, viral response 24 weeks after treatment discontinuation, and treatment discontinuation as occurred in the trial whether due to an adverse event or other cause (Table 1).

We modified a previously published computer simulation model using current data regarding the natural history of chronic hepatitis C in Japan to estimate the long-term outcomes for each treatment arm. The original model has been previously validated by showing that predicted estimates match closely results found in natural history studies [11,12].

Table 1
Japanese randomized controlled trial of combination therapy vs. interferon[a]

Patient characteristics (n = 126)	
Mean age (years)	49.6
Female	31 (39)
Body weight > 60 kg	50 (63)
Genotype 1b	68 (86)
High viral load	77 (96)
Histology	
Mild hepatitis	41 (51)
Moderate hepatitis	54 (67)
Cirrhosis	4 (5)

	Response rates	
	Interferon alone	Combination therapy
Overall	(n = 64)	(n = 62)
Sustained viral negative[b]	9.4 (6)	35.5 (22)
Remission–relapse[c]	46.9 (30)	48.4 (30)
Withdrawal	9.4 (6)	8.1 (5)
Genotype 1b and high viral load	(n = 36)	(n = 37)
Sustained viral negative[b]	0 (0)	10.8 (4)
Remission–relapse[c]	47.2 (17)	67.6 (25)
Withdrawal	8.3 (3)	8.1 (3)

[a] Values are percentage (number) unless otherwise indicated.
[b] 24 weeks after treatment discontinuation.
[c] Temporarily viral negative but viral positive again 24 weeks after treatment.

In the base-case, we performed analyses for two cohorts: (1) patients similar to all those enrolled in the trial and (2) the subgroup of patients with genotype 1b and a high viral load. High viral load was defined as a viral titer exceeding 100k copies/ml by the RT-PCR assay and 1 Meq/ml by the branched DNA assay. The subgroup of patients with genotype 1b and high viral load comprised 34% of the study population.

3. Decision analytic model

Our updated Markov simulation model consisted of 13 health states: viral positive and negative mild chronic hepatitis, viral positive and negative moderate chronic hepatitis, viral positive and negative compensated cirrhosis, decompensated cirrhosis (ascites, first year or subsequent years following hepatic encephalopathy, first year or subsequent years following variceal hemorrhage), hepatocellular carcinoma, and the dead state.

For cohorts of hypothetically identical patients that matched the mean age and the initial distribution of liver histology of the clinical trial population, we applied the viral responses observed in the trial to our model to estimate the subsequent long-term prognosis. The Markov model simulated the prognosis of each treatment group by tracking each cohort as they moved through alternative states of disease defined by clinical and histological descriptors.

Table 2
Health states and annual probability of disease progression

Initial health state	Subsequent health state	
Mild hepatitis	Spontaneous remission	0.002[a]
	Moderate hepatitis	0.041[a]
Moderate hepatitis	Cirrhosis	0.073[a]
	Heptocellular carcinoma	0.030[b]
Cirrhosis	Ascites	0.025[a]
	Variceal hemorrhage	0.011[a]
	Hepatic encephalopathy	0.004[a]
	Heptocellular carcinoma	0.079[b]
Ascites	Death	0.110[a]
	Heptocellular carcinoma	0.079[b]
Variceal hemorrhage	Death, first year	0.400[a]
	Death, subsequent year	0.130[a]
	Heptocellular carcinoma	0.079[b]
Hepatic encephalopathy	Death, first year	0.680[a]
	Death, subsequent year	0.400[a]
	Heptocellular carcinoma	0.079[b]
Heptocellular carcinoma	Death	0.300[c]

[a] Bennett et al. [11].
[b] Yoshida et al. [7].
[c] Oka et al. [64].

Table 3
Health-related quality of life adjustments health state QOL weight[a]

Health state	QOL weight[a]
Mild hepatitis	
Viral positive	0.87
Viral negative	0.92
Moderate hepatitis	
Viral positive	0.80
Viral negative	0.84
Cirrhosis	
Viral positive or negative	0.65
Ascites	0.52
Hepatic encephalopathy	0.40
Variceal hemorrhage	0.33
Hepatocellular carcinoma	0.38
Interferon therapy	0.97
Combination therapy	0.94
Abortion	−1 week

[a] QOL: quality of life.

Time was represented by annual cycles during which patients remained in the same histological or clinical state, died from liver disease, or died from other causes based on gender and attained age (Table 2). The computer simulation continued until all patients died.

As would likely occur in clinical practice in Japan, we continued treatment in patients who remained viral positive after 12 weeks of interferon alone or combination therapy, as opposed to practice in the US where treatment would be discontinued. By recording the proportion of the cohort remaining alive and their medical costs for each year, the simulation estimated the average life expectancy and lifetime cost associated with each treatment. Simulations and analyses were performed with Decision Maker 7.0 (Pratt Medical Group, Boston).

To reflect the morbidity associated with some states of disease, we also adjusted life expectancy for quality of life on a scale from 0 (death) to 1 (perfect health), based on assessments by family practice doctors in Japan using a modified Delphi technique. These physicians received a description of the Markov model health states and an explanation of the time-trade off and standard reference gamble techniques. They were then asked to assess the utilities for each health state. Patients who were alive but in less desirable states of health were not given full credit for each year lived and instead received only partial credit (e.g. 0.65 quality-adjusted year or 7.8 quality-adjusted months for living 1 year with cirrhosis) (Table 3).

Because ribavirin has been shown to be teratogenic in animal studies, we decreased quality of life by 1 week for patients undergoing an elective abortion for an unplanned pregnancy during ribavirin treatment. For antiviral treatment, combination therapy was assumed to have twice the negative impact on quality of life as interferon alone.

4. Data sources

4.1. Likelihood of events

The annual likelihood of transition from one health state to another was estimated from published studies that we judged to be the best currently available (Table 2).

4.2. Cost

Because of differences in the health insurance system in Japan compared with other countries, direct resource consumption in Japan is difficult to estimate. We applied reimbursement from health insurance data to estimate the annual cost of each health state (Table 4). For outpatient care costs associated with mild chronic hepatitis, moderate chronic hepatitis and compensated cirrhosis, we estimated resource utilization for office visits and treatment according to expert opinion and guidelines from the Japan Society of Hepatology.

For the decompensated cirrhosis and hepatocellular carcinoma states of health, we surveyed actual reimbursement data for patients at Yamaguchi University Hospital and obtained average annual costs including hospital admissions and subsequent office visits. These estimated costs included periodic screening tests for hepatocellular carcinoma with tumor markers, abdominal ultrasonography and computer tomography as performed widely in Japan because of the effectiveness of screening for high risk patients.

We assumed that patients treated with either combination therapy or interferon alone would be admitted to the hospital for a month and would visit the hospital three times a week

Table 4
Cost data

	Total	Admission	Outpatient
Cost of antiviral treatment (Japanese yen)			
Mild chronic hepatitis			
Interferon only	1,626,000	978,000	648,000
Combination therapy	2,228,000	1,122,000	1,107,000
Moderate chronic hepatitis			
Interferon only	1,710,000	978,0007	732,000
Combination therapy	2,305,000	1,121,000	1,183,000
Annual cost of care for health states (Japanese yen)			
Mild hepatitis			
Viral positive	16,500		16,500
Viral negative	6,980		6,980
Moderate hepatitis			
Viral positive	183,000		183,000
Viral negative	76,000		76,000
Cirrhosis			
Viral positive or negative	267,000		267,000
Decompensated cirrhosis			
With ascites	1,156,000	730,000	426,000
With hepatic encephalopathy	1,050,000	624,000	426,000
With variceal hemorrhage	1,557,000	1,131,000	426,000
Hepatocellular carcinoma	1,326,000	1,009,000	317,000

Interferon: interferon alpha-2b and costs ¥1784 per mega unit; Combination therapy: interferon alpha-2b and ribavirin with ribavirin costs: ¥937 per capsule and includes costs for contraception and accidental pregnancy.

after discharge until the end of treatment. Drug dosage was as received during the trial and included discontinuation for adverse events. Ribavirin was recently approved by the Ministry of Health, Labor and Welfare in Japan and assigned a cost of ¥937 for one 200 mg pill based on insurance reimbursement.

As in the US study, we assumed that women younger than 50 years of age had a qualitative pregnancy test before beginning treatment and every month thereafter. We further assumed that ribavirin-treated women and men would use contraception with condoms (¥100 each based on the mid-range cost at local pharmacies) which would be used three times a week and would continue for 6 months after discontinuation of ribavirin. We assumed a 1.2% likelihood of pregnancy with condom contraception and assumed patients and their partners would elect to have an abortion at a cost of ¥30,000 including initial and follow-up office visits should they or their partner become pregnant [14]. Finally, the analysis took the insurance system perspective and excluded indirect or time costs (e.g. time lost from work or nonmedical costs).

4.3. Outcome measures and threshold for "cost-effectiveness"

Summing all of the costs, annual survival, quality-adjusted survival for each treatment strategy yielded the average expected lifetime costs, life expectancy, and quality-adjusted life expectancy associated with that treatment. As recommended, survival and costs were discounted at an annual 3% rate, but a discount rate of 5% was also applied to permit comparison to previously published studies.

The incremental cost-effectiveness ratio of combination therapy was calculated as the additional cost divided by the increase in life expectancy compared with interferon alone.

Most well-accepted medical interventions have incremental cost-effectiveness ratio falling below ¥6.0 million per discounted quality-adjusted life year gained (US$ 50,000 at ¥120 for a US dollar). For incremental cost-effectiveness ratios falling below this specific threshold amount, we considered the intervention to be "cost-effective."

4.4. Treatment response

Because viral negativity correlates better with long-term response than normalization of alanine aminotransferase (ALT), we used a viral negative response 24 weeks after treatment discontinuation as the primary endpoint. The results of the trial are shown in Table 1.

4.5. Histology data

To match the histological states defined by our model, cirrhosis required an International Classification System fibrosis score of 4, same as the Knodell score [15,16]. In the absence of cirrhosis, we defined mild chronic hepatitis as a fibrosis score of 0–1 (no fibrosis to fibrous portal expansion), moderate chronic hepatitis as a fibrosis score of 2–3 (bridging fibrosis: portal–portal or portal–central linkage), respectively. Bridging fibrosis could not be considered a distinct state of health because of insufficient data to estimate the likelihood of progression. However, patients with bridging fibrosis would have a poorer prognosis than those with moderate hepatitis [17,18], and because our model included patients with bridging fibrosis among those with moderate hepatitis, we thus assumed a better prognosis for these patients than most likely occurs. This assumption biased our analysis against antiviral therapy by underestimating disease progression, and because those treated with interferon alone are less likely to respond and more likely to progress, this assumption affects combination therapy more than interferon alone.

4.6. Assumptions of the model

1. We assumed that patients who did not have a sustained viral response after treatment would be managed with regular office visits and the periodic screening program as recommended by the guidelines of the Japan Society of Hepatology.
2. We assumed that patients who did not have a sustained viral response after treatment and whose disease was felt to be highly active received Strong Neo Minophagen C® (glycyrrizin) and ursodeoxychoric acid. As long-term

efficacy of glycyrrizin in preventing liver carcinogenesis in chronic hepatitis has been reported by Arase et al. [19] and these medications have for years been quite commonly administered in Japan to patients with highly active chronic hepatitis, we assumed that their effect would be reflected in the baseline rate of occurrence of hepatocellular carcinoma. Therefore, only the costs of these medications were added to the model.

3. We assumed that the subsequent prognosis of patients who did not respond (non-responders) or who only temporarily responded (relapsers) to initial treatment would be identical to those who had never had any antiviral treatment at all except for those who responded temporarily and relapsed after antiviral treatment. These patients were assumed to have a prognosis between that of patients with complete remission and that of non-responders. For example, the annual transitional probability from chronic moderate hepatitis to compensated cirrhosis equaled 0.073 for non-responders and 0.065 (=0.073 × 0.890) for relapsers [20].
4. We assumed that the risk of occurrence of hepatocellular carcinoma would be reduced among patients in whom sustained or temporary viral eradication had been achieved by interferon therapy or combination therapy. From the results of a national surveillance program conducted in Japan (the Inhibition of Hepatocarcinogenesis by Interferon Therapy [IHIT] Study) [7], the relative risk was assigned a value of 0.197 among sustained virological responders and 0.631 among temporary responders. Our model did not consider biochemical responders without virological response.
5. We assumed that patients who lose HCV either spontaneously or from treatment would have a greatly reduced but non-zero likelihood of developing progressive liver disease compared with those who were not treated. For example, the annual likelihood of the progression from mild chronic hepatitis with sustained viral response to moderate chronic hepatitis was 0.0002.
6. We did not consider liver transplantation for hepatocellular carcinoma or decompensated liver cirrhosis, because it is not possible or appropriate for most patients in Japan.
7. Although the model incorporated quality of life decrements for possible adverse reactions from antiviral therapies, it did not consider any additional quality of life decrements for treatment discontinuation. The frequency of withdrawal, however, from combination therapy and from interferon monotherapy was nearly equal.

Table 5
Results

	Interferon alone	Combination therapy	
(a) Base-case analysis[a]: all patients			
Progression			
Developed cirrhosis	40%	26%	33%[a]
Developed HCC	48%	34%	28%[a]
Died from liver disease	56%	40%	28%[a]
Lifetime costs			
Annual discount rate			
0%	6,734,000	6,325,000	−409,000[b]
3%	4,992,000	4,871,000	−121,000[b]
5%	4,296,000	4,301,000	5,000[c]
Quality-adjusted life years			
Annual discount rate			
0%	17.10	20.20	3.10[c]
3%	11.73	13.37	1.64[c]
5%	9.57	10.71	1.14[c]
Incremental cost-effectiveness ratio of combination therapy vs. interferon alone			
Annual discount rate			
0%		D	
3%		D	
5%		4,530	
(b) Subgroup analysis: subgroup with genotype 1b and high viral load			
Progression			
Developed cirrhosis	43%	36%	18%[b]
Developed HCC	52%	44%	16%[b]
Died from liver disease	61%	51%	16%[b]
Lifetime costs			
Annual discount rate			
0%	7,075,000	7,095,000	21,000[c]
3%	5,210,000	5,390,000	181,000[c]
5%	4,465,000	4,717,000	252,000[c]
Quality-adjusted life years			
Annual discount rate			
0%	16.17	18.02	1.85[c]
3%	11.26	12.22	0.97[c]
5%	9.25	9.91	0.67[c]
Incremental cost-effectiveness ratio of combination therapy vs. interferon alone			
Annual discount rate			
0%		11,000	
3%		187,000	
5%		377,000	

D: combination therapy dominated interferon therapy alone by extending survival and reducing costs.
[a] Relative risk reduction.
[b] Incremental cost.
[c] Incremental effectiveness.

5. Results

5.1. Base-case analysis

Model projections suggested that retreatment for initial interferon relapsers or non-responders with combination therapy decreased the lifetime risk of cirrhosis, hepatocellular carcinoma, or liver-related death by 28–33% compared with interferon alone (Table 5a). The cost of combination therapy using actual dosages administered in the trial would be ¥0.6 million more than interferon alone (Table 4). However, when considering only the undiscounted cost of future liver disease complications, combination therapy would

reduce lifetime undiscounted hepatitis C complication costs by ¥1.0 million because of its higher efficacy. These future savings completely offset the higher initial drug costs when compared with interferon alone. Therefore, over a lifetime time horizon, combination treatment was cost saving and would increase life expectancy by 3.1 quality-adjusted life years. Although discounting at a 3% per year rate reduced the benefit of future economic savings and of improved survival, combination therapy still improved prognosis by 1.65 discounted quality-adjusted years and still cost less than interferon alone. For an annual discount rate of 5%, the incremental cost-effectiveness ratio of combination therapy became ¥4 thousand per quality-adjusted year gained.

For the subgroup of patients with genotype 1b and high viral load who also had either relapsed or not responded, 24 weeks of combination therapy reduced the lifetime incidence of cirrhosis, hepatocellular carcinoma or mortality from liver disease by 16–18% compared to interferon alone (Table 5b). Without discounting, combination therapy increased lifetime costs by ¥20 thousand and increased life expectancy by 1.8 quality-adjusted life years compared with interferon alone, for an incremental cost-effectiveness ratio of ¥11 thousand per quality-adjusted life year gained. With annual discounting rates of 3 and 5%, the incremental cost-effectiveness ratio of combination therapy rose to ¥0.19 and 0.38 million per quality-adjusted life year gained, respectively, but still fell well within the cost-effectiveness range of other widely accepted medical interventions. Thus, these analyses suggest that combination therapy should be considered to be cost saving or cost-effective for a ribavirin cost of ¥973 per capsule.

To examine the robustness of these results, we performed additional incremental cost-effectiveness analyses for subgroups defined by gender, histology, genotype and viral load using the observed sustained virological responses for these subgroups (Table 6). Combination treatment for individuals with moderate hepatitis provided more benefit (in quality-adjusted life years) and was also more cost-effective than treatment for individuals with mild hepatitis because patients with moderate hepatitis are more likely to develop hepatic complications sooner. Also as expected, the effectiveness and cost-effectiveness of combination therapy for the subgroups with genotype other than 1b or with low viral load were superior to those for genotype 1b or for high viral load, respectively.

5.2. Sensitivity analysis

The results of the analysis changed little when the values of each model parameter were varied over a wide range. The exceptions included the annual probability of liver disease progression, the probability of sustained response, the cost of ribavirin and age at treatment. Even, however, in the worst case scenario where the progression rate and sustained viral negative response were assumed to be one-third of the baseline rates, the incremental cost-effectiveness ratio of combination therapy still fell well within the cost-effectiveness range of other widely accepted medical interventions. This was also true for the subgroup with genotype 1b and high viral load (Table 7).

Fig. 1 shows the sensitivity analysis of varying the cost of ribavirin. For an annual 3% discount rate, combination therapy for all patients (including some with genotype 1b and high viral load) was cost saving for ribavirin costs below ¥1144. Even for ribavirin costs up to ¥17,900 (19 times the baseline cost), the incremental cost-effectiveness ratio of combination therapy still fell below ¥6.0 million and would be considered "cost-effective." For the subgroup of patients with genotype 1b and high viral load, ribavirin costs below ¥10,540 yielded incremental cost-effectiveness ratio for combination therapy that fell within the range considered to be "cost-effective."

As expected, the survival benefit and cost-effectiveness of combination therapy for chronic hepatitis C decreased

Table 6
Subgroup analyses

Subgroup	Probability of sustained viral negative		Discounted (3%) increase in QALYs	Discounted incremental C/E
	Interferon only	Combination therapy		
Male	0.13	0.36	1.42	D
Female	0.00	0.35	2.34	D
Histology				
Mild hepatitis	0.13	0.33	0.60	564,000
Moderate hepatitis	0.07	0.35	2.36	D
Genotype				
1b	0.02	0.19	1.33	25,000
Other than 1b	0.24	0.74	1.75	D
Viral load[a]				
High	0.06	0.23	1.28	26,000
Low	0.21	0.73	2.18	D

C/E: cost-effectiveness ratio; D: combination therapy is dominates interferon therapy alone: lifetime cost saving.

[a] Patients with a viral titer exceeding 100k copies/ml by the RT-PCR assay or 1 Meq/ml by b-DNA assay were classified as having a high viral load.

Table 7
Effects of varying baseline assumptions

Assumption	Increase of QALYs with combination therapy	Incremental cost-effectiveness ratio of combination therapy (yen per QALYs gained)		
		Not discounted	Discounted (3%)	Discounted (5%)
For all patients				
Progression rate[a]				
1/2 baseline	2.05	D*	D	118,000
1/3 baseline	1.55	D	3,800	236,000
Sustained viral negative response rate				
1/2 baseline	1.68	27,000	224,000	434,000
1/3 baseline	1.20	164,000	482,000	810,000
Progression rate and sustained viral negative response rate				
1/2 baseline	1.11	48,000	414,000	792,000
1/3 baseline	0.60	370,000	1,150,000	1,940,000
For subgroup with genotype 1b high virus load				
Progression rate				
1/2 baseline	1.20	38,000	377,000	729,000
1/3 baseline	0.90	95,000	578,000	1,067,000
Sustained viral negative response rate				
1/2 baseline	1.08	250,000	624,000	1,006,000
1/3 baseline	0.83	428,000	951,000	1,481,000
Progression rate and sustained viral negative response rate				
1/2 baseline	0.71	395,000	1,063,000	1,747,000
1/3 baseline	0.40	936,000	2,246,000	3,598,000

D*: Combination therapy dominated interferon therapy alone by extending survival and reducing lifetime costs.
[a] Simultaneously reducing the annual probabilities of histologic progression from mild to moderate hepatitis and from moderate hepatitis to compensated cirrhosis, developing hepatocellular carcinoma from moderate hepatitis or from cirrhosis and cirrhotic decompensation.

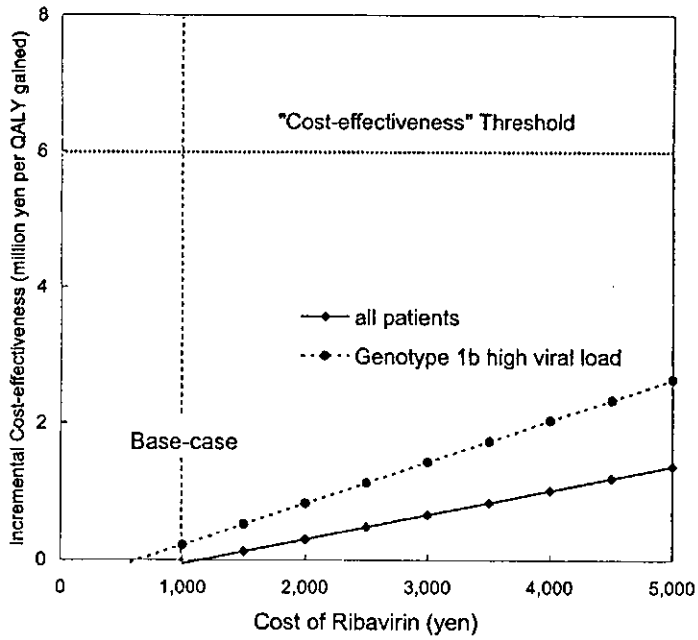

Fig. 1. Sensitivity analysis of the effects of varying the cost of ribavirin with a 3% annual discount rate. Each of the lines represents the incremental cost-effectiveness of combination therapy compared to interferon. The vertical line indicates the base-case cost of ribavirin. The horizontal line at ¥6 million indicates the threshold incremental cost-effectiveness ratio. Values falling below this line can be considered to be "cost-effective" when compared to the incremental cost-effectiveness of widely accepted medical interventions. Even if the cost of ribavirin were five times more than the base-case, the incremental cost-effectiveness ratio of combination therapy still fell well within the range of other widely accepted medical intervention and thus could be considered to be "cost-effective".

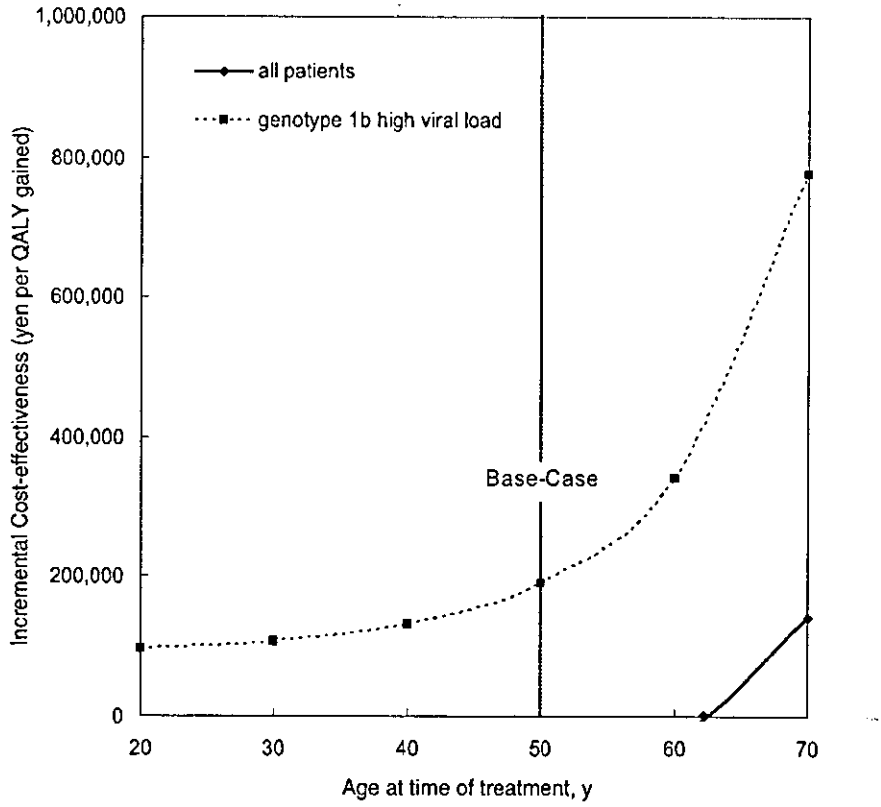

Fig. 2. Sensitivity analysis of the effects of age at start of treatment for chronic hepatitis C on the discounted (3%) incremental cost-effectiveness ratio. The vertical line indicates the base-case age of treatment. The incremental cost-effectiveness of combination therapy for all patient groups was superior to that of interferon monotherapy and the incremental cost-effectiveness ratio was less than 0 until age 63 years.

with age at start of treatment and the incremental cost-effectiveness ratio thus also increased (Fig. 2). At an annual 3% discount rate, combination therapy for all patients up to 63 years old was cost saving and even in the subgroup of patients with genotype 1b and high viral load aged up to 70 years, the incremental cost-effectiveness ratio fell below ¥0.8 million per quality-adjusted life year and therapy was considered "cost-effective".

6. Discussion

Chronic hepatitis C infection rarely resolves spontaneously [21]. Persistent infection with hepatitis C virus can lead to liver cirrhosis after 20–30 years and to hepatocellular carcinoma after 30–40 years [22]. Interferon therapy has been broadly accepted since 1992 in Japan, and although some patients have a sustained viral response, most have either a transient response (relapsers) or no response (non-responders). For patients with genotype 1b, which comprises about 70% of hepatitis C patients in Japan, sustained viral response occurs at best in 15% [23–25].

Recent studies in the US and Europe have found that combination therapy with interferon alpha-2b and ribavirin for relapsers and non-responders was more effective than interferon therapy alone, so it has become the standard therapy in those countries. From 1998 to 2000, an analogous randomized trial was conducted in Japan and found clinical results similar to those observed outside of Japan [26].

Interferon has been shown to be "cost-effective," but drug costs for ribavirin with interferon alpha-2b exceed those for interferon therapy alone by about ¥0.6 million. Moreover, despite the remarkable recent expansion of knowledge of the consequences of chronic hepatitis C virus infection and of the short and intermediate-term benefits of successful treatment, many uncertainties remain. These include an accurate understanding of the natural history of untreated patients and of the long-term benefit of treatment. These uncertainties raise questions about the cost-effectiveness of combination treatment. Therefore, we conducted a cost-effectiveness analysis to estimate lifelong costs and clinical outcomes using the results of the recent study in Japan.

While a randomized controlled study targeting endpoints such as long-term survival and decreases in liver disease complications would be ideal, such a trial is not available. Nonetheless, antiviral treatment for chronic hepatitis C infection has been shown to decrease the risk for development of hepatocellular carcinoma and to improve viral eradication, hepatic histology, and survival in clinical studies. In the absence of a long-term randomized trial, computer simulation analyses such as the one presented here can help estimate lifelong outcomes resulting from antiviral treatment.

Although a number of studies have reported the cost-effectiveness of combination therapy in the US and Europe [27–34], our study was stimulated by a number of differences between Japan and the US or other countries in the management of patients with chronic hepatitis and in the characteristics of the target patients. Firstly, medication with glycyrrhizin or ursodeoxychoric acid is common for chronic hepatitis in Japan but is not standard in other countries. Secondly, in Japan, the mortality rate from hepatocellular carcinoma is the highest of the seven major industrialized countries [1] and periodic screening for hepatocellular carcinoma in cases of chronic hepatitis or cirrhosis is recommended [13,35], although its cost-effectiveness remains a contentious issue because of the uncertain improvement in survival. It is therefore not regularly recommended as the standard or may be performed at longer intervals in the US and Europe than in Japan [36,37]. Thirdly, the standard therapeutic approach to decompensated liver cirrhosis and hepatocellular carcinoma in Japan does not include liver transplantation. Fourthly, the mean age of patients with chronic hepatitis C enrolled in the randomized trial was 50 years, older than in the US, where the mean age ranged from 42 to 44 years [29,32].

Our findings suggest that combination therapy for relapsers or non-responders to initial interferon therapy should decrease the lifetime risk of progression from chronic hepatitis to cirrhosis and hepatocellular carcinoma by 28–33% compared with interferon therapy alone. In addition, from an economic standpoint, combination therapy was either cost saving or "cost-effective" falling within the cost-effectiveness range of other well-accepted medical interventions. Despite wide variation in the values of model variables in sensitivity analysis, the cost-effectiveness results remained robust.

However, several limitations exist. First, the trial only examined virological response at 24 weeks after treatment discontinuation and did not capture long-term hard clinical outcomes such as liver disease mortality. However, several studies support the hypothesis that eradication of hepatitis C virus should improve prognosis compared to non-responders [38–42]. Additional studies suggest histological improvement and decreased risk of hepatocellular carcinoma following antiviral treatment [43–52].Nonetheless, a randomized trial showing improvement of hard clinical endpoints such as survival or decompensated liver disease has not been performed.

Second, the natural history of hepatitis C remains uncertain. Our base-case model has been applied previously for analyses in the US and Europe [11,32,33,53–55]. For comparison, we extrapolated the results of five prospective studies of transfusion-associated non-A, non-B hepatitis from the time of onset of disease [56] and assumed a linear rate of progression to cirrhosis yielding a 20-year cumulative incidence of cirrhosis of 24%, with a range from 14 to 45%. Assuming that about 30% of those with posttransfusion hepatitis resolve their hepatitis C infection spontaneously, the computer simulation model estimated a 19% 20-year incidence of cirrhosis which falls within this range. Because it is lower, the model may underestimate liver disease complications, and this may bias our results against combination therapy.

Third, the viral response data used in the model are from a randomized trial and may not represent the true effectiveness of treatment in general practice. However, the trials done in US and Europe showed a similar viral response rate. For example, Davis et al. reported that 49% of relapsers to initial interferon had a sustained viral negative response 24 weeks after combination therapy, but only 5% of those retreated with interferon group achieved a sustained viral response [26]. Cheng et al. [57] and Cummings et al. [58] also performed a meta-analysis of the effect of combination therapy in patients previously nonresponsive to interferon. Their results showed that the pooled sustained virological response rates for combination therapy with interferon alpha were 13 and 14%, respectively. The patients enrolled in the study of Toyoda et al. [10] included both relapsers and non-responders for initial interferon therapy, and the virological response rate fell between the results observed by Davis and the results of these meta-analyses. Even if the sustained viral response rate of combination therapy were assumed to be one-third of that observed in the trial, lower than that found in the meta-analyses, the incremental cost-effectiveness ratio would still rise only to ¥482,000 per QALY gained (discounted at 3% per year) in sensitivity analysis, and therefore would still be "cost-effective" (Table 7).

Fourth, it was demonstrated that interferon therapy for chronic hepatitis C reduces the rate of development of hepatocellular carcinoma in both sustained virological and biochemical responders, and even in transient biochemical responders [59]. Changes in the amino acid sequence of the major clone after interferon treatment may be related to the decrease in alanine aminotransferase activity in biochemical responders even in the presence of HCV RNA [60]. In the present analysis, the biological effect of interferon was incorporated in the reduction of the relative risk of occurrence of hepatocellular carcinoma using the results of an IHIT study [7] which showed the reduction of risk among both virological and biochemical responders. However, because of the lack of data, our model incorporated the results of only sustained virological response or temporary response, which underestimated the effect from both therapies and may have biased our results in favor of combination therapy.

Fifth, the recent improvement in the management of esophageal varices, including universal screening endoscopy followed by prophylactic therapy such as sclerotherapy or ligation, may have influenced the probability of variceal hemorrhage in cirrhotic patients. Although we could not obtain any precise figure for the annual rate of variceal hemorrhagic in Japan from literature review, even if the annual hemorrhagic rate were assumed to be one-fifth of the baseline probability, the incremental cost-effectiveness ratio changes by less than two percent of the original and the

results remain good, with combination therapy remaining cost-effective or cost saving in sensitivity analysis.

Sixth, although we divided the mortality rate in variceal hemorrhage and hepatic encephalopathy between the first year and the subsequent years according to the original model [11], we used the averaged annual costs of hospitalization and office visits subsequent to the first event of complication in patients experiencing such complications. As it is common to perform periodic screening for varices followed by preventive procedure if the risk of bleeding is high, the frequency of variceal bleeding has reduced, and we were unable to obtain the annual cost after dividing between the first and subsequent years. Our data showed that the frequency of hospitalization from encephalopathy in subsequent years was the same as in the first year [13], and we therefore estimated that the annual cost of encephalopathy in subsequent years was the same as in the first year. Accordingly, we performed sensitivity analysis of the cost of variceal hemorrhage and confirmed that the influence was so small that the result was little changed.

Finally, our quality of life estimates were from a panel of general physicians. Current guidelines recommend that such assessments be done in the general population [61]. However, studies suggest that community-based estimates of quality of life are lower than those of physicians or those of patients with the disease of interest. Therefore, if quality of life estimates were obtained from the general population and were lower than those provided by our physician panel, the quality-life benefit and the incremental cost-effectiveness of combination therapy would improve.

Long-term interferon monotherapy offers a plausible therapeutic option to deal with patients with chronic hepatitis C who are predicted to be refractory to the standard therapy [62,63]. Wong et al. report that, in the initial treatment of chronic hepatitis C, 24 or 48 weeks of combination therapy with interferon and ribavirin prolongs life and is cost-effective when compared with 48 weeks of interferon monotherapy. Although there were some differences in the type and dose of interferon and the characteristics of the patients, their results allow optimism about the cost-effectiveness of 48-week or longer combination therapy in relapsers or non-responders to previous interferon monotherapy [32].

Despite these limitations, the results are similar to those reported in the US and Sweden. Even when accounting for differences in medical practice in Japan and in costs based on the Japanese health insurance system, our study still suggests that combination therapy should be cost saving or at least cost-effective, in part because of the higher progression rate to hepatocellular carcinoma reported in Japan than in other countries.

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7. Conclusion

For patients similar to those enrolled in the interferon alpha-2b and ribavirin trial, combination therapy should be cost saving or cost-effective with the higher drug treatment costs nearly completely offset by future savings through the reduction of future liver complications resulting from hepatitis C infection. For patients who had relapsed or not responded to prior interferon therapy, interferon alpha-2b plus ribavirin should reduce future complications from hepatitis C, prolong life and be cost-effective in Japan.

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Interferon therapy as chemoprevention of hepatocarcinogenesis in patients with chronic hepatitis C

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Hepatocellular carcinoma (HCC) is currently a very common malignancy and its incidence is increasing, both in Japan and the USA. Persistent hepatitis C virus (HCV) infection is a major risk factor for the development of HCC. A number of large-scale retrospective cohort studies have demonstrated that interferon therapy reduces the incidence of HCC not only in sustained virological responders but also in transient biochemical responders without the elimination of HCV. We also demonstrated that retreatment with interferon at certain intervals reduced the incidence of HCC in patients with chronic hepatitis C, even if eradication of HCV was not achieved by retreatment. We cannot, however, explain how a transient normalization of serum alanine aminotransferase levels induced by a maximum 6 months of interferon treatment reduces the incidence of HCC during the progression of chronic hepatitis to cirrhosis or HCC, which requires dozens of years. In this article, we discuss how interferon treatment might reduce the incidence of HCC even in transient biochemical responders, especially in view of antiproliferative or antioxidative activity of interferon-α.

Keywords: cell cycle, hepatocellular carcinoma, MEK/ERK pathway, oxidative stress

Introduction

Hepatocellular carcinoma (HCC) is currently a very common malignancy and its incidence is increasing, both in Japan and the USA. Persistent hepatitis C virus (HCV) infection is a major risk factor for the development of HCC. Approximately 80% of Japanese HCC patients are also diagnosed with HCV-associated cirrhosis or chronic hepatitis C. It has also been shown that the risk of HCC increases with the degree of liver fibrosis.[1] Thus, HCV patients are a high-risk group for the development of HCC, and inhibition of hepatocarcinogenesis remains a crucial issue in treating patients with HCV-related chronic liver disease.

A number of large-scale, retrospective, cohort studies conducted in Japan have demonstrated that interferon therapy reduces the incidence of HCC, not only in sustained virological responders but also in transient biochemical responders, without eliminating HCV (Table 1).[1–6] On the other hand, the incidence of HCC has been shown to increase 5 years or more after interferon therapy in transient biochemical responders, suggesting that, in this population, interferon's effects are time sensitive.[7] In this respect, we demonstrated that re-treatment with interferon at certain intervals reduced the incidence of HCC in patients with chronic hepatitis C, even if eradication of HCV was not achieved by re-treatment.[8] It seems plausible that eradicating HCV would result in a reduced incidence of HCC. We cannot, however, explain how a transient normalization of serum alanine aminotransferase (ALT) levels, induced by a maximum 6 months of interferon treatment, reduces the incidence of HCC during the progression of chronic hepatitis to cirrhosis or HCC, which requires dozens of years. We discuss herein how interferon treatment might reduce the incidence of HCC even in transient biochemical responders.

Hypercarcinogenic condition in HCV-associated chronic hepatitis or liver cirrhosis

We need to find out the molecular mechanism of hepatocarcinogenesis in HCV infection, which remains unclear, to understand how interferon therapy reduces the incidence of HCC in transient biochemical responders. In persistent HCV infection, hepatocarcinogenesis is closely related to the presence of chronic hepatitis with advanced liver fibrosis or liver cirrhosis, which represents a precancerous state accompanied by increased DNA synthesis. In fact, it has been shown in a prospective manner that cirrhotic patients with high liver cell proliferative activity, estimated by proliferating cell nuclear antigen staining, are more likely to develop HCC as compared with those without it.[9] It has been suggested that HCV core protein enhances cell proliferation via activation of mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK).[10] Activation of MAPK/ERK has also been reported in human HCC tissues.[11] The mitogen-activated protein kinase kinase (MEK)/ERK signalling pathway is fundamental in controlling cell development, proliferation and the cell cycle.[12,13] There is clear evidence that the MEK/ERK pathway is essential for the activation of the molecular events regulating cell cycle progression, such as degradation of

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Table 1. Reduction in the development of hepatocellular carcinoma in sustained virological responders and transient biochemical responders: characteristics of Japanese selected studies

Reference	Number of patients[a]	Observation period (years)	Estimated cumulative incidence of HCC at the 5th year (%)			Risk ratio[b]	
			SVR	TBR	NR	SVR	TBR
Kasahara *et al.*[2]	1022	3.1 ± 12.9	4.3	4.7	21.4	0.13	NA
Imai *et al.*[3]	563	4.0	0.9[c]	6.1[c]	12.8[c]	0.06	0.51
Ikeda *et al.*[4]	1643	5.1 (0.1–11.3)	1.4	1.9	2.9	0.32[d]	
Yoshida *et al.*[1]	2890	4.4	NA	NA	NA	0.25	0.27[e]
Tanaka *et al.*[5]	738	4.8 ± 1.2	1.2	3.7	10.0	0.16	0.27
Okanoue *et al.*[6]	1370	5.6	NA	NA	NA	0.10	0.55

SVR, sustained virological responders; TBR, transient biochemical responders; NR, non-responders; HCC, hepatocellular carcinoma; NA, not assessed.
[a]These numbers include untreated patients except for references 2 and 6.
[b]Adjusted risk ratios for development of HCC were calculated compared with untreated patients in references 1, 3, 4 and 5, and with non-responders in references 2 and 6.
[c]These figures represent the 4 year incidence of HCC.
[d]This risk ratio was for the groups that responded; these included SVR and TBR.
[e]This risk ratio was for the patients who had normal serum ALT levels and were positive for HCV RNA.

mitotic inhibitors ($p21^{Waf1}$ and $p27^{Kip1}$) and the induction of the cyclin–cyclin dependent kinase (Cdk) complexes.[14,15]

A recent study has revealed that protein levels and kinase activities of cyclin D1, Cdk4, cyclin E, cyclin A and Wee1 are significantly elevated in HCV-associated HCC compared with surrounding cirrhotic tissues.[16] More importantly, these kinases are already activated in cirrhosis before the development of HCC, compared with normal liver tissues, suggesting that this activation is an early event in hepatocarcinogenesis and that HCV-associated cirrhosis is a pre-cancerous condition. Thus, in a chronic hepatitis state, the cell cycle progresses and hepatocytes divide rapidly. As a result, irregular regeneration is bound to happen, accelerating genomic instability. Of course, the MEK/ERK pathway is not the only pathway potentially leading to the development of HCC. For, instance, there is considerable interest in the wnt/β-catenin pathway, specifically in the context of HCV-associated HCC.[17] The complexity of all the biochemical pathways implicated in HCC development is well described in a broad review on the genetics of HCC.[18]

Another scenario for hepatocarcinogenesis in HCV infection is the involvement of oxidative stress, which can produce genetic mutations as well as gross chromosomal alterations. HCV core protein has been shown to produce reactive oxygen species (ROS) derived from mitochondria in inducible cell culture systems.[19] A positive feedback effect of ROS on mitochondrial ROS generation further sensitizes cells to other oxidative insults, which may finally cause both mitochondrial and chromosomal DNA damage. In a transgenic mouse model for HCV-associated hepatocarcinogenesis, it is also demonstrated that HCV core protein causes a state of oxidative stress in the absence of inflammation.[20]

Although these results suggest the direct induction of oxidative stress by HCV proteins, the consequences of impaired mitochondrial function and abnormal ROS generation would be exacerbated by the immune-mediated inflammatory process present in patients with chronic hepatitis C, and the additional oxidant load it would present to the HCV-infected liver. Continuous ROS generation is likely to cause 8-hydroxy-2′-deoxyguanosine (8-OHdG) to accumulate in DNA. Kato *et al.*[21] reported that lowering levels of 8-OHdG by phlebotomy potentially decreased the risk of hepatocarcinogenesis in patients with chronic hepatitis C. According to them, hepatic 8-OHdG levels decreased significantly in the short-term (initial iron reduction phase) and were almost completely normalized by the end of therapy (6 years later) by keeping a state of mild iron deficiency, defined by either <10 μg/L serum ferritin and/or 11 g/dL blood haemoglobin concentration. Thus, oxidative stress appears to be responsible, in part, for the development of HCV-associated HCC.

Clinical evidence suggesting the anti-hepatocarcinogenic effect of interferon in patients with HCV-associated chronic liver disease

As mentioned above, chronic hepatitis C with advanced liver fibrosis or liver cirrhosis is hypercarcinogenic at the molecular level. This is supported clinically in Japan by the high annual incidences of HCC in non-treated chronic hepatitis C patients with F3 staging[22] of liver fibrosis (2%–3%) and those with liver cirrhosis (6%–7%). The rate of recurrence of HCC after complete surgical resection is much higher than these figures, suggesting that the post-operative state is more hypercarcinogenic.[23]

A recent randomized study has shown that interferon-β prevents the recurrence of HCC after complete resection or ablation of the primary tumour in patients with HCV-associated cirrhosis.[24] This inhibitory effect on HCC recurrence by interferon was not associated with biochemical and virological improvement. Therefore, these results clearly suggest that interferon acts as an anti-hepatocarcinogenic agent in patients with HCV-associated chronic liver diseases.

Molecular mechanism by which interferon prevents hepatocarcinogenesis in patients with chronic hepatitis C

Taking into account the molecular mechanisms underlying the hypercarcinogenic condition in HCV infection, we focused on the mechanism responsible for the antiproliferative or antioxidative activity of interferon-α. The regulatory signals triggered by interferon-α are transduced to the nucleus through the Janus tyrosine kinase/signal

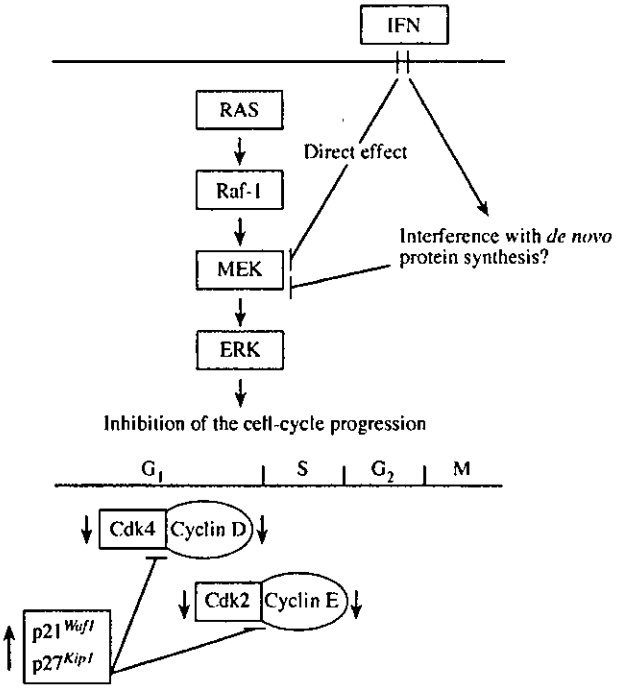

Figure 1. A schematic diagram illustrating the proposed mechanisms of action by which interferon might inhibit carcinogensis through the regulation of the MEK/ERK pathway. Interferon has been shown to inhibit MEK/ERK function without affecting Ras and Raf-1 activity. Mechanisms by which interferon regulates MEK phosphorylation may involve interference with *de novo* protein synthesis and/or regulation of a specific gene(s). Analysis of downstream events controlled by the MEK/ERK pathway showed reduced activity of Cdk2 and Cdk4, high levels of mitogenic inhibitors ($p21^{Waf1}$ and $p27^{Kip1}$), and decreased cyclin D and E expression. Cdk4 and Cdk2 are activated by binding to cyclin D and cyclin E, respectively. Cyclin D–Cdk4 complexes are required for G1 phase progression. Cyclin E–Cdk2 complexes are required for the G1/S transition. Cdk activity is curtailed by $p21^{Waf1}$ and $p27^{Kip1}$.

transducers of activation and transcription (Jak/STAT) pathway, whereby ligand-activated Jak kinases phosphorylate STAT proteins, which subsequently dimerize and migrate to the nucleus to regulate gene expression. Interferon-α was initially described as an antiviral cytokine able to inhibit viral replication, and thereafter additional properties of this multifunctional cytokine that can affect the growth, differentiation and function of many cell types were discovered. The cross-talk between the Jak/STAT and the MEK/ERK pathways was demonstrated by the observation that interferon-β can directly activate ERK, which associates with STAT1.[25] Romerio & Zella[26] demonstrated that treatment with interferon-α hindered the transition from G0/G1 to the S phase in purified primary CD4 cells stimulated with anti-CD3 and interleukin 2. This inhibitory effect of interferon-α was linked to the impairment of the MEK/ERK function without affecting Ras and Raf-1 activity. Their analysis of downstream events controlled by the MEK/ERK pathway showed reduced activity of Cdk2 and Cdk4, high levels of mitogenic inhibitors ($p21^{Waf1}$ and $p27^{Kip1}$), and decreased cyclin D and E expression (Figure 1). Interestingly, these downstream events inhibited by interferon-α have been shown to be activated in HCV-associated HCC or cirrhotic tissues as compared with normal liver tissues by another group.[16] In a number of different cellular systems it has been shown that inhibition of mitogenic induction of MEK and ERK results in impairment of cell-cycle progression and proliferation. Therefore, the inhibitory effect on MEK/ERK function by interferon may be one of the important mechanisms involved in anti-hepatocarcinogenic actions.

Another cell cycle analysis of G1-synchronized, interferon-α-treated HCC cell lines revealed a substantial delay in S-phase progression, but no alteration of G1/S-phase transition.[27] Reflecting the time course of S-phase accumulation, cell cycle-dependent induction of cyclin A and cyclin B was demonstrated to be impaired. The ability of interferon-α to interfere with cyclin A expression in HCC is noteworthy in view of the reported overexpression of cyclin A in ~40% of tumour tissues from HCC patients.[28] The mechanism by which interferon-α inhibits cell-cycle progression and proliferation may be influenced by the cell line systems analysed, but its variation, alternatively, reflects differences in the available spectrum of interferon-α-susceptible growth-relevant effector molecules because of specific oncogenic alterations present in the target cell.

Interferon-α has been shown to reduce intrarenal oxidative stress in rats with carbon tetrachloride-induced nephrotoxicity.[29] Another study revealed that interferon-α dose-dependently increased the protein levels of copper-, zinc- and manganese-dependent superoxide dismutase, as well as the enzyme activities of glutathione peroxidase, and decreased the lipid peroxidation product levels in oxidative-stressed rat hepatocytes.[30] As HCV RNA levels are usually decreased or undetectable, even though uncommonly unchanged, during interferon therapy in transient biochemical responders, such antioxidative actions of interferon may be amplified in a condition where oxidative stress is attenuated due to decreased HCV load. In fact, 2 months interferon therapy has been shown to decrease the serum lipid peroxidation products (thiobarbituric acid reactive substances) of hepatitis C patients, whose serum ALT levels fall to the normal range.[31]

Conclusions

Needless to say, eradication of HCV and normalization of the serum ALT level by interferon are the most important issues for chemoprevention of hepatocarcinogenesis in patients with chronic hepatitis C. However, the antiproliferative activity of interferon-α also seems to play a critical role in preventing chronic hepatitis C patients from developing HCC. Furthermore, interferon may have a direct antitumour effect on clinically undetectable HCC, since combination therapy with interferon-α and intraarterial 5-fluorouracil has been shown to be effective in reducing tumours in patients with HCC.[32] With respect to this issue, a very recent study demonstrated the integration of interferon-α/β signalling to p53 responses in tumour suppression, which resulted in enhancement of cancer cell apoptosis by interferon.[33] We need to ascertain whether the anti-proliferative action of interferon is actually elicited in transient biochemical responders, not in non-responders, and induces a normo- or hypocarcinogenic condition in those patients.

There is no strong clinical evidence linking the antioxidative action of interferon to the inhibition of HCC development in patients with chronic hepatitis C. Thus, further studies are required to determine how the antioxidative activity of interferon is involved in reducing the HCC incidence in HCV infection.

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