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Hepatology Research 28 (2004) 125–136
Hepatology Research
www.elsevier.com/locate/ihepcom

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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Received 27 March 2003; received in revised form 19 September 2003; accepted 10 November 2003

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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doi:10.1016/j.hepres.2003.11.002

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].

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.

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.

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.

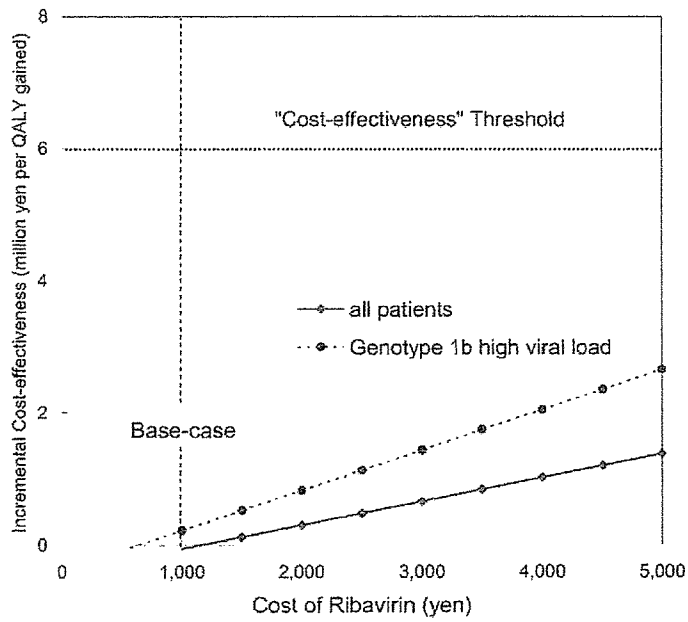

Fig. 1. Sensitivity analysis of the effects of varying the cost of ribavirin with a 3% annual discount rate. Each of the lines represents the incremental cost-effectiveness of combination therapy compared to interferon. The vertical line indicates the base-case cost of ribavirin. The horizontal line 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".

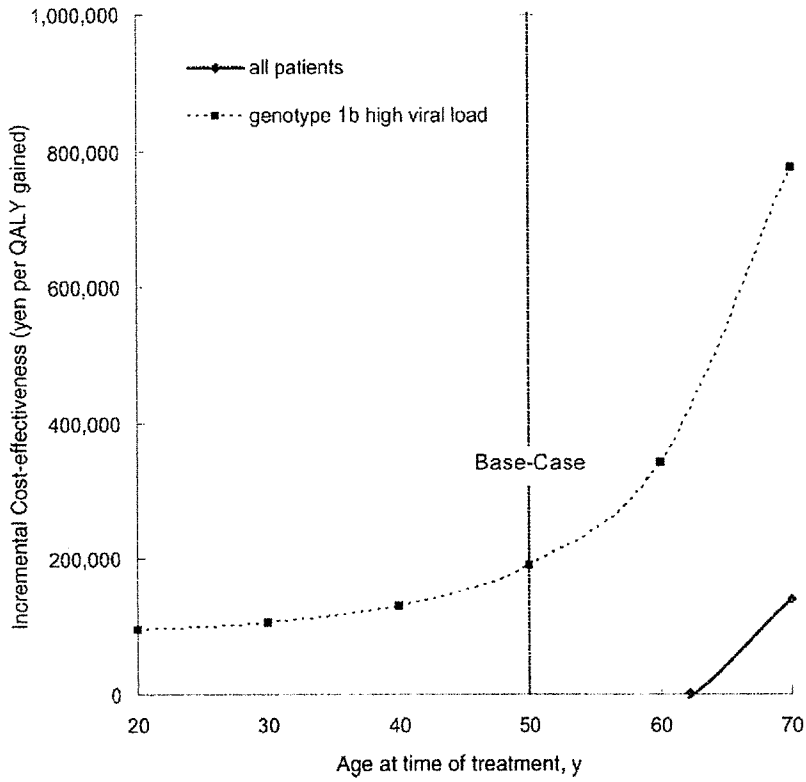

Fig. 2. Sensitivity analysis of the effects of age at start of treatment for chronic hepatitis C on the discounted (3%) incremental cost-effectiveness ratio. The vertical line indicates the base-case age of treatment. The incremental cost-effectiveness of combination therapy for all patient groups was 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.

The study was funded in part by an unrestricted grant from Schering-Plough, Japan to the investigators' institutions. The grant recipient had complete independence regarding study design, data analysis, manuscript preparation and decision to submit the paper for publication. The Schering-Plough, Japan provided raw data, but the authors performed all analyses.

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.

Acknowledgements

The authors are grateful to Ms. Chisato Watanabe for her assistance.

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Journal of Viral Hepatitis, 2004, 11, 148–156

Interferon treatment improves survival in chronic hepatitis C patients showing biochemical as well as virological responses by preventing liver-related death

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Received June 2003; accepted for publication June 2003

SUMMARY. Interferon therapy for chronic hepatitis C reduces the risk of hepatocellular carcinoma, especially among virological and biochemical responders. However, little is known about the effect of interferon therapy on mortality. We studied the long-term effect of interferon therapy on mortality in patients with chronic hepatitis C. For this retrospective cohort study, 2954 patients with chronic hepatitis C were recruited, of whom 2698 received interferon therapy and 256 did not. The effect of interferon therapy on survival was assessed by standardized mortality ratio (SMR) based on published mortality data for the general Japanese population and by risk ratio calculated by proportional hazard regression. Over 6.0 ± 2.2 years follow-up, death from liver-related diseases was observed in 69 (68%) of 101 deaths among interferon-treated patients and in 42 (81%) of 52 deaths among untreated patients. Compared with the general population, overall mortality was high among untreated patients (SMR: 2.7; 95% CI: 2.0–3.6) but not among interferon-treated patients (SMR: 0.9; 95% CI: 0.7–1.1). Liver-related mortality was extremely high among untreated patients (SMR: 22.2; 95% CI: 16.0–30.0) and less among interferon-treated patients (SMR: 5.5; 95% CI: 4.3–6.9). The risk of death from all causes was lower for interferon-treated than untreated patients (risk ratio: 0.47; 95% CI: 0.261–0.836; $P = 0.01$). The risk of death from liver-related diseases was significantly lower for sustained virological responders (risk ratio: 0.04; 95% CI: 0.005–0.301; $P = 0.002$) compared with untreated patients, but not for nonsustained virological responders. Sustained biochemical responders (risk ratio: 0.03; 95% CI: 0.004–0.230; $P < 0.001$) and transient biochemical responders (risk ratio: 0.18; 95% CI: 0.063–0.532; $P = 0.002$) showed a significantly reduced risk of death from liver-related death, whereas biochemical nonresponders did not. Hence interferon treatment improved survival in chronic hepatitis C patients showing a biochemical as well as a virological response by preventing liver-related deaths.

Keywords: chronic hepatitis C, interferon, liver-related mortality, multivariate analysis, standardized mortality ratio.

Abbreviations: HCC, hepatocellular carcinoma; SMR, standardized mortality ratio.

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INTRODUCTION

Hepatitis C virus (HCV) infection rarely resolves spontaneously once it becomes chronic [1]. Consequently, most patients in Japan with chronic HCV infection are likely to progress steadily to liver cirrhosis and hepatocellular carcinoma (HCC), which develops approximately 30 years after blood transfusion [2–4]. HCC is one of the most common malignancies, especially in Southeast Asia, and a major cause of death for patients with chronic HCV infection. In the early 1990s, interferon was introduced worldwide as a therapy for patients with chronic hepatitis C and was effective in inducing normalization of serum alanine aminotransferase (ALT) [5,6], eliminating HCV RNA [7,8], and improving liver histological findings [9–11] in patients with chronic hepatitis C.

To evaluate the effect of interferon therapy on the incidence of HCC and the risk of mortality for chronic hepatitis C patients, a randomized controlled trial is needed. However, a prospective randomized trial with untreated control patients is ethically impossible, because interferon therapy has already been established as a standard treatment for patients with chronic hepatitis C. Therefore, almost all chronic hepatitis C patients, except for cases with medical conditions such as depression, autoimmune disease and severe diabetes mellitus, have been treated with interferon in Japan. Recently, several investigators have reported this therapy as being effective for reducing the incidence of HCC among patients who showed normalization of ALT during and after interferon therapy, as well as among those in whom HCV was eradicated [12–17]. However, a reduced risk of HCC does not necessarily lead to improvement in survival. Indeed, little is known about the effects of interferon therapy on the mortality of patients with chronic hepatitis C. Several investigators [14, 18–23] have tried to evaluate the impact of interferon therapy on mortality. Four of these studies indicated that interferon therapy significantly reduced the mortality of compensated HCV-related cirrhotic patients [18,20] or of chronic hepatitis C patients including patients with compensated cirrhosis [21,23]. However, lack of analysis on response to interferon [18,20–23] or lack of information on disease-specific mortality [20,21] has made it difficult to evaluate the benefits of interferon for survival. Recently, Yoshida *et al.* [24] demonstrated that interferon therapy improved survival by preventing liver-related deaths of chronic hepatitis C patients showing a sustained virological response. However, whether a biochemical response to interferon therapy results in a reduced risk of mortality has not been investigated.

We conducted a multi-centre, large-scale, retrospective cohort study of patients with chronic hepatitis C, who had been enrolled at the end of 1997 at participating hospitals in order to analyse the effect of interferon therapy on the incidence of HCC. The aim of the present study was to examine the effect of interferon therapy on the mortality and causes of death among chronic hepatitis C patients.

PATIENTS AND METHODS

Patients

We recruited chronic hepatitis C patients from four previous studies which were conducted to assess the effect of interferon therapy on the incidence of HCC [12,14,15,17]. All patients meeting the following criteria were included in this study: (i) histological diagnosis of chronic hepatitis or cirrhosis; (ii) no history of clinical signs at entry into the study of complications of cirrhosis, i.e. ascites, jaundice, encephalopathy, or variceal bleeding; (iii) no evidence of HCC at entry into the study as assessed by ultrasonography and/or computed tomography; (iv) absence of serum hepatitis B surface antigen; (v) absence of co-existing liver diseases such as autoimmune hepatitis or primary biliary cirrhosis; (vi) absence of excessive alcohol consumption (>80 g/day); and (vii) absence of human immunodeficiency virus antibodies, as described previously [12,14,15,17]. A total of 3025 patients who met these criteria and whose initial sera tested positive for anti-HCV as determined by either first- or second-generation ELISA (Ortho Diagnostics, Tokyo, Japan) and HCV RNA were included in the study. The sera of patients who had been diagnosed as non-A, non-B hepatitis before anti-HCV testing became available (i.e. before 1989) had been frozen at −80 °C and were retrospectively assayed.

Of the 3025 chronic hepatitis C patients, 2762 had received interferon after 1987, when interferon became available in Japan. Interferon-treated patients received a 4–12-month course of interferon therapy, which was initiated within 1 month of liver biopsy. The remaining 263 patients did not undergo interferon therapy or any other antiviral therapy, including almost all patients with biopsy-proven chronic hepatitis who had refused interferon treatment due to adverse effects, lack of time for therapy, or their inability to undergo treatment as a consequence of depression, severe diabetes mellitus or other medical conditions.

Criteria for biochemical and virological responses to interferon therapy

The biochemical response during the follow-up up to 6 months after the completion of interferon therapy was defined according to previously described criteria with minor modifications [8,9]. In the sustained response group, ALT levels decreased to the normal range during therapy and remained within that range up to 24 weeks after therapy without any abnormal elevation. In the transient response group, ALT levels decreased to the normal range by the end of therapy, remained normal during therapy but returned to abnormal levels during the 24 weeks following interferon therapy. In the no-response group, ALT levels did not decrease to the normal range, or fluctuated during therapy and the subsequent 24 weeks. Both biochemical transient

and nonresponders were designated as nonsustained biochemical responders.

A sustained virological response was defined as HCV RNA negativity at more than 6 months after the cessation of interferon therapy. Patients showing positive HCV RNA at the same time were designated as nonsustained virological responders.

Histological evaluation

Liver biopsy was carried out before interferon therapy in all cases. Specimens were fixed in formaldehyde and embedded in paraffin. The sections were stained with haematoxylin-eosin and Azan-Mallory and analysed by two pathologists without any knowledge of the clinical and laboratory data. Histological findings were scored according to the classification of Desmet *et al.* [25].

Follow-up

The starting date of the follow-up for both the interferon-treated and untreated groups was defined as the date of liver biopsy. Biochemical examinations including α-fetoprotein and abdominal ultrasonography were carried out before interferon therapy and every 3–6 months thereafter at the outpatient clinic of the respective hospitals. The end of the follow-up was the date of death or the latest confirmation of survival. Follow-up data on the patients were obtained from the participating hospitals. Follow-up data that were not available from the hospitals were collected from the resident registry of the local municipal office. Death from liver-related disease was defined as death from HCC, liver failure determined by the presence of one or more of ascites, jaundice and hepatic encephalopathy, or variceal bleeding diagnosed on the basis of endoscopic findings of patients presenting with upper gastrointestinal haemorrhage.

Five untreated patients were observed for over 162 months, which corresponded to the longest period of observation of those treated with interferon. In these subjects, only the follow-up data up to 162 months were considered. Seventy-one patients whose follow-up period was shorter than 12 months were excluded from the study. The final numbers of study subjects were 2698 for the interferon-treated group and 256 for the untreated group.

Informed consent was obtained from each patient included in the study. The study protocol was in accordance with the Helsinki Declaration of 1975 (revised in 1983) and approved by the Ethical Committee of the Osaka University Graduate School of Medicine.

Statistical analysis

The chi-square test was used to compare the frequency of gender between the interferon-treated and untreated groups. The difference in age at liver biopsy and ALT between the two groups, expressed as median, was assessed for significance with the Student's *t*-test. The Wilcoxon rank-sum test was used to compare the distribution of age at liver biopsy and histological staging. Cumulative survival curves were determined with the Kaplan–Meier method, and the log-rank test was used to compare the cumulative survival rates.

The observed number of deaths was compared with the expected number, which was calculated by applying sex, 5-year age, 5-year calendar time, and cause-specific mortality rates for the general population in Japan, as prepared by the Statistics and Information Department, Japan Ministry of Health and Welfare [26]. The standardized mortality ratio (SMR) was expressed by dividing the observed number of deaths by the expected number of deaths. The standard error and the 95% CI of SMR were estimated by assuming Poisson's distribution, and differences in mortality between the study cohort and the general population were considered to be significant if the CI did not include unity.

Survival was also analysed by using Cox proportional hazards regression controlling for age (continuous variable), gender, stages of liver fibrosis (stage: 0/1/2/3/4) and time at liver biopsy (1991/1992). Risk ratios attributable to biochemical sustained, transient and no responses and to virological sustained and nonsustained responses were calculated in comparison with no treatment by using dummy variables.

Data analysis was performed with the SAS/PC statistical package (SAS Institute, Cary, NC, USA). All reported *P*-values were two-sided and $P < 0.05$ was considered to be significant.

RESULTS

Patient characteristics at entry

Of the 2698 patients treated with interferon, 901 (33.3%) had a sustained biochemical response, 701 (26.0%) a transient biochemical response and the remaining 1096 patients (40.6%) were classified as biochemical nonresponders. Serum HCV RNA remained negative at more than 6 months after cessation of interferon therapy in 738 (81.9%) of the sustained biochemical responders, designated as sustained virological responders, whereas serum HCV RNA remained positive in 133 (14.8%). Serum HCV RNA was not examined after the termination of interferon therapy in 30 sustained biochemical responders, who were excluded from the analysis according to virological responses to interferon. Positive HCV RNA after interferon therapy was detected in all of the biochemical transient and nonresponders.

The demographic and clinical features of interferon-treated patients according to virological and biochemical responses to interferon and of untreated patients at the time of enrolment are summarized in Table 1. Untreated patients were significantly older than interferon-treated patients ($P = 0.04$), but frequency distribution of age at liver biopsy

Table 1 Characteristics of interferon-treated patients according to virological and biochemical responses to interferon and of untreated patients

	Interferon-treated							
	Virological response		Biochemical response					
	SVR (n = 738)	non-SVR (n = 1930)	SBR (n = 901)	TBR (n = 701)	BNR (n = 1096)	Total (n = 2698)	Untreated (n = 256)	P-value
Median age (range)	51 (20–72)	54 (20–76)	52 (20–73)	53 (20–75)	54 (20–76)	53 (20–76)	54 (21–72)	0.04
Age at biopsy (%)								
≤49	337 (45.7)	687 (35.6)	392 (43.5)	277 (39.5)	369 (33.7)	1038 (38.5)	75 (29.3)	0.12
50–59	240 (32.5)	759 (39.3)	303 (33.6)	280 (39.9)	428 (39.1)	1011 (37.5)	123 (48.9)	
≥60	161 (21.8)	484 (25.1)	206 (22.9)	144 (20.5)	299 (27.3)	649 (24.1)	58 (22.7)	
Sex (M/F)	507/231	1210/720	595/306	440/261	703/393	1738/960	157/99	0.32
Median ALT (U/L), SD	91	92	87	79	103	92	98	0.57
(range)	(7–1110)	(11–1195)	(7–1110)	(13–1195)	(13–828)	(7–1195)	(9–563)	
Stage of fibrosis (%)								
0	5 (0.7)	11 (0.6)	7 (0.8)	4 (0.6)	5 (0.9)	16 (0.6)	9 (3.5)	0.34
1	259 (35.1)	476 (24.7)	337 (37.4)	228 (32.5)	190 (17.3)	755 (28.0)	84 (32.8)	
2	263 (35.6)	614 (31.8)	297 (33.0)	238 (34.0)	349 (31.8)	884 (32.8)	40 (15.6)	
3	189 (25.6)	725 (37.6)	235 (26.1)	209 (29.8)	471 (43.0)	915 (33.9)	93 (36.3)	
4	22 (3.0)	104 (5.4)	25 (2.8)	22 (3.1)	81 (7.4)	128 (4.7)	30 (11.7)	

SVR, sustained virological responders; SBR, sustained biochemical responders; TBR, transient biochemical responders; BNR, biochemical nonresponders; ALT, alanine aminotransferase.

and the stages of liver fibrosis, gender and ALT did not differ significantly. In sustained biochemical responders, the ratio of male patients and median ALT levels were significantly higher for patients with HCV eradication than for those without it ($P < 0.001$, each), whereas median age and the frequency distribution of the stages of liver fibrosis were not significantly different between the two groups.

Follow-up data

The mean period of observation (total cases: 6.0 ± 2.2 years) of the interferon-treated and untreated patients was 5.8 and 8.0 years, respectively, with the former being significantly shorter than the latter ($P = 0.0001$) because interferon therapy was not introduced in Japan until 1987.

Table 2 Follow-up data for interferon-treated patients according to virological and biochemical responses to interferon and for untreated patients

	Interferon-treated						
	Virological response		Biochemical response				
	SVR (n = 738)	non-SVR (n = 1930)	SBR (n = 901)	TBR (n = 701)	BNR (n = 1096)	Total (n = 2698)	Untreated (n = 256)
Mean period of observation, year (SD)	5.7 (2.0)	5.8 (1.9)	5.6 (2.0)	5.7 (1.8)	5.9 (1.9)	5.8 (1.9)	8.0 (3.4)
No. of deaths	7	94	10	10	81	101	52
Liver-related deaths	1	68	1	5	63	69	42
Death from HCC	1	57	1	4	53	58	31
Death from other liver diseases	0	11	0	1	10	11	11
Liver-unrelated deaths	9	26	9	5	18	32	10

SVR, sustained virological responders; SBR, sustained biochemical responders; TBR, transient biochemical responders; BNR, biochemical nonresponders; HCC, hepatocellular carcinoma.

The sustained virological responders, nonsustained virological responders, sustained biochemical responders, transient biochemical responders and biochemical nonresponders were observed for a mean of 5.7, 5.8, 5.6, 5.7 and 5.9 years, respectively (Table 2).

We identified 153 deaths from all causes during the follow-up. The 153 patients who died consisted of 10 sustained biochemical responders (seven of whom were sustained virological responders and three of whom were sustained biochemical responders without HCV eradication), 10 transient biochemical responders, 81 biochemical nonresponders and 52 cases without interferon treatment. Death from all causes did not occur in 30 sustained biochemical responders whose serum HCV RNA was not examined after cessation of interferon therapy. Death from liver-related disease was identified in 111 (73%) of the 153 patients who died: only one death (10%) from liver-related disease (death from HCC) was found among sustained responders with HCV eradication, five (50%) among transient biochemical responders (death from HCC in four cases), 63 (78%) among biochemical nonresponders (death from HCC in 53 cases) and 42 (81%) among untreated patients (death from HCC in 31 cases) (Table 2).

Cumulative survival

The cumulative survival rates from all causes of death were found to be significantly higher for interferon-treated than for untreated patients ($P < 0.001$) (Fig. 1a) The respective 5-year survival rates of interferon-treated and untreated groups were 97.8 and 95.3%, and the 10-year survival rates 87.2 and 77.1%. The cumulative survival rates for sustained virological responders were significantly higher than for nonsustained virological responders ($P < 0.001$) (Fig. 1b), with 5-year survival rates of 99.5 and 97.1%, and 10-year survival rates of 97.8 and 81.9%, respectively. The cumulative survival rates for sustained biochemical responders were significantly higher than for nonsustained biochemical responders ($P < 0.001$). When nonsustained biochemical responders were divided into transient biochemical responders and biochemical nonresponders, the cumulative survival rates for the transient biochemical responders were significantly higher than for the biochemical nonresponders ($P < 0.001$) (Fig. 1c). The respective cumulative survival rates for sustained biochemical responders, transient biochemical responders and biochemical nonresponders were 99.2, 99.1 and 95.8% at the end of the fifth year and 97.8, 97.6 and 72.6% at the end of the 10th year. Among sustained biochemical responders, the cumulative survival rates for sustained virological responders and sustained biochemical responders without HCV eradication were 99.5 and 99.2% at the end of fifth year and 97.8 and 99.2% at the end of the 10th year, showing no statistical significance ($P = 0.18$).

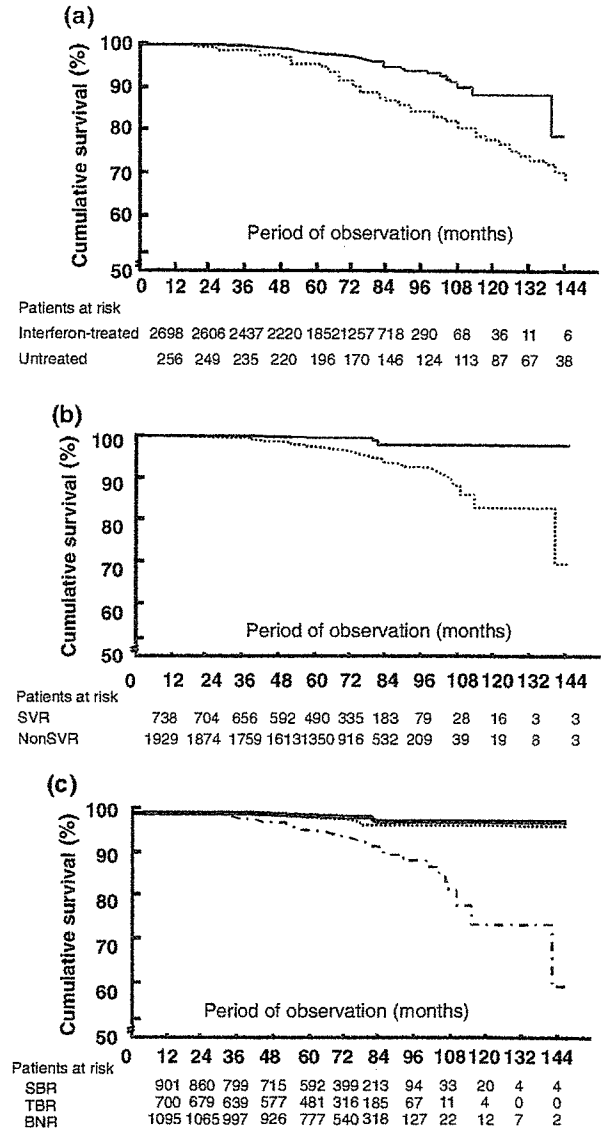

Fig. 1 Cumulative survival rates from all causes of death for patients with chronic hepatitis C. (a) For interferon-treated patients (solid line) and untreated patients (dotted line). (b) According to the virological response to interferon therapy; sustained virological responders (SVR) (solid line) and nonsustained virological responders (non-SVR) (dotted line). (c) In terms of the biochemical responses to interferon, sustained biochemical responders (SBR) (solid line), transient biochemical responders (TBR) (dotted line) and biochemical nonresponders (BNR) (dash-and-dot line).

Standardized mortality ratio

Differences in mortality among interferon-treated and untreated patients from the general population were further assessed by calculating SMR, the ratio of the observed number of deaths to the expected number. Overall mortality

Table 3 Standardized mortality ratios (SMR) in patients with chronic hepatitis C according to virological and biochemical responses to interferon

	Overall deaths			Liver-related deaths			Liver-unrelated deaths		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
Untreated	52	19.2	2.7 (2.0–3.6)	42	1.9	22.2 (16.0–30.0)	10	17.3	0.6 (0.3–1.1)
Interferon-treated	101	112.7	0.9 (0.7–1.1)	69	12.6	5.5 (4.3–6.9)	32	100.0	0.3 (0.2–0.5)
Virological response									
Sustained (HCV RNA negative)	7	29.8	0.2 (0.1–0.5)	1	3.3	0.3 (0.0–1.7)	6	26.5	0.2 (0.1–0.5)
Nonsustained (HCV RNA positive)	94	82.2	1.1 (0.9–1.4)	68	9.2	7.4 (5.8–9.4)	26	73.0	0.4 (0.2–0.5)
Biochemical response									
Sustained response	10	36.5	0.3 (0.1–0.5)	1	4.0	0.3 (0.0–1.4)	9	32.5	0.3 (0.1–0.5)
Transient response	10	27.5	0.4 (0.2–0.7)	5	3.2	1.6 (0.5–3.7)	5	24.3	0.2 (0.1–0.5)
No response	81	48.8	1.7 (1.3–2.1)	63	5.4	11.6 (8.9–14.9)	18	43.3	0.4 (0.3–0.7)

Difference from the expected number of deaths was considered significant if 95% CI of SMR did not include unity.

for untreated patients (SMR: 2.7; 95% CI: 2.0–3.6) but not for the interferon-treated patients (SMR: 0.9; 95% CI: 0.7–1.1) was significantly higher than for the general population. Liver-related mortality was high for untreated patients (SMR: 22.2; 95% CI: 16.0–30.0) and also for interferon-treated patients, although to a lesser degree (SMR: 5.5; 95% CI: 4.3–6.9) (Table 3). For sustained virological responders overall mortality was low (SMR: 0.2; 95% CI: 0.1–0.5), and liver-related mortality (SMR: 0.3; 95% CI: 0.0–1.7) was equivalent to that for the general population. In contrast, liver-related mortality was high for nonsustained virological responders (SMR: 7.4; 95% CI: 5.8–9.4).

Sustained and transient biochemical responders showed a low overall mortality compared with that for the general population (SMR: 0.3; 95% CI: 0.1–0.5, and SMR: 0.4; 95% CI: 0.2–0.7, respectively), whereas overall mortality was high for biochemical nonresponders (SMR: 1.7; 95% CI: 1.3–2.1). Liver-related mortality was not high for sustained and transient biochemical responders (SMR: 0.3; 95% CI: 0.0–1.4, and SMR: 1.6; 95% CI: 0.5–3.7, respectively) compared with that for the general population, but it was high for biochemical nonresponders (SMR: 11.6; 95% CI: 8.9–14.9) (Table 3). Overall and liver-related mortality for sustained biochemical responders without HCV eradication was equivalent to that for the general population (SMR: 0.5; 95% CI: 0.1–1.5, and SMR: 0.0; 95% CI: 0.0–6.1, respectively).

Interferon-treated patients had a statistically lower risk of liver-unrelated death than the general population (SMR: 0.3; 95% CI: 0.2–0.5), whereas untreated patients did not (SMR: 0.6; 95% CI: 0.3–1.1).

Multivariate analysis

The effect of interferon on the risk of death was assessed by Cox proportional hazards regression controlling for age, gender, score of liver fibrosis and time at liver biopsy. Interferon therapy significantly reduced the risk of overall death to a ratio of only 0.47, in comparison with no treatment. When patients were classified according to virological responses to interferon, sustained virological responders showed reduced risks of overall death (risk ratio: 0.14; 95% CI: 0.056–0.352; $P < 0.001$) and liver-related death (risk ratio: 0.04; 95% CI: 0.005–0.301; $P = 0.002$) compared with untreated patients, whereas nonsustained virological responders did not. Similarly, sustained biochemical responders showed a lower risk of death from all causes (risk ratio: 0.16; 95% CI: 0.069–0.354; $P < 0.001$) and liver-related diseases (risk ratio: 0.03; 95% CI: 0.004–0.230; $P < 0.001$). Transient biochemical responders had a high, but still significantly reduced risk of overall death (risk ratio: 0.19; 95% CI: 0.083–0.445; $P < 0.001$) and liver-related death (risk ratio: 0.18; 95% CI: 0.063–0.532; $P = 0.002$), whereas the risk for nonresponders and untreated patients did not

Table 4 Risk of death in patients with chronic hepatitis C according to virological and biochemical responses to interferon

	All causes of deaths			Liver-related deaths		
	Risk ratio	95% CI	*P*-value	Risk ratio	95% CI	*P*-value
Untreated	1.00			1.00		
Interferon-treated	0.47	0.261–0.836	0.010	0.59	0.312–1.097	0.095
Virological response						
Sustained (HCV RNA negative)	0.14	0.056–0.352	<0.001	0.04	0.005–0.301	0.002
Nonsustained (HCV RNA positive)	0.59	0.327–1.057	0.08	0.76	0.402–1.417	0.380
Biochemical response						
Sustained response	0.16	0.069–0.354	<0.001	0.03	0.004–0.230	<0.001
Transient response	0.19	0.083–0.445	<0.001	0.18	0.063–0.532	0.002
No response	0.78	0.432–1.393	0.394	1.02	0.543–1.900	0.962

Adjusted for age, sex, score of liver fibrosis and period at liver biopsy.

change (Table 4). The risk of overall death for sustained biochemical responders without HCV eradication was lower than for untreated patients, although it did not reach a statistical significance (risk ratio: 0.31; 95% CI: 0.09–1.07; $P = 0.06$).

DISCUSSION

We previously demonstrated that interferon treatment could reduce the risk of HCC development in patients with chronic hepatitis C [12]. Following this, five retrospective studies [13–17] showed a similar effect of interferon on the risk of HCC, especially for virological and biochemical responders. These results suggest that interferon therapy for chronic hepatitis C can prevent the development of HCC, possibly leading to improvement in long-term survival. However, only a few previous studies have assessed the effects of interferon therapy on survival [18–24], and whether interferon therapy also reduces mortality from liver-related disease in patients with chronic HCV infection has not been thoroughly investigated. It is also still unclear what type of response to interferon results in the improvement of long-term survival.

To evaluate the effect of interferon therapy on the risk of mortality for chronic hepatitis C patients, a randomized controlled trial should be carried out. However, a prospective randomized trial with untreated control patients is ethically impossible, because interferon therapy has already been established as the standard modality for patients with chronic hepatitis C. Only two randomized controlled trials of a small number of HCV-related cirrhotic cases have evaluated the effect of interferon therapy on mortality [19,21], but with discrepant results. In contrast, large-scale prospective and retrospective cohort studies [23,24] indicate that interferon therapy for HCV-related cirrhosis or chronic hepatitis C improves long-term survival. In particular, Yoshida *et al.* [24] demonstrated in their recent retrospective cohort study that interferon therapy improved survival of chronic hepatitis C patients by preventing liver-related deaths. However, its beneficial effect was considered to be limited to patients with a sustained virological response.

As ours is a retrospective cohort study, it may be subject to several biases. The interferon-treated and untreated groups had different demographic characteristics, including age and gender. These factors were adjusted for multivariate regression analysis and considered when calculating SMR by applying the corresponding mortality for the general population. Severity of chronic liver disease was adjusted by using the stage of liver fibrosis for multivariate analysis. As the time of liver biopsy of untreated patients was earlier than for interferon-treated patients, mortality for untreated patients may be generally higher than for interferon-treated patients. To avoid this bias, we adjusted the time at liver biopsy for multivariate analysis, and 5-year time-specific mortality rates for the general population were prepared in the SMR analysis. Moreover, the number of untreated patients was small, because most Japanese chronic hepatitis C patients, except for cases with medical problems, have been treated with interferon. However, the relatively small number of untreated patients in comparison with the large number of interferon-treated patients is not likely to have resulted in a substantial overestimation of the effect of interferon therapy on survival as several of the biases already mentioned were controlled in the analyses.

When we compared the observed mortality with the expected mortality for the matched general population by calculating SMR, we were able to demonstrate that chronic hepatitis C patients had higher overall and liver-related mortality than the general population, and that the majority of deaths were liver-related. However, interferon-treated patients had a significantly lower risk of liver-unrelated mortality, whereas untreated patients did not. This may represent a selection bias in the use of interferon therapy, which included patients with no medical problems

except for having chronic liver diseases. However, our multivariate regression analysis clearly showed that interferon therapy reduced the risk of liver-related death in virological responders by 96% and in biochemical responders by 82–97%. These findings indicate that a significant reduction in the risk of death from all causes for patients treated with interferon, shown in the analysis of SMR, was not caused by a selection bias but is mainly attributable to the prevention of liver-related death by interferon therapy.

Our multivariate analysis made it clear that the risks of overall and liver-related deaths for chronic hepatitis C patients displaying a sustained virological response were 86 and 96% lower than for untreated patients. The risk reduction for sustained biochemical responders was almost equal to that for sustained virological responders. Similarly, the SMR analyses showed that liver-related mortality for these patients was equivalent to that for the general population. Thus, and as expected, when patients treated with interferon belong to the sustained virological or biochemical response group, they appear to have the highest long-term survival rate.

Of nonsustained virological responders, the risk of death from all causes and liver-related diseases for transient biochemical responders was significantly lower than for untreated patients, but higher than for sustained biochemical and virological responders. The same effects of interferon therapy on survival were observed in the SMR analyses. Although the follow-up period was not sufficiently long for a reliable and accurate examination of mortality, we would like to emphasize that the risk of death from all causes and liver-related diseases was significantly lower for chronic hepatitis C patients for whom interferon was effective in normalizing ALT than for patients who did not receive interferon, even when HCV was not eradicated. However, the risk of death from all causes and liver-related diseases was not reduced in biochemical nonresponders.

In conclusion, the findings reported here indicate that interferon therapy improves long-term survival in chronic hepatitis C patients showing a biochemical as well as a virological response by preventing liver-related deaths.

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