J Gastroenterol 2004, 39:1069–1077
DOI 10.1007/s00535-004-1448-0

Journal of Gastroenterology

Interferon therapy for aged patients with chronic hepatitis C: improved survival in patients exhibiting a biochemical response

Yasuharu Imai[1], Akinori Kasahara[2], Hideo Tanaka[3], Takeshi Okanoue[4], Naoki Hiramatsu[5], Hirohito Tsubouchi[6], Kentaro Yoshioka[7], Sumio Kawata[8], Eiji Tanaka[9], Keisuke Hino[10], Katsuhiro Hayashi[6], Shinji Tamura[11], Yoshito Itoh[5], Yutaka Sasaki[12], Kendo Kiyosawa[9], Shinichi Kakumu[13], Kiwamu Okita[10], and Norio Hayashi[4]

[1]Department of Internal Medicine, Ikeda Municipal Hospital, 3-1-18 Johnan, Ikeda 563-8510, Japan
[2]Department of General Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[3]Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan
[4]Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan
[5]Department of Molecular Therapeutics, Osaka University Graduate School of Medicine, Osaka, Japan
[6]Second Department of Internal Medicine, Miyazaki Medical College, Miyazaki, Japan
[7]Division of Gastroenterology, Department of Internal Medicine, Nagoya University School of Medicine, Nagoya, Japan
[8]Second Department of Medicine, Yamagata University School of Medicine, Yamagata, Japan
[9]Internal Medicine, Shinshu University School of Medicine, Matsumoto, Japan
[10]Department of Gastroenterology and Hepatology, Yamaguchi University School of Medicine, Yamaguchi, Japan
[11]Department of Internal Medicine and Molecular Science, Osaka University Graduate School of Medicine, Osaka, Japan
[12]Department of Gastroenterology and Hepatology, Graduate School of Medical Science, Kumamoto University, Kumamoto, Japan
[13]Department of Internal Medicine, Division of Gastroenterology, Aichi Medical University School of Medicine, Aichi, Japan

Editorial on page 1123

Background. In Japan, generally, patients with chronic hepatitis C are aged. The aim of this study was to investigate the effect of interferon (IFN) therapy on the mortality of chronic hepatitis C patients over age 60. ***Methods.*** Seven-hundred and seven patients with histologically proven chronic hepatitis C were enrolled in this study; 649 received IFN therapy (IFN group) and 58 did not (control group). The standardized mortality ratio (SMR) and Cox proportional hazard regression analysis were used to evaluate the effect of IFN on the survival of the patients. ***Results.*** Mean follow-up periods in the IFN and control groups were 5.7 and 6.7 years, respectively. During follow-up, 13 patients in the control group died (7 of liver-related diseases) and 42 in the IFN group died (29 of liver-related diseases). The SMRs of the control and IFN groups were 1.40 (95% confidence interval [CI], 0.76–2.45) and 0.73 (95% CI, 0.52–0.98) for overall death, and 10.70 (95% CI, 4.29–22.05) and 5.05 (95% CI, 3.38–7.26) for liver-related death, respectively. Sustained and transient biochemical responders in the IFN group (SMR, 0.53; 95% CI, 0.01–2.97 and SMR, 3.25; 95% CI, 0.87–8.32, respectively) showed lower liver-related mortality compared with the control group. In patients with sustained virological response, liver-related mortality was also very low (SMR, 0.65; 95% CI, 0.01–3.61). The risk for liver-related death of sustained and transient biochemical responders was also low compared with that of the control group (adjusted risk ratios 0.10 [95% CI, 0.01–0.95] and 0.50 [95% CI, 0.11–2.21], respectively). ***Conclusions.*** These results suggest that IFN treatment could reduce liver-related mortality in chronic hepatitis C patients over age 60, notably in patients showing a biochemical response and in those showing a sustained virological response.

Key words: interferon, chronic hepatitis C, aged, liver-related mortality, standardized mortality ratio

Introduction

A high prevalence of hepatitis C virus (HCV) infection is observed in patients with hepatocellular carcinoma (HCC) in Japan.[1–4] In the early 1990s, interferon (IFN) was introduced, and it is now widely used worldwide, as well as in Japan, for the treatment of patients with chronic hepatitis C. Hitherto, many studies, including our own reports, have shown that IFN therapy reduced the incidence of HCC in patients with chronic hepatitis C.[5–10]

Recently, several groups have studied the effect of IFN therapy on survival in patients with chronic hepatitis C. Most of these studies reported that IFN therapy improved the survival of HCV-related chronic hepatitis and cirrhosis, although some studies did not find any efficacy of IFN therapy on survival.[10–19] We also reported the beneficial effect of IFN therapy on survival in chronic hepatitis C patients. In that report, we also

Received: December 28, 2003 / Accepted: March 24, 2004
Reprint requests to: Y. Imai

showed that the effect of IFN therapy on survival was notable in the patients exhibiting sustained and transient biochemical responses, as well as in those showing sustained virological response.[20]

Many clinical trials showed that IFN therapy resulted in normalization of serum aminotransferase levels and eradication of serum HCV RNA, although a sustained virological response was achieved in a limited number of patients.[21-25] Recently, a combination therapy of ribavirin and IFN, or pegylated IFN, has been shown to have efficacy superior to IFN monotherapy for chronic hepatitis C.[26-28]

Patients in Japan with chronic hepatitis C are, generally, aged.[29,30] Also, patients with HCV-related HCC have been shown to be old, with a peak around age 70.[31] Despite the beneficial effects of IFN therapy or combination therapy of IFN and ribavirin for chronic hepatitis C patients, these treatments have several adverse effects which are not tolerable, especially for aged patients who have illnesses other than liver disease.[32] If IFN therapy does not prolong life expectancy in aged patients with chronic hepatitis C, the indications for IFN therapy in these patients may be very limited. Therefore, it is very important to investigate whether IFN therapy could improve survival in aged patients with chronic hepatitis C.

The aim of this study was to evaluate the effect of IFN therapy on mortality in aged patients with chronic hepatitis C. We conducted a multicenter, large-scale, retrospective cohort study of chronic hepatitis C patients over 60 years of age.

Patients and methods

Patients

We found previously that IFN therapy improved the survival in patients with chronic hepatitis C.[20] Of the 2954 patients with chronic hepatitis C in that study, we enrolled 707 patients over age 60 in the present study, to investigate the effect of IFN therapy on mortality in aged patients. Accordingly, the inclusion criteria were the same as those of the previous study: (1) histological diagnosis of chronic hepatitis or cirrhosis; (2) no history of clinical signs, at entry into the study, of complications of cirrhosis, i.e., ascites, jaundice, encephalopathy, or variceal bleeding; (3) no evidence of HCC at entry into the study, as assessed by ultrasonography and/or computed tomography; (4) absence of serum hepatitis B surface antigen; (5) absence of coexisting liver diseases, such as autoimmune hepatitis or primary biliary cirrhosis; (6) absence of excessive alcohol consumption (>80 g/day); and (7) absence of human immunodeficiency virus antibodies.[20]

The IFN group comprised 649 patients who had started IFN therapy between 1992 and 1997 and had received a 4- to 12-month course of IFN, which was initiated within 1 month after liver biopsy. None of the patients had received IFN therapy before entry into this study. The control group consisted of 58 patients who had received liver biopsies between 1986 and 1997, but who did not undergo IFN therapy.

Biochemical responses to IFN therapy were categorized as follows. Patients whose alanine aminotransferase (ALT) levels decreased to the normal range during therapy and remained normal for up to 24 weeks after the end of the therapy were considered to have a sustained biochemical response. Patients whose 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 the end of the IFN therapy were considered to have a transient biochemical response. All other ALT patterns were classified as showing biochemical non-response. A sustained virological response was defined as persistent HCV RNA negativity during IFN therapy and follow-up. Patients showing positive HCV RNA after IFN therapy were classified as virological non-responders.

Follow-up

Abdominal ultrasonography or computed tomography and biochemical examinations, including α-fetoprotein, were carried out before a liver biopsy and every 3 to 6 months during follow-up, equally in the IFN and control groups. The starting date of follow-up for patients in the control and IFN groups was defined as the date of liver biopsy. Follow-up data that were not available were collected from the resident registry of the local municipal office. In the patients residing in Osaka whose follow-up data were not obtained, the Osaka Cancer Registry was used, and the data were available until the end of 1999.[6] Therefore, it was decided to use the date of death or the end of 1999 as the end of follow-up. Because the longest observation period of the patients in the IFN group was 96 months, only the follow-up data for the first 96 months were considered in the control group. Causes of death were divided into liver-related and liver-unrelated deaths. Causes of liver-related death included HCC, liver failure, and esophageal variceal bleeding.

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 was approved by the Ethics Committee of the Osaka University Graduate School of Medicine.

Table 1. Baseline characteristics of 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)	P value
Age (years; mean ± SD)	63.6 ± 3.0	63.3 ± 2.9	63.8 ± 3.1	63.0 ± 2.8	63.1 ± 2.8	63.3 ± 2.9	64.1 ± 3.1	0.06
Age distribution (years; %)								
60–64	67.7	71.1	63.6	75.0	72.9	70.4	56.9	0.03
≥65	32.3	28.9	36.4	25.0	27.1	29.6	43.1	
Male/Female	110/51	272/212	134/72	80/64	171/128	385/264	31/27	0.38
Histologic staging score (%)								
0	0.6	0.2	0.5	0.0	0.3	0.3	5.2	0.06
1	24.8	18.2	27.7	25.0	12.4	20.0	31.0	
2	29.2	27.7	26.7	28.5	28.8	28.0	20.7	
3	39.8	46.9	40.3	39.6	50.5	44.8	31.0	
4	5.6	7.0	4.9	6.9	8.0	6.8	12.1	
ALT (IU/l; mean ± SD)	113 ± 82	107 ± 68	110 ± 86	87 ± 45	117 ± 69	108 ± 71	105 ± 80	0.75

Histological evaluation

In all patients, liver biopsy was undertaken before IFN therapy. Sections were stained with hematoxylin-eosin and Azan-Mallory and analyzed by two pathologists in a blinded manner. For the assessment of liver histology, the classification of Desmet et al.[33] was used.

Statistical analysis

To compare the distribution of age at liver biopsy and histological staging between the IFN and control groups, the Wilcoxon rank-sum test was used. Differences in age at liver biopsy and ALT between the two groups was assessed for significance by Student's t-test. The χ^2 test was used to compare sex differences. The Kaplan-Meier method was used to compare the cumulative survival rates in the IFN and control groups.

We compared the observed number of deaths with the expected number of deaths, 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.[34] The standardized mortality ratio (SMR) was expressed by dividing the observed number of deaths by the expected number of deaths. Survival was also analyzed by Cox proportional hazards regression. For analysis, age, sex, stage of liver fibrosis (stages 0,1/2/3/4), time of liver biopsy (until 1992/after 1993), and IFN therapy were used as variables. SMRs and hazard risk ratios were expressed with 95% confidence intervals (CIs).

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

Results

Baseline characteristics

In the IFN group, 206 patients (31.7%) had a sustained biochemical response, 144 (22.2%) had a transient biochemical response, and 299 patients (46.1%) were biochemical non-responders. Four sustained biochemical responders whose serum HCV RNA was not examined during follow-up were excluded from the analysis. Accordingly, 161 patients (25.0%) of the 645 IFN-treated patients were classified as sustained virological responders. Table 1 shows the baseline characteristics of the IFN and control groups. Age at entry, sex, histologic staging score, and serum ALT level did not differ between the two groups. The proportion of patients more than 65 years of age in the control group was higher than that in the IFN group (P = 0.03).

Table 2. Cumulative survival rate calculated from overall deaths

	Interferon group					
	Virological response		Biochemical response			
	Sustained response	Non-response	Sustained response	Transient response	Non-response	Total	Control group
Mean follow-up period (years; mean ± SD)	5.7 ± 1.6	5.7 ± 1.7	5.6 ± 1.7	5.7 ± 1.8	5.8 ± 1.6	5.7 ± 1.7	6.7 ± 1.7
4-Year survival rate	99.3%	96.2%	98.4%	99.2%	95.0%	97.0%	93.0%
8-Year survival rate	94.6%	86.8%	94.3%	93.0%	83.4%	88.7%	73.9%
P Value[a]	<0.001	0.0197	<0.001	0.0036	0.1212	0.0031	

[a] The log rank test was used to determine the difference against the control group

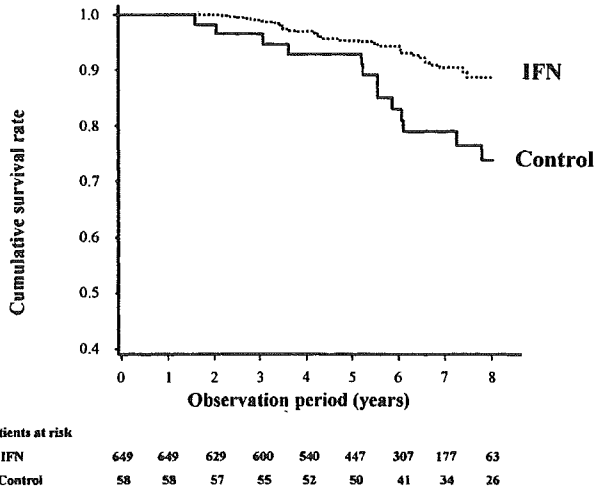

Fig. 1. Cumulative survival rates in the interferon (*IFN*; *dotted line*) and control (*solid line*) groups. Log-rank test of the two curves showed a significant difference between the two groups ($P = 0.003$)

Cumulative survival and cause of death

The mean follow-up periods of the IFN and control groups were 5.7 and 6.7 years, respectively. The mean follow-up periods of the patients with each response in the IFN group are shown in Table 2. Figure 1 shows the cumulative survival rates of the IFN and control groups, estimated by the Kaplan-Meier method. The 8-year survival rates of the IFN and control groups were 88.7% and 73.9%, respectively (log-rank test; $P = 0.003$; Table 2). The cumulative survival rates of sustained virological responders were significantly higher than those for virological non-responders (log-rank test; $P = 0.02$). The 8-year survival rates of sustained virological responders and virological non-responders were 94.6% and 86.8%, respectively (Table 2). The cumulative survival rates of both the sustained and transient biochemical responders were significantly higher than that of the biochemical non-responders (log-rank test; $P = 0.007$ and $P = 0.049$; Fig. 2). The 8-year survival rates of sustained and transient biochemical respon-ders and biochemical non-responders were calculated to be 94.3%, 93.0% and 83.4%, respectively (Table 2).

During follow-up, 42 of the 649 IFN-treated patients and 13 of the 58 control patients died. The numbers of liver-related and liver-unrelated deaths in the IFN and control groups are shown in Table 3. Liver-related deaths corresponded to 69% of all deaths (29/42) in the IFN group and 54% of all deaths (7/13) in the control group. HCC was the major cause of liver-related deaths in both groups. Only one liver-related death (17%) was found in the deaths of sustained biochemical respond-

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

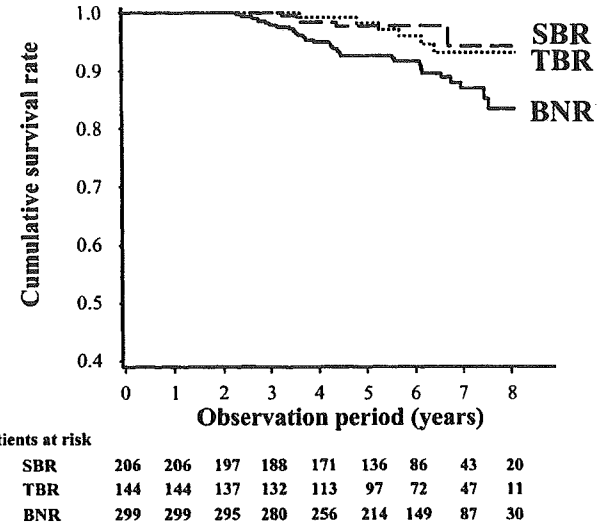

Fig. 2. Cumulative survival rates in the IFN-treated patients, categorized by sustained biochemical response (*SBR*; *dashed line*), transient biochemical response (*TBR*; *dotted line*), and biochemical non-response (*BNR*; *solid line*). Log-rank test showed significant differences between SBR and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

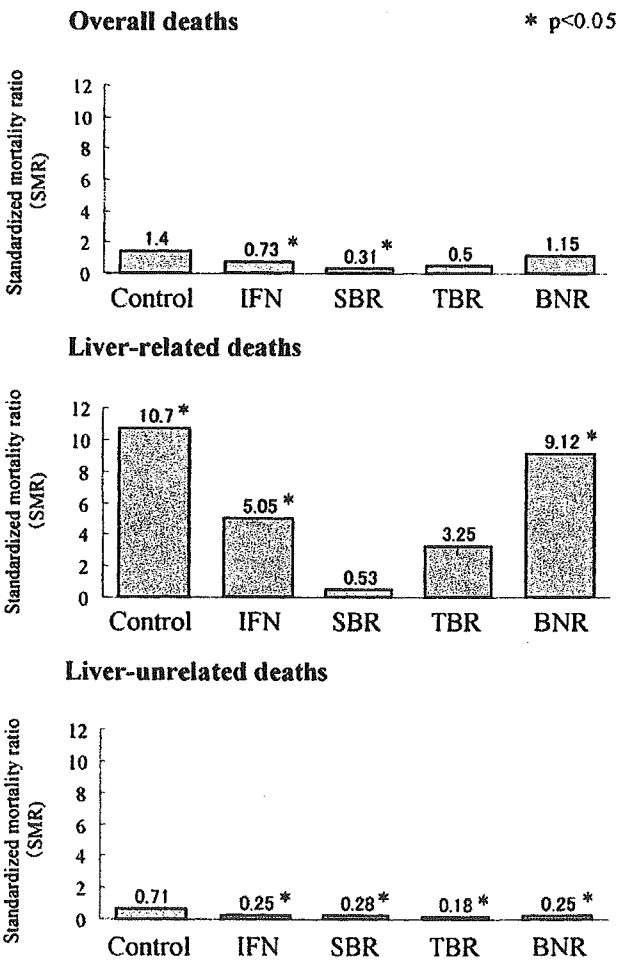

Fig. 3. Standardized mortality ratios (*SMR*s) for overall, liver-related, and liver-unrelated deaths. *SBR*, sustained biochemical response; *TBR*, transient biochemical response; *BNR*, biochemical non-response. When the SMR did not include unity, we considered the difference from the expected number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

References

1. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. Semin Liver Dis 1995;15:64–9.
2. Nishioka K, Watanabe J, Furuta S, Tanaka E, Iino S, Suzuki H, et al. A prevalence of antibody to the hepatitis C virus in patients with hepatocellular carcinoma in Japan. Cancer 1991;67:429–33.
3. Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med 1993; 328:1797–801.
4. Ikeda K, Saitoh S, Koida I, Arase Y, Tsubota A, Chayama K, et al. A multivariate analysis of risk factors for hepatocellular carcinogenesis: a prospective observation of 795 patients with viral and alcoholic cirrhosis. Hepatology 1993;18:47–53.
5. Kasahara A, Hayashi N, Mochizuki K, Takayanagi M, Yoshioka K, Kakumu S, et al. Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Hepatology 1998;27:1394–402.
6. Imai Y, Kawata S, Tamura S, Yabuuchi I, Noda S, Inada M, et al. Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Ann Intern Med 1998;129:94–9.
7. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. Ann Intern Med 1999; 131:174–81.
8. Okanoue T, Itoh Y, Minami M, Sakamoto S, Yasui K, Sakamoto M, et al. Interferon therapy lowers the rate of progression to hepatocellular carcinoma in chronic hepatitis C but not significantly in an advanced stage: a retrospective study of 1146 patients. J Hepatol 1999;30:653–9.
9. Ikeda K, Saitoh S, Arase Y, Chayama K, Suzuki Y, Kobayashi M, et al. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1643 patients using statistical bias correction with proportional hazard analysis. Hepatology 1999;29:1124–30.
10. Tanaka H, Tsukuma H, Kasahara A, Hayashi N, Yoshihara H, Masuzawa M, et al. Effect of interferon therapy on the incidence of hepatocellular carcinoma and mortality of patients with chronic hepatitis C: a retrospective cohort study of 738 patients. Int J Cancer 2000;87:741–9.
11. Benvegnu L, Chemello L, Noventa F, Fattovich G, Pontisso P, Alberti A. Retrospective analysis of the effect of interferon therapy on the clinical outcome of patients with viral cirrhosis. Cancer 1998;83:901–9.
12. Valla DC, Chevallier M, Marcellin P, Payen JL, Trepo C, Fonck M, et al. Treatment of hepatitis C virus-related cirrhosis: a randomized, controlled trial of interferon alfa-2b versus no treatment. Hepatology 1999;29:1870–5.
13. Serfaty L, Aumaitre H, Chazouilleres O, Bonnand AM, Rosmorduc O, Poupon RE, et al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology 1998; 27:1435–40.
14. Nishiguchi S, Shiomi S, Nakatani S, Takeda T, Fukuda K, Tamori A, et al. Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. Lancet 2001;357:196–7.
15. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112:463–72.
16. Niederau C, Lange S, Heintges T, Erhardt A, Buschkamp M, Hurter D, et al. Prognosis of chronic hepatitis C: results of a large prospective cohort study. Hepatology 1998;28:1687–95.
17. Yoshida H, Arakawa Y, Sata M, Nishiguchi S, Yano M, Fujiyama S, et al. Interferon therapy prolonged life expectancy among chronic hepatitis C patients. Gastroenterology 2002;123:483–91.
18. Okanoue T, Itoh Y, Kirishima T, Daimon Y, Toyama T, Morita A, et al. Transient biochemical response in interferon therapy decreases the development of hepatocellular carcinoma and improves the long-term survival of chronic hepatitis C patients. Hepatology Res 2002;23:62–77.

19. Imazeki F, Yokosuka O, Fukai K, Saisho H. Favorable prognosis of chronic hepatitis C after interferon therapy by long-term cohort study. Hepatology 2003;38:493–502.
20. Kasahara A, Tanaka H, Okanoue T, Imai Y, Tsubouchi H, Yoshioka K, et al. Interferon treatment improves survival in chronic hepatitis C patients showing biochemical as well as virological responses by preventing liver-related death. J Viral Hepat 2004;11:148–56.
21. Davis GL, Balart LA, Schiff ER, Lindsay K, Bodenheimer HC, Perrillo RP, et al. Treatment of chronic hepatitis C with recombinant interferon alpha. A multicenter randomized controlled trial. N Engl J Med 1989;321:1501–6.
22. Di Bisceglie AM, Martin P, Kassianides C, Lisker-Melman M, Murray L, Waggoner J, et al. Recombinant interferon alpha therapy for chronic hepatitis C. A randomized, double blind placebo-controlled trial. N Engl J Med 1989;321:1506–10.
23. Hagiwara H, Hayashi N, Mita E, Hiramatsu N, Ueda K, Takehara T, et al. Quantitative analysis of hepatitis C virus RNA in serum during interferon alfa therapy. Gastroenterology 1993;104:877–83.
24. Kasahara A, Hayashi N, Hiramatsu N, Oshita M, Hagiwara H, Katayama K, et al. Ability of prolonged interferon treatment to suppress relapse after cessation of therapy in patients with chronic hepatitis C: a multicenter randomized controlled trial. Hepatology 1995;21:291–7.
25. Shiratori Y, Kato N, Yokosuka O, Imazeki F, Hashimoto E, Hayashi N, et al. Predictors of the efficacy of interferon therapy in chronic hepatitis C virus infection. Gastroenterology 1997;113:558–66.
26. McHutchison JG, Gordon SC, Schiff ER, Schiffman ML, Lee WM, Rustgi VK, et al. Interferon alpha 2b alone or combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998;339:1485–92.
27. Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, et al. Randomized trial of interferon alpha 2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998;352:1426–32.
28. Fried MW, Schiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL. Peginterferon alpha-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975–82.
29. Tanaka H, Tsukuma H. Hepatitis C virus. In: J Tooze, editor. Cancer survey, vol. 33. New York: Cold Spring Harbor Laboratory Press; 1999. p. 213–35.
30. Yoshizawa H. Trends of hepatitis virus carriers. Hepatology Res 2002;24:S28–39.
31. Tanaka H, Tsukuma H. Characteristics of Japanese patients with liver cancer—epidemiological study based on a comparison between male and female patients. Hepatology Res 2002;24:S11–20.
32. Okanoue T, Yasui K, Sakamoto S, Minami M, Nagao Y, Itoh Y, et al. Side effects of high-dose interferon therapy for chronic hepatitis C. J Hepatol 1996;25:283–91.
33. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Sheuer PJ. Classification of chronic hepatitis: grading and staging. Hepatology 1994;19:1513–20.
34. Statistics and Information Department, Japan Ministry of Health and Welfare. Vital statistics in Japan (in Japanese). Tokyo: Health and Welfare Statistics Association; 2002.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Hepatology Research 29 (2004) 142–147
Hepatology Research
www.elsevier.com/locate/ihepcom

The significance of interferon and ribavirin combination therapy followed by interferon monotherapy for patients with chronic hepatitis C in Japan

Naoki Hiramatsu[a], Akinori Kasahara[b], Fumihiko Nakanishi[c], Takashi Toyama[c], Masahiko Tsujii[c], Shingo Tsuji[c], Tatsuya Kanto[a], Tetsuo Takehara[a], Michio Kato[d], Harumasa Yoshihara[e], Masafumi Naito[f], Kazuhiro Katayama[f], Taizo Hijioka[g], Hideki Hagiwara[h], Shinji Kubota[i], Masahide Oshita[j], Haruya Meren[j], Manabu Masuzawa[j], Yoshimichi Haruna[k], Eiji Mita[l], Kunio Suzuki[l], Norio Hayashi[a,*]

[a] *Department of Molecular Therapeutics, Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita City, Osaka 565-0871, Japan*
[b] *Department of General Medicine, Osaka University Graduate School of Medicine, Osaka, Japan*
[c] *Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine, Osaka, Japan*
[d] *Osaka National Hospital, Osaka, Japan*
[e] *Osaka Rousai Hospital, Osaka, Japan*
[f] *Osaka Kouseinenkin Hospital, Osaka, Japan*
[g] *National Osaka South Hospital, Osaka, Japan*
[h] *Higashiosaka City Central Hospital, Osaka, Japan*
[i] *Kansai-Rousai Hospital, Hyoga, Japan*
[j] *Osaka Police Hospital, Osaka, Japan*
[k] *Osaka Prefectural Hospital, Osaka, Japan*
[l] *Saiseikai senri Hospital, Osaka, Japan*

Received 26 December 2003; received in revised form 16 March 2004; accepted 25 March 2004

Abstract

One hundred seventy-one patients with chronic hepatitis C were included in this study (genotype1 and high viral loads (1H), $n = 130$; non-1H, $n = 37$; N.D., $n = 4$). The combination therapy of interferon and ribavirin for 24 weeks with an additional 24 weeks of interferon monotherapy (48-week treatment) was undergone by 42 1H patients and 5 non-1H patients. The combination therapy of interferon and ribavirin was administered for 24 weeks in 67 1H patients and 22 non-1H patients. Among the 1H patients, the HCV relapse rate was significantly higher in those receiving 24-week combination treatment than in those receiving 48-week treatment (78% versus 42%, $P = 0.003$). Among the non-1H patients, no significant difference was found between them. Sustained virological response (SVR) rates were observed to decrease as the timing of HCV RNA disappearance was delayed. In spite of the small rate (16%), SVR was obtained from the patients who became negative for HCV RNA by week 24 (beyond week 12) only in those receiving 48-week treatment. In 1H patients, 24-week combination treatment followed by interferon monotherapy for 24 weeks was concluded to be the treatment offering the most hope among those that the medical insurance can be applied in Japan.

Keywords: Chronic hepatitis C; Interferon and ribavirin combination therapy; Combination therapy followed by IFN monotherapy

1. Introduction

Interferon is the only available treatment for patients with chronic hepatitis C since HCV was discovered in 1989 [1–4]. Thirty percent of patients with chronic hepatitis C achieved SVR by interferon therapy but the efficacy was not satisfactory. Furthermore, in the patients considered to be the most treatment-resistant, that is, the 1H patients, only 5–8% showed SVR. In Japan, 40–50% of the patients with chronic hepatitis C belong to the 1H group. Therefore, finding how to eradicate the HCV RNA

* Corresponding author. Tel.: +81-6-6879-3441; fax: +81-6-6879-3449.
E-mail address: hayashin@moltex.med.osaka-u.ac.jp (N. Hayashi).

1386-6346/$ – see front matter © 2004 Published by Elsevier B.V.
doi:10.1016/j.hepres.2004.03.008

of 1H patients is most important for the treatment of chronic hepatitis C.

Recently, ribavirin, a nucleic acid analogue, exhibiting in vitro activity against various kinds of DNA and RNA viruses has been developed. The combination therapy of ribavirin and interferon has been shown to be very useful in the eradication of HCV in patients with chronic hepatitis C [5–7], although the mechanism of action of ribavirin remains speculative and ribavirin monotherapy led to no significant decrease of the amount of HCV RNA in the patients with chronic hepatitis C [8]. Most recent studies, performed with large numbers of naïve patients, have shown that the combination therapy of interferon and ribavirin can increase the SVR rate two-fold compared with interferon monotherapy for patients with chronic hepatitis C [9–12]. Especially, in the 1H patients, the combination therapy of interferon and ribavirin was more useful than in the other patients. Furthermore, Poynard et al. [10] showed that 1H patients treated by combination therapy for 48 weeks had a higher SVR rate than those treated for 24 weeks (28% versus 8%). Therefore, the combination therapy of interferon and ribavirin for 48 weeks is recommended as the standard therapy for 1H patients in Europe and the United States [13,14].

In Japan, the combination therapy of interferon and ribavirin was approved in 2001. However, the duration of the combination therapy is limited to 24 weeks in the medical insurance. As mentioned above, the SVR rate in 1H patients treated by the combination therapy for 24 weeks was clearly lower than those treated for 48 weeks. Furthermore, prolonged interferon monotherapy was reported to suppress relapse after cessation of therapy and to achieve a higher SVR rate in patients with chronic hepatitis C [15]. This study assessed the efficacy of the combination therapy of interferon and ribavirin for 24 weeks with an additional 24 weeks of interferon monotherapy compared with that of the combination therapy for 24 weeks.

2. Patients and methods

2.1. Patients

The current study was conducted at Osaka University Hospital and the institutions of the Osaka Liver Disease Study Group. The 171 patients included in this study had HCV RNA detectable in serum by the polymerase chain reaction (PCR) method, had elevated ALT (above the upper limit of the normal) and had been histologically proven to have chronic hepatitis. No patients were positive for hepatitis B surface antigen and anti-human immunodeficiency virus antibody or had other forms of liver disease (such as alcoholic liver disease and autoimmune liver disease). This study protocol was carried out according to the ethical guidelines of the 1975 Declaration of Helsinki and informed consent was obtained from each patient.

2.2. Determination of HCV RNA levels and HCV genotype

Serum HCV RNA levels were quantified using branched DNA (bDNA) probe assay (version 2; Chiron, Dai-ichi Kagaku, Tokyo) [16,17] or combined PCR assay (Amplicor-HCV monitor assay) [18]. In this study, a high viral load, as described previously [16,18,19], was designated as the condition of a serum HCV RNA level of more than 10^6 equivalents/ml by bDNA assay or more than 10^5 copies/ml serum by Amplicor-HCV monitor assay. HCV genome typing was classified by serological genotyping assay [20].

2.3. Treatment schedule

Of the 171 patients with chronic hepatitis C enrolled in this study, 130 had HCV RNA with genotype 1 and high viral loads (1H group), which were difficult to eradicate by anti-viral therapy. Of the remaining 41 patients, 37 had HCV RNA with genotype 2 or low viral loads (non-1H group); genotype or viral levels could not be determined for four. One hundred thirty-six patients in whom treatment had been done without the discontinuation of interferon till the end of the scheduled duration were studied (1H, $n = 109$; non-1H, $n = 27$).

The combination therapy of interferon-α-2b and ribavirin was administered for 24 weeks in 67 patients of the 1H group and 22 patients of the non-1H group. In this protocol, interferon-α-2b was given intramuscularly every day for the first 2 weeks and then three times a week for the following 22 weeks in combination with ribavirin at a daily dose of 600 or 800 mg, depending on body weight (<60 or ≥ 60 kg, respectively). The combination therapy of interferon-α-2b and ribavirin for 24 weeks, followed by interferon-α-2b monotherapy three times a week for a further 24 weeks, was administered to 42 patients of the 1H group and 5 patients of the non-1H group. The pretreatment characteristics of the patients were similar (Table 1).

The starting doses of interferon-α-2b were 10 MU per day for 38, 6 MU per day for 127, and 3 MU per day for 6 patients. With ribavirin, 800 mg per day was started in 92, 600 mg per day in 77, and 400 mg per day in 2 patients. Among the 171 patients, the interferon dose was decreased in six patients during the treatment, and the interferon was stopped along with ribavirin in 33 patients (19%) due to side effects. The ribavirin dose was decreased in 43 patients (25%) during the treatment, and stopped without discontinuance of interferon in six patients. Eighty-seven patients (51%) completed treatment without discontinuance or dosage decrease of both drugs.

After the sufficient informed consent at the end of the combination therapy of interferon and ribavirin, the patients themselves decided whether to be treated for 24 or 48 weeks. The information included the results of clinical trials of the combination therapy for 24 and 48 weeks in other countries, such as the SVR rate, HCV relapse rate.

Table 1
Baseline characteristics of patients according to therapeutic protocol

	24-week treatment		48-week treatment
	1H group	Non-1H group	1H group
	67	22	42
Age (yo)	55.8 ± 10.9	55.7 ± 12.8	54.0 ± 11.7
M/F	40/27	15/7	28/14
ALT (IU/L)	107 ± 71	102 ± 45	103 ± 58
Fibrosis	1.9 ± 0.9	1.9 ± 1.2	1.8 ± 1.1
History of IFN treatment			
Naïve	34	11	17
Relapser	21	7	17
Non-responder	11	4	8
Unknown	1	0	0

Note: All comparisons are not significant. Twenty-four-week treatment, interferon plus ribavirin treatment for 24 weeks; 48-week treatment, interferon plus ribavirin treatment for 24 weeks followed by interferon monotherapy for 24 weeks. 1H group, patients with genotype 1 and high viral load; non-1H group, patients other than 1H group. Fibrosis, Knodell's histological score (category 4).

Also, side effects were presented and the combination therapy of interferon-α-2b and ribavirin for 48 weeks was explained as not being covered by medical insurance in Japan. In the 47 patients who agreed to receive the additional 24 weeks of interferon monotherapy, the starting doses of interferon-α-2b were 10 MU per day for 10, 6 MU per day for 35, and 3 MU per day for 2 patients. All patients completed the additional treatment although interferon was decreased only in one patient from 10 to 6 MU per day.

2.4. Statistical analysis

Age, histological scores before interferon therapy, and serum ALT levels are expressed as mean ± S.D. The chi-squared test was used for statistical analysis of the comparison between group frequencies. When appropriate, the clinical and laboratory features of the two groups were compared by Student's *t*-test. Histological evaluation was substituted as a variable for Knodell's histological scores [21].

3. Results

3.1. Results of interferon and ribavirin combination therapy

Seventy-five percent of all of the patients of 1H group (82/109), including not only patients who received 24-week treatment but also those who received 48-week treatment, had no detectable HCV RNA at 24 weeks after the beginning of combination therapy of interferon and ribavirin. This was also the case for 100% of the non-1H patients (27/27). In patients given 24-week treatment of combined interferon and ribavirin, 45 out of 67 of the 1H group were negative for HCV RNA at the end of therapy, but only 22% of the patients (10/45) showed no detectable HCV RNA at 24 weeks after cessation of therapy. On the other hand, HCV RNA was negative in all non-1H patients at the end of the 24-week treatment, and the SVR rate was 86% (19/22) (Fig. 1). In patients with 48-week treatment (24-week combination treatment, followed by 24-week interferon monotherapy), HCV RNA reappeared during interferon monotherapy (break through) in 11 out of 37 patients (30%) who were negative for HCV RNA at the end of 24-week combination therapy: SVR was finally reached in 15 out of 26 patients who continued to be sero-negative for HCV RNA at the end of 48-week treatment. On the other hand, HCV RNA was not cleared even by 48-week treatment in all five patients who were positive for HCV RNA at the end of 24-week treatment (Fig. 2). In the non-1H patients who received 48-week treatment, HCV RNA was negative in all five patients at the end of the 24-week treatment, and SVR was attained by 80% (4/5).

The HCV RNA relapse rate after treatment was compared according to the duration of treatment. In all patients, 57% of those receiving 24-week treatment (38/67) had HCV RNA relapse, as compared with 39% of those receiving 48-week treatment (12/31). Among the 1H patients, a significant dif-

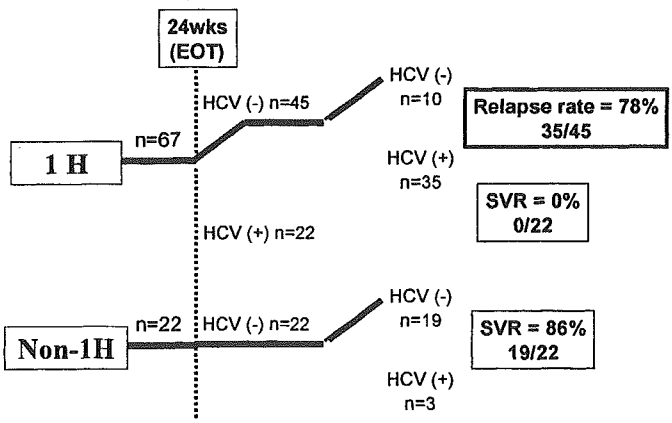

Fig. 1. Efficacy of the combination therapy (24-week treatment). 1H group, patients with genotype 1 and high viral load; non-1H group, patients other than those of the 1H group. EOT, end of treatment. HCV, serum HCV RNA positivity by polymerase chain reaction.

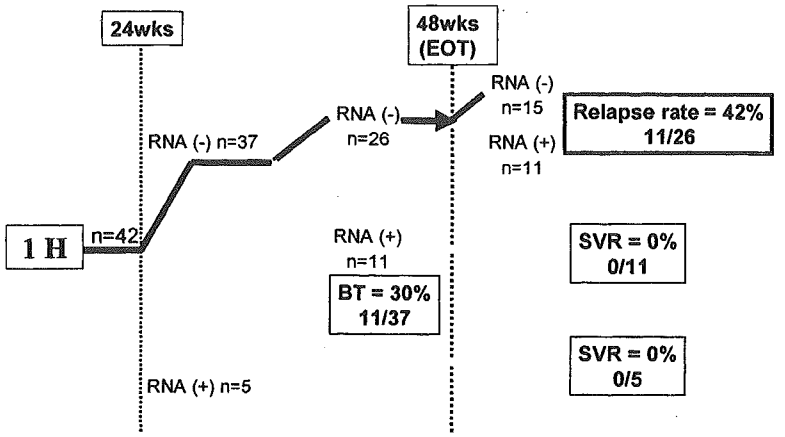

Fig. 2. Efficacy of the combination therapy followed by interferon monotherapy (48-week treatment). 1H group, patients with genotype 1 and high viral load; non-1H group, patients other than those of the 1H group. EOT, end of treatment. HCV, serum HCV RNA positivity by polymerase chain reaction. BT, break through.

ference was found in HCV relapse rate between those receiving 24-week treatment and those receiving 48-week treatment (78% versus 42%, $P = 0.003$). Among the non-1H patients, HCV RNA relapsed in 14% (3/22) of those receiving 24-week treatment (Fig. 1) and 20% (1/5) of those receiving 48-week treatment.

3.2. Timing of HCV RNA disappearance and efficacy of treatment

The relationship between the timing of HCV RNA disappearance and SVR rate according to the duration of treatment was evaluated. As shown in Fig. 3A, in all patients receiving 24-week treatment, 71% (12/17) of the patients who had no detectable HCV RNA by week 4, 61% (11/18) by week 8 (beyond week 4), and 21% (4/19) by week 12 (beyond week 8) had SVR. Although 11 patients became negative for HCV RNA by week 24 (beyond week 12), none of them attained SVR. A tendency for a decrease in the SVR rate was observed as the timing of the HCV RNA disappearance was delayed. In the patients receiving 48-week treatment, 86% (6/7) of those who had no detectable HCV RNA by week 4, 100% (6/6) by week 8 (beyond week 4), 40% (4/10) by week 12 (beyond week 8), and 16% (3/19) by week 24 (beyond week 12) attained SVR.

Among the 1H patients, the same tendency was also observed (Fig. 3B). In the patients receiving 24-week treatment, 50% (3/6) of those who had no detectable HCV RNA by week 4, 40% (4/10) by week 8 (beyond week 4), and 18% (3/17) by week 12 (beyond week 8) attained SVR. None of the 10 patients who became negative for HCV RNA by week 24 (beyond week 12) showed SVR. In the patients receiving 48-week treatment, 80% (4/5) of those who had no detectable HCV RNA by week 4, 100% (5/5) by week 8 (beyond week 4), 38% (3/8) by week 12 (beyond week 8), and 16% (3/19) by week 24 (beyond week 12) had SVR. In spite of the small rate (16%), SVR was obtained from the patients who became negative for HCV RNA by week 24 (beyond week 12) only in those receiving 48-week treatment.

Fig. 4 shows the relationship between the timing of HCV RNA disappearance and the prediction value in 1H patients who received the combination therapy of interferon and ribavirin for 24 weeks. As the timing of the HCV RNA disappearance was late, the positive prediction value decreases and the negative prediction value increases. In particular, the negative prediction value at week 12 was 100%, that is, none

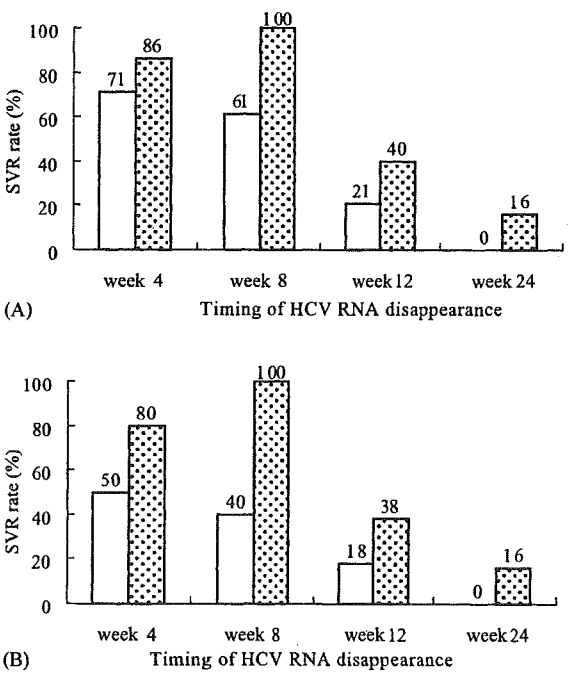

Fig. 3. Timing of HCV RNA disappearance and SVR rate (A) all patients, (B) patients with genotype 1 and high viral loads. (□) Combination therapy of interferon and ribavirin (24-week treatment); (▨) combination therapy followed by interferon monotherapy (48-week treatment).

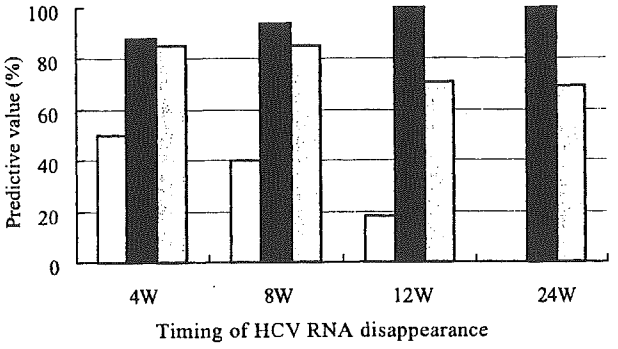

Fig. 4. Timing of HCV RNA disappearance and prediction value in patients with genotype 1 and high viral loads who received the combination therapy of interferon and ribavirin for 24 weeks. (□) Positive prediction value; (▩) negative prediction value; (■) predictive accuracy.

of the patients who were positive for HCV RNA at week 12 attained SVR.

4. Discussion

In Japan, randomized control studies were performed on the combination therapy of interferon and ribavirin for 24 weeks in patients with chronic hepatitis C, and the combination therapy was approved in November 2001. However, the duration of the combination therapy is limited to 24 weeks in the medical insurance because of the lack of clinical mega-trial evidence for the combination therapy for 48 weeks in Japan. From the results of international trials, the SVR rate in 1H patients treated by the combination therapy for 48 weeks has been shown to be higher than that of those treated for 24 weeks [10]. Moreover, for interferon monotherapy, prolonged interferon treatment was reported to suppress relapse after cessation of therapy and to lead to a higher SVR rate in patients with chronic hepatitis C [15]. Our strategy, the interferon and ribavirin combination therapy with an additional 24 weeks of interferon monotherapy, was conducted against this background.

Poynard et al. [22,23] evaluated the HCV RNA relapse rates after cessation of the combination therapy in naïve patients with chronic hepatitis C. Among patients with genotype 1, the relapse rates were 62% in those treated by interferon and ribavirin combination therapy for 24 weeks and 26% in those treated for 48 weeks: among patients with genotype 2/3, 21% in those for 24 weeks and 15% in those for 48 weeks. Among patients with genotype 1, the SVR rate increased due to suppression of the relapse rate by the combination therapy for 48 weeks. On the other hand, the patients with genotype 2/3 require only 24 weeks of therapy. In our study, patients with genotype 1 and high viral load (1H group) were evaluated, distinguishing them from others (non-1H group) since the efficacy of anti-viral therapy for the 1H patients has been known to be remarkably low. Among the 1H patients, the HCV relapse rate was significantly higher in those receiving 24-week combination treatment than in those receiving 48-week treatment, 24-week combination treatment followed by interferon monotherapy for 24 weeks (78% versus 42%, $P = 0.003$). Among the non-1H patients, no significant difference was found between those receiving 24-week treatment and those receiving 48-week treatment (14% versus 20%). These results indicate that our strategy of 48-week treatment is useful for the 1H group; the non-1H group seems to require only 24 weeks of therapy, similar to the patients with genotype 2/3 in the above-mentioned.

In the 1H patients receiving 48-week treatment, HCV RNA reappeared during interferon monotherapy in 11 out of 37 patients (30%) who were negative for HCV RNA at the end of 24-week combination therapy. The break through phenomenon should be taken into account when the efficacy of this treatment is evaluated. The SVR ratio in 1H patients receiving 48-week treatment can be calculated from the prevalence of undetectable HCV RNA at 24 weeks after the beginning of combination therapy of interferon and ribavirin (75%, 82/109), of break though (30%, 11/37) and of HCV relapse rate (42%, 11/26); the expected SVR is 30% ($(82/109) \times (1 - (11/37)) \times (1 - (11/26)) \fallingdotseq 0.30$). In the same manner, the SVR ratio in 1H patients receiving 24-week treatment is expected to be 17% $(82/109) \times (1 - (35/45)) \fallingdotseq 0.17$. In 1H patients, 48-week treatment, 24-week combination treatment followed by interferon monotherapy for 24 weeks, may be the useful treatment which can be actually performed in Japan.

The relationship between the timing of HCV RNA disappearance and the SVR rate according to the duration of treatment was evaluated. SVR rates decreased with a delay in the timing of HCV RNA disappearance in patients receiving 24-week treatment; the negative prediction value at week 12 was 100%, that is, none of the patients who were positive for HCV RNA at week 12 had SVR. In spite of the small rate (16%), SVR was attained for patients who became negative for HCV RNA by week 24 (beyond week 12) only in those receiving 48-week treatment. Accordingly, treatment withdrawal should be offered to patients who remain HCV RNA-positive after 12 weeks of therapy if the patient cannot continue treatment for 48 weeks for reasons including side effects and social issues. The patients who were positive for HCV RNA at week 24 should stop treatment because additional interferon monotherapy for 24 weeks could not clear HCV RNA in all five patients who were positive for HCV RNA at week 24.

Pol et al. [24] have reported the synergistic effect of ribavirin and interferon in 343 patients with the genotype 1b. In the study, ribavirin was administered for 4, 6, 12 months in combination with interferon-α for 12 months. A 12-month course of ribavirin achieved significantly greater virological efficacy than 6 or 4 months at the end of the 12-month course of interferon-α (59, 49, and 29%), the same trend seen at the end of follow-up duration (43, 36, and 21%). These results indicate that the maximum efficacy can be obtained

when ribavirin is administered for 12 months in combination with interferon. In our study, the break through ratio was expected to decrease with the administration of ribavirin for 48 weeks. In fact, a patient to whom ribavirin was given again after the break through, achieved marked decrease of HCV RNA (data not shown). Thus, in some patients who were negative for HCV RNA during the combination treatment, the additional ribavirin can be essential for eradicating HCV RNA. Longer duration of combination therapy with interferon and ribavirin is also most effective for suppressing HCV RNA relapse after 24 weeks of therapy [22,23]. Therefore, we would like to emphasize that combination therapy of ribavirin and interferon for 48 weeks should be permitted even in Japan. At present, 24-week combination therapy followed by 24-week interferon monotherapy is thought to be the most useful therapy that the medical insurance can be applied in Japan for suppressing the relapse rate of HCV RNA, leading to SVR.

Acknowledgements

In addition to the study authors, the following institutions and physicians were participants in the Osaka Liver Disease Study Group (Digestive Disease Study Group of Osaka Renaissance): Osaka National Hospital, R. Sakamori; Osaka Rousai Hospital, N. Kurashige, O. Nishiyama, and S. Shinzaki; Osaka Kouseinenkin Hospital, M. Kurokawa and A. Uemura; National Osaka South Hospital, T. Oze and N. Tsuda; Kansai Rousai Hospital, T. Yoshio; Osaka Police Hospital, K. Koga; Osaka Prefectural Hospital, A. Arimitsu; and Osaka University Graduate School of Medicine, S. Yamaguchi, M. Miyazaki, H. Miyatake, I. Itose, S. Egawa, and T. Nishida.

This work was supported by a Grant-in-Aid for Research on Hepatitis and BSE from the Ministry of Health Labour and Welfare of Japan, and Scientific Research from the Ministry of Education, Science, and Culture of Japan.

References

[1] Davis GL, Balart LA, Schiff ER, et al. Treatment of chronic hepatitis C with recombinant interferon alpha. A multicenter randomized controlled trial. N Engl J Med 1989;321:1501–6.

[2] Di Bisceglie AM, Martin P, Kassianides C, et al. Recombinant interferon alpha therapy for chronic hepatitis C. A randomized, double blind placebo-controlled trial. N Engl J Med 1989;321:1506–10.

[3] Hiramatsu N, Hayashi N, Kasahara A, et al. Improvement of liver fibrosis in chronic hepatitis C patients treated with natural interferon alpha. J Hepatol 1995;22:135–42.

[4] Kasahara A, Hayashi N, Mochizuki K, et al. Pretreatment viral load and response to interferon therapy for liver cirrhosis caused by hepatitis C virus: a multicenter controlled study. Hepatol Res 2000;16:124–38.

[5] Kakumu S, Yoshioka K, Wakita T, et al. A pilot study of ribavirin and interferon beta for the treatment of chronic hepatitis C. Gastroenterology 1993;105:507–12.

[6] Brillanti S, Garson J, Foli M, et al. A pilot study of combination therapy with ribavirin plus interferon alpha for alpha-interferon resistant chronic hepatitis C. Gastroenterology 1994;107:812–7.

[7] Lai MY, Kao JH, Yang PM, et al. Long-term efficacy of ribavirin plus interferon alfa in the treatment of chronic hepatitis C. Gastroenterology 1996;111:1307–12.

[8] Bondenheimer Jr HC, Lindsay KL, Davis GL, et al. Tolerance and efficacy of oral ribavirin treatment of chronic hepatitis C: a multicenter trial. Hepatology 1997;26:473–7.

[9] McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alpha-2b and ribavirin as initial treatment of relapse of chronic hepatitis C. N Engl J Med 1998;339:1485–92.

[10] Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon alpha-2b and ribavirin for 48 weeks or for 24 weeks versus interferon alfa-2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998;352:1426–32.

[11] Reichard O, Norkrans G, Fryden A, et al. Randomized double-blind, placebo-controlled trial of interferon alpha-2b with and without ribavirin for chronic hepatitis C. Lancet 1998;351:83–6.

[12] Davis GL, Esteban-Mur R, Rustgi V, et al. Interferon alpha-2b alone or in combination with ribavirin for the treatment or relapse of chronic hepatitis C. N Engl J Med 1998;339:1493–9.

[13] Consensus statement. EASL international consensus conference on hepatitis C. Paris, 26–28 February 1999. J Hepatol 1999;30:956–61.

[14] Bisceglie AM, Hoofnagle JH. Optimal therapy of hepatitis C. Hepatology 2002;36:S121–7.

[15] Kasahara A, Hayashi N, Hiramatsu N, et al. Ability of prolonged interferon treatment to suppress relapse after cessation of therapy in patients with chronic hepatitis C: a multicenter randomized controlled trial. Hepatology 1995;21:291–7.

[16] Yuki N, Hayashi N, Kasahara A, et al. Pretreatment viral load and response to prolonged interferon-α course for chronic hepatitis C. J Hepatol 1995;22:457–63.

[17] Lau YN, Davis G, Kniffen J, et al. Significance of serum hepatitis C virus RNA levels in chronic hepatitis C. Lancet 1993;341:1501–4.

[18] Shiratori Y, Kato N, Yokosuka O, et al. Predictors of the efficacy of interferon therapy in chronic hepatitis C virus infection. Gastroenterology 1997;113:558–66.

[19] Hagiwara H, Hayashi N, Mita E, et al. Quantitative analysis of hepatitis C virus RNA in serum during interferon alfa therapy. Gastroenterology 1993;104:877–83.

[20] Tanaka T, Tsukiyama-Kohara K, Yamaguchi K, et al. Significance of specific antibody assay for genotyping of hepatitis C virus. Hepatology 1994;19:1347–53.

[21] Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981;1:431–5.

[22] Poynard T, Marcellin P, Lee SS, et al. Randomized trial of interferon α2b plus ribavirin for 48 weeks or for 24 weeks versus ineterferon α2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C. Lancet 1998;352:1426–32.

[23] Poynard T, McHutchison J, Goodman Z, et al. Is an "A la Carte" combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? Hepatology 2000;31:211–8.

[24] Pol S, Nalpas B, Bourliere M, et al. Combination of Ribavirin and interferon-alfa surpasses high doses of interferon-alfa alone in patients with genotype-1b-related chronic hepatitis C. Hepatology 2000;31:1338–44.

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

A. Kasahara,[1] H. Tanaka,[2] T. Okanoue,[3] Y. Imai,[4] H. Tsubouchi,[5] K. Yoshioka,[6] S. Kawata,[7] E. Tanaka,[8] K. Hino,[9] K. Hayashi,[5] S. Tamura,[7] Y. Itoh,[3] K. Kiyosawa,[8] S. Kakumu,[10] K. Okita[9] and N. Hayashi[11] [1]*Department of General Medicine, Osaka University Graduate School of Medicine;* [2]*Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka;* [3]*Third Department of Internal Medicine, Kyoto Prefectural University of Medicine, Kyoto;* [4]*Department of Internal Medicine, Ikeda Municipal Hospital, Ikeda;* [5]*Second Department of Internal Medicine, Miyazaki Medical College, Miyazaki;* [6]*Third Department of Medicine, Nagoya University Graduate School of Medicine, Nagoya;* [7]*Department of Internal Medicine and Molecular Science, Osaka University Graduate School of Medicine, Osaka;* [8]*Second Department of Medicine, Shinshu University School of Medicine, Shinshu;* [9]*First Department of Medicine, Yamaguchi University School of Medicine, Yamaguchi;* [10]*Department of Internal Medicine, Division of Gastroenterology, Aichi Medical University School of Medicine, Aichi; and* [11]*Department of Molecular Therapeutics, Osaka University Graduate School of Medicine, Osaka, Japan*

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.

Correspondence: Akinori Kasahara MD, PhD, Department of General Medicine, Osaka University Graduate School of Medicine, 2-15, Yamadaoka, Suita, Osaka 565-0871, Japan. E-mail: kasahara@hp-gm.med.osaka-u.ac.jp

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.

