

Discussion

Lamivudine-resistant HBV mutants have been reported in patients with chronic hepatitis B treated with lamivudine for more than 6 months, and the reported rate of emergence during the therapy ranges from 14 to 43% during the first year [4–6, 8, 9]. Several studies attest to the emergence rates of YMDD mutants increasing gradually with the duration of lamivudine from 14% at 1 year to 38% at 2 years, and further to 53% at 3 years [9, 20]. There have been few reports, however, in which the rate of early emergence of YMDD mutants was investigated in sequential sera from patients within 6 months of lamivudine therapy. In most studies, YMDD mutants were detected in patients who had already developed virological breakthroughs with the emergence of YMDD mutants after long-term lamivudine [11, 12, 15]. This is attributed to direct sequencing or even the RFLP assay not being sensitive enough for detecting YMDD mutants coexisting with a huge excess of the wild-type HBV during an early stage of lamivudine treatment.

We have previously reported a highly sensitive method utilizing PNA and RFLP for the detection of YMDD mutant [16]. This PNA-mediated PCR clamping with RFLP assay made it possible to detect YMDD mutants coexisting with the wild-type HBV in as little as 0.01–0.001% of total HBV DNA with a sensitivity 100- to 1,000-fold higher than that of the conventional RFLP assay. By means of this sensitive method, YMDD mutants are found even in chronic hepatitis B patients who have not received lamivudine [16]. Paik et al. [19] previously reported early detection of YMDD mutants at 2 weeks (14.3%), as well as a high rate of their appearance at 12 weeks (60.7%) [19] with an RFLP assay. In the present study, a more sensitive assay than they used was applied for the detection of YMDD mutants in an early phase of lamivudine treatment. Furthermore, the difference of the effect of lamivudine therapy was evaluated and the features of the emergence of YMDD mutants were compared between cirrhotic and noncirrhotic patients.

The results obtained clearly demonstrated that YMDD mutants had been detected since a very early stage such as 1 month (13%) and 3 months (18%), which is attributed to a high sensitivity of the detection system employed [16]. YMDD mutants (YMDD) were also detected in pre-treatment serum from a cirrhotic patient, in confirmation of preexisting mutants in patients with chronic hepatitis B who had not received lamivudine [16] and the detection of YMDD mutants in some lamivudine-naive asymptomatic HBV carriers [21].

The appearance rate of YMDD mutant was 39% at 1 year and not markedly different from those of previous reports. The cumulative appearance rate of YMDD mutants at 12 months, however, was surprisingly high and reached 59%. The appearance rate of YMDD mutants at 3 months was 18.4% and lower than the 60.7% previously reported [19]. It is hard to explain the discrepancy, because the method used for detecting YMDD mutants in the present study is more sensitive than the one they used. Although the reason is unclear, differences in HBV genotypes, geographic factors either endemic or nonendemic, and ethnic backgrounds of the patients studied may have led to inconsistent findings.

The cumulative appearance rate was considerably higher than the emergence rate of YMDD mutants at each point. It is remarkable that this was caused by YMDD mutants that would have appeared temporarily and disappeared later. Taken altogether, the emergence of YMDD mutants would not always be related to breakthrough hepatitis. There is a certain possibility that YMDD mutants had been got rid of by the host immunity that is known to clear them after acute exacerbation [18], or that these YMDD mutants are minor strains of replication-incompetent HBV variants. To comprehend whether detected mutants can induce breakthrough hepatitis, other potential factors such as HBV DNA levels of mutants and host immune responses to HBV should be analyzed.

The appearance rate of YMDD mutants was higher in cirrhotic than noncirrhotic patients. Especially, the appearance rate of YMDD mutants in cirrhotic patients at 12 months (83%) was much higher than that of noncirrhotic patients (27%); it was responsible for lower rates of HBV DNA loss in cirrhotic patients at 12 months. Previous studies have implicated HBV DNA levels and ALT levels, as well as HBeAg titers, in the appearance of YMDD mutants and DNA breakthrough [22, 23]. The results obtained suggest that the progression of liver disease would be related to the appearance of YMDD mutants.

In conclusion, the present study has demonstrated with the use of a highly sensitive method that YMDD mutants emerge more frequently in cirrhotic than noncirrhotic patients on lamivudine therapy. These mutants, however, were not always related to breakthrough hepatitis. Further and prolonged studies with larger numbers of patients are needed to explain this issue. It is to be hoped that the highly sensitive method is instrumental in monitoring YMDD mutants in patients during or before lamivudine treatment to obtain more insight into the therapeutic strategies to be adopted for treating chronic hepatitis B.

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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. Okita⁹ and N. Hayashi¹¹ ¹Department of General Medicine, Osaka University Graduate School of Medicine; ²Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; ³Third Department of Internal Medicine, Kyoto Prefectural University of Medicine, Kyoto; ⁴Department of Internal Medicine, Ikeda Municipal Hospital, Ikeda; ⁵Second Department of Internal Medicine, Miyazaki Medical College, Miyazaki; ⁶Third Department of Medicine, Nagoya University Graduate School of Medicine, Nagoya; ⁷Department of Internal Medicine and Molecular Science, Osaka University Graduate School of Medicine, Osaka; ⁸Second Department of Medicine, Shinshu University School of Medicine, Shinshu; ⁹First Department of Medicine, Yamaguchi University School of Medicine, Yamaguchi; ¹⁰Department of Internal Medicine, Division of Gastroenterology, Aichi Medical University School of Medicine, Aichi; and ¹¹Department of Molecular Therapeutics, Osaka University Graduate School of Medicine, Osaka, Japan

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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

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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						Total (n = 2698)	Untreated (n = 256)	P-value
	Virological response		Biochemical response						
	SVR (n = 738)	non-SVR (n = 1930)	SBR (n = 901)	TBR (n = 701)	BNR (n = 1096)				
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 (range)	91 (7–1110)	92 (11–1195)	87 (7–1110)	79 (13–1195)	103 (13–828)	92 (7–1195)	98 (9–563)	0.57	
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					Total (n = 2698)	Untreated (n = 256)
	Virological response		Biochemical response				
	SVR (n = 738)	non-SVR (n = 1930)	SBR (n = 901)	TBR (n = 701)	BNR (n = 1096)		
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 ($P = 0.18$).

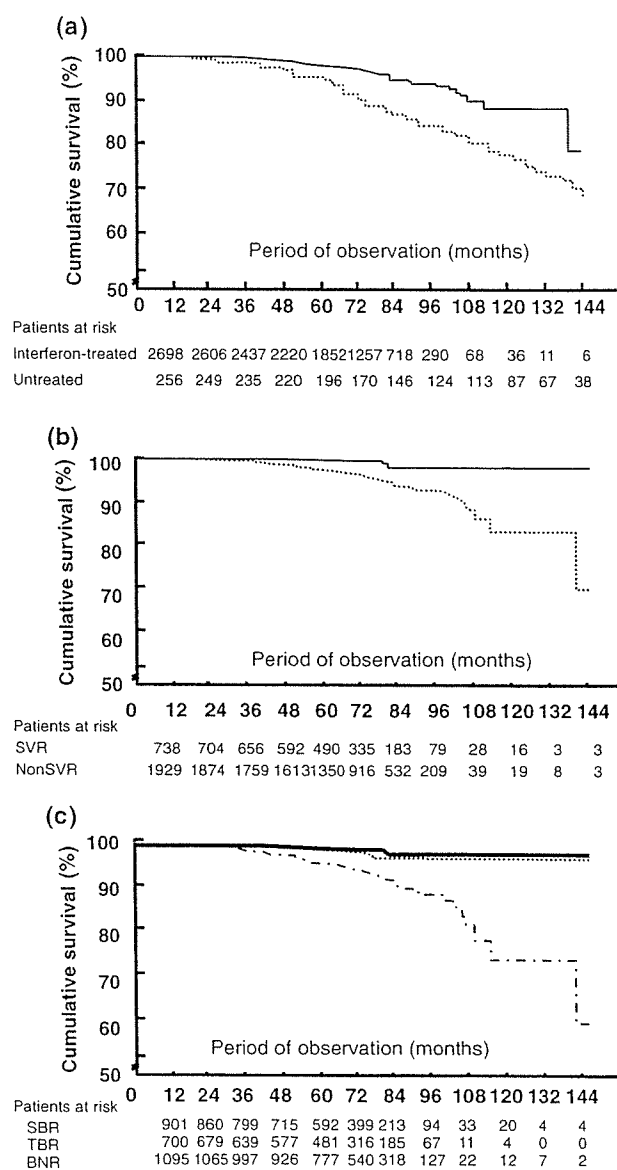


Fig. 1 Cumulative survival rates from all causes of death for patients with chronic hepatitis C. (a) For interferon-treated patients (solid line) and untreated patients (dotted line). (b) According to the virological response to interferon therapy; sustained virological responders (SVR) (solid line) 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
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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Interferon therapy for aged patients with chronic hepatitis C: improved survival in patients exhibiting a biochemical response

YASUHARU IMAI¹, AKINORI KASAHARA², HIDEO TANAKA³, TAKESHI OKANOUE⁴, NAOKI HIRAMATSU⁵, HIROHITO TSUBOUCHI⁶, KENTARO YOSHIOKA⁷, SUMIO KAWATA⁸, EIJI TANAKA⁹, KEISUKE HINO¹⁰, KATSUHIRO HAYASHI⁶, SHINJI TAMURA¹¹, YOSHITO ITOH⁵, YUTAKA SASAKI¹², KENDO KIYOSAWA⁹, SHINICHI KAKUMU¹³, KIWAMU OKITA¹⁰, and NORIO HAYASHI⁴

¹Department of Internal Medicine, Ikeda Municipal Hospital, 3-1-18 Johnan, Ikeda 563-8510, Japan

²Department of General Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

³Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

⁴Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan

⁵Department of Molecular Therapeutics, Osaka University Graduate School of Medicine, Osaka, Japan

⁶Second Department of Internal Medicine, Miyazaki Medical College, Miyazaki, Japan

⁷Division of Gastroenterology, Department of Internal Medicine, Nagoya University School of Medicine, Nagoya, Japan

⁸Second Department of Medicine, Yamagata University School of Medicine, Yamagata, Japan

⁹Internal Medicine, Shinshu University School of Medicine, Matsumoto, Japan

¹⁰Department of Gastroenterology and Hepatology, Yamaguchi University School of Medicine, Yamaguchi, Japan

¹¹Department of Internal Medicine and Molecular Science, Osaka University Graduate School of Medicine, Osaka, Japan

¹²Department of Gastroenterology and Hepatology, Graduate School of Medical Science, Kumamoto University, Kumamoto, Japan

¹³Department 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

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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							P value	
	Virological response			Biochemical response					
	Sustained response (n = 161)	Non-response (n = 484)	Total (n = 645)	Sustained response (n = 206)	Transient response (n = 144)	Non-response (n = 299)	Total (n = 649)		
Age (years: mean \pm SD)	63.6 \pm 3.0	63.3 \pm 2.9	63.3 \pm 2.9	63.8 \pm 3.1	63.0 \pm 2.8	63.1 \pm 2.8	63.3 \pm 2.9	64.1 \pm 3.1	0.06
Age distribution (years: %)									
60-64	67.7	71.1	71.1	63.6	75.0	72.9	70.4	56.9	0.03
≥ 65	32.3	28.9	28.9	36.4	25.0	27.1	29.6	43.1	
Male/Female	110/51	272/212	272/212	134/72	80/64	171/128	385/264	31/27	0.38
Histologic staging score (%)									
0	0.6	0.2	0.2	0.5	0.0	0.3	0.3	5.2	0.06
1	24.8	18.2	18.2	27.7	25.0	12.4	20.0	31.0	
2	29.2	27.7	27.7	26.7	28.5	28.8	28.0	20.7	
3	39.8	46.9	46.9	40.3	39.6	50.5	44.8	31.0	
4	5.6	7.0	7.0	4.9	6.9	8.0	6.8	12.1	
ALT (IU/l: mean \pm SD)	113 \pm 82	107 \pm 68	107 \pm 68	110 \pm 86	87 \pm 45	117 \pm 69	108 \pm 71	105 \pm 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						Total	Control group
	Virological response		Biochemical response		Non-response	Total		
	Sustained response	Non-response	Sustained response	Transient response				
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		

^aThe log rank test was used to determine the difference against the control group

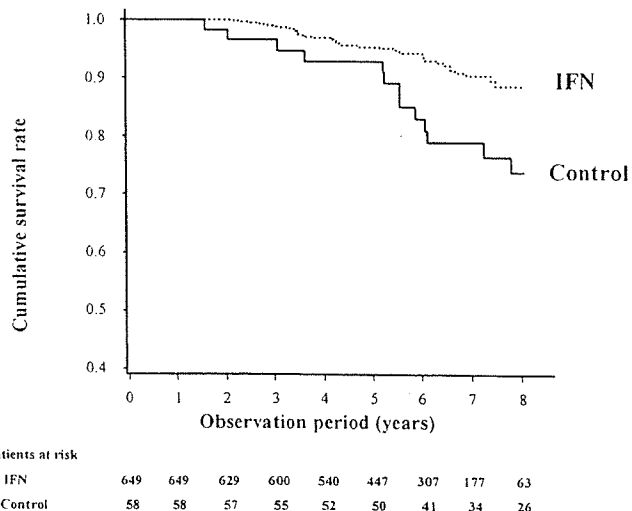


Fig. 1. Cumulative survival rates in the interferon (IFN; dotted line) and control (solid line) groups. Log-rank test of the two curves showed a significant difference between the two groups ($P = 0.003$)

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

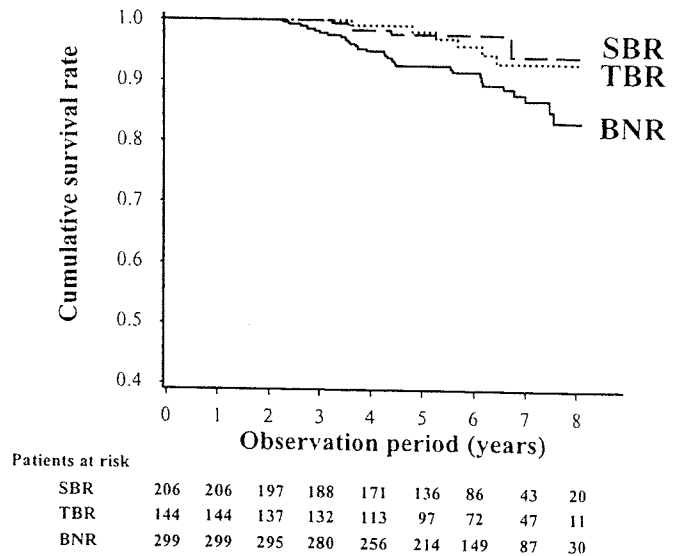


Fig. 2. Cumulative survival rates in the IFN-treated patients, categorized by sustained biochemical response (SBR; dashed line), transient biochemical response (TBR; dotted line), and biochemical non-response (BNR; solid line). Log-rank test showed significant differences between SBR and BNR ($P = 0.007$)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

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

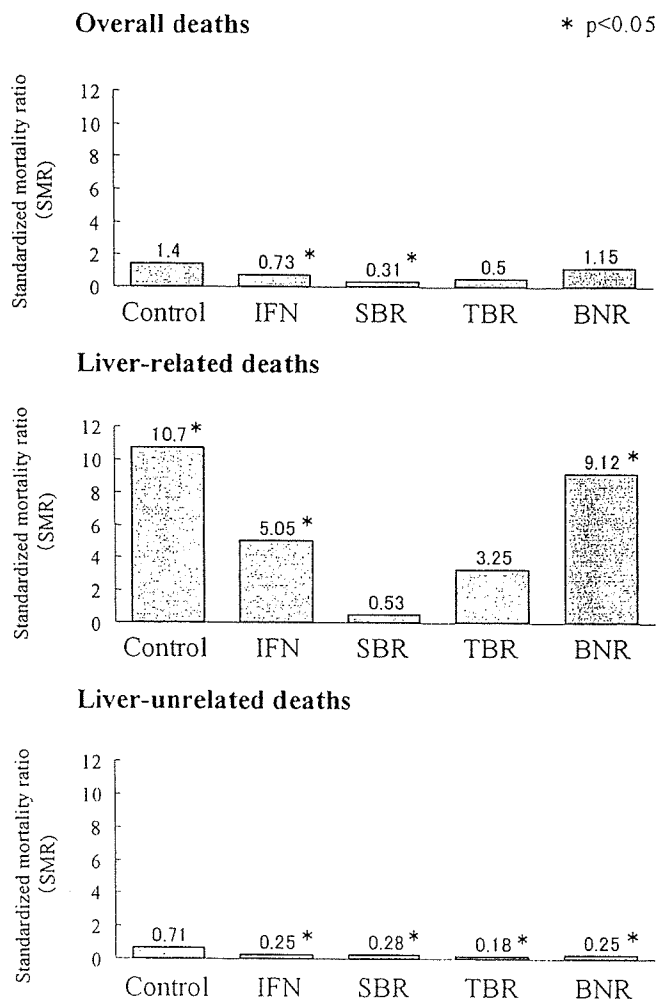


Fig. 3. Standardized mortality ratios (SMRs) for overall, liver-related, and liver-unrelated deaths. *SBR*, sustained biochemical response; *TBR*, transient biochemical response; *BNR*, biochemical non-response. When the SMR did not include unity, we considered the difference from the expected number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

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

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

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

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

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

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

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

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

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