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CLINICAL RESEARCH STUDY

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Necessities of Interferon Therapy in Elderly Patients with Chronic Hepatitis C

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ABSTRACT

BACKGROUND: The significance of antiviral therapy for elderly patients with chronic hepatitis C virus (HCV) infection has not been elucidated.

PATIENTS AND METHODS: Among 5645 patients with HCV-related chronic liver disease, the prognosis of 1917 elderly patients aged 60 years or more was analyzed. A total of 454 patients underwent interferon (IFN) therapy. By using multivariate analysis, carcinogenesis and survival were analyzed according to initial findings.

RESULTS: At 10 and 15 years, cumulative survivals in untreated elderly patients were 90.7% and 72.7% in the high platelet ($\geq$150,000/mm^3) group, 78.6% and 47.8% in the intermediate (100,000-149,000/mm^3) group, and 52.5% and 25.0% in the low platelet group ($<$100,000/mm^3), respectively. At 5 and 10 years, hepatocarcinogenesis rates in the intermediate and low platelet groups were 10.9% and 21.6% in the IFN group (N = 217) and 19.5% and 43.0% in the untreated group (N = 459), respectively ($P = .0005$). IFN independently decreased carcinogenesis risk with a hazard ratio of 0.56 ($P = .035$). In the high platelet group, 5- and 10-year carcinogenesis rates were 3.7% and 8.3% in the IFN-treated group (N = 228) and 5.1% and 14.0% in the untreated group (N = 585), respectively ($P = .69$). IFN treatment significantly increased cumulative survivals in the lower platelet subgroup ($P = .0001$) but did not affect the higher platelet subgroup ($P = .08$). IFN was independently associated with a longer survival in the lower platelet subgroup (hazard ratio 2.33, $P = .005$).

CONCLUSION: In elderly patients with chronic HCV, IFN for a subgroup with intermediate and low platelet counts had significant advantages in regard to hepatocarcinogenesis and survival.

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KEYWORDS: Chronic hepatitis C virus; Elderly; Hepatocellular carcinogenesis; Interferon; Survival

Hepatitis C virus (HCV) is one of the principal causes of hepatocellular carcinoma and often causes high morbidity and mortality in many countries.[1-5] Because interferon (IFN) has antiviral, antifibrotic, and anti-inflammatory actions, it is still a main arm in the treatment of chronic HCV.[6,7] Many authors have demonstrated that IFN prevents hepatocarcinogenesis and eventually prolongs the survival period of patients.[8-13] Radical eradication of HCV by IFN depends on viral load, HCV subtype, certain mutations of hepatitis virus gene, liver histology, modes of IFN administration, and various host factors, including a patient's age.[14-16] When a significant side effect occurs during IFN therapy, cessation or early withdrawal of the therapy often failed to attain a successful result. Early withdrawal and treatment failure are likely more common in elderly patients and patients with an advanced stage of liver disease.

The number and rate of elderly patients with HCV-positive chronic hepatitis are currently increasing in the United States and Japan[17-19] because of a significant decrease of new blood-borne HCV infections and an aging

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society, such as in Japan. In elderly patients with chronic hepatitis or cirrhosis type C, adverse effects of IFN are more prevalently found and hematologic disorders often disturb the completion of the therapy. As a result, IFN administration is considered less effective in elderly patients.[16,20-22] Because the fibrotic stage of liver disease is often correlated with a patient's age, an elderly patient naturally has a high risk of carcinogenesis and mortality. IFN is effective in reducing hepatocarcinogenesis and improving the survival of patients with HCV-related chronic hepatitis, but the clinical influence of IFN is considered less advantageous in elderly patients because of the short life expectancy. There has been little information on the prognosis of elderly patients with HCV-related chronic liver disease and the significance of antiviral therapy for elderly patients.

To clarify whether IFN had similar advantages between young and elderly patients, we analyzed a large cohort of HCV-positive elderly patients in regard to hepatocellular carcinogenesis and survival at a single institution. We also attempted to elucidate favorable indications and the best candidates for IFN therapy among elderly patients, if any.

CLINICAL SIGNIFICANCE

- Significant differences in hepatocarcinogenesis and survival exist among patients with HCV, according to initial platelet count.
- IFN for a subgroup with intermediate and low platelet counts had significant advantages in regard to hepatocarcinogenesis and survival of elderly patients with chronic HCV.
- Asymptomatic elderly patients with HCV should be observed carefully as to hepatocarcinogenesis by using ultrasonography when the platelet count is 150 × 1000/mm^3 or less.
- IFN therapy should be considered in elderly patients when they have intermediate and low platelet counts.
- In view of the side effects in elderly patients, treatment should be initiated as soon as possible after diagnosis of chronic HCV.

PATIENTS AND METHODS

Entire Population and Analyzed Cohorts

A total of 7235 patients were diagnosed with HCV-positive chronic liver disease with positive anti-HCV antibody and detectable HCV-RNA (nested polymerase chain reaction) and negative hepatitis B surface antigen from 1974 to 2004 at the Department of Hepatology, Toranomon Hospital, Tokyo. Anti-HCV and HCV-RNA were assayed using stored frozen sera. There were 4121 men and 3114 women, with a median age of 54 years (range, 1-92 years). We excluded 1144 patients with acute hepatitis, overt alcoholic liver disease or fatty liver, association of other types of liver disease (eg, primary biliary cirrhosis, autoimmune hepatitis), or association with hepatocellular carcinoma or other. We also excluded 446 patients with a short observation period (<6 months).

There were 3728 patients aged less than 60 years and 1917 patients aged 60 years or more. The diagnosis was established by peritoneoscopy or biopsy in 636 patients and by clinical data in 1281 patients. The ratio of women was higher (36.9% vs 54.4%, $P < .001$) and history of IFN therapy was lower (60.3% vs 23.7%, $P < .001$) in elderly patients. Median albumin value was lower (4.3 vs 4.1 g/dL, $P < .001$) and platelet count was lower (181,000 vs 155,000/mm^3, $P < .001$) in elderly patients. This study analyzed 1917 elderly patients with HCV: 454 patients (23.7%) with IFN therapy and 1463 patients (76.3%) without IFN therapy.

Interferon Treatment and Judgment of Effect

Among 454 patients with IFN therapy, 413 received IFN monotherapy and 41 received IFN plus ribavirin combination therapy as an initial antiviral therapy. Of 413 patients with IFN monotherapy, 272 patients received IFN every day for the first 2 to 8 weeks and then 2 to 3 times per week for the following 16 to 96 weeks (median, 24 weeks), 108 patients received IFN 3 times per week for 24 to 104 weeks, and 33 patients received IFN for 4 to 8 weeks. Among 346 patients without viral elimination after initial IFN therapy, 186 patients underwent repeated IFN therapy including IFN plus ribavirin combination therapy. The age at the time of initiation of therapy ranged from 60 to 84 years, with a median of 64 years.

Most patients (N = 451) with IFN therapy showed varied degrees of influenza-like symptoms, leukocytopenia, and thrombocytopenia. Forty-three patients discontinued IFN therapy because of significant adverse reactions: depression in 10 patients, marked anorexia in 9 patients; psychosis, epilepsy, or loss of consciousness in 8 patients; ophthalmic diseases in 3 patients; severe cytopenia in 3 patients; interstitial pneumonia in 2 patients; and other conditions in 8 patients. No patients had decompensated liver disease with ascites, encephalopathy, jaundice, or variceal bleeding.

Judgment of IFN effect was classified according to elimination of HCV RNA and alanine aminotransferase for 6 months after the end of treatment. Sustained virologic response was defined as persistent disappearance of HCV RNA after therapy, biochemical response was defined as normal alanine aminotransferase values without elimination of HCV RNA for at least 6 months after therapy, and no response was defined as persistently abnormal or only transient normalization of alanine aminotransferase for less than 6 months. Because 12 patients (2.6%) were lost to follow-up and 49 patients (10.8%) were still in the course of IFN therapy, the judgment was made in 393 (86.6%) of 454 patients.

Table 1 Profiles and Laboratory Data of 1917 Elderly Patients at the Initial Visit to Toranomon Hospital

	No Therapy N = 1463	IFN Therapy N = 454	P^c
Demography			
Sex (M/F)	660/803	214/240	.45
Age (y)[a]	65 (60-88)	62 (60-80)	<.001
Observation period (y)[a]	5.91 (0.5-27.6)	6.23 (0.5-17.6)	.23
Lost to follow-up (y)	165 (11.3%)	12 (2.6%)	<.001
Laboratory Data[b]			
Albumin (g/dL)	4.1 (3.8-4.3)	4.1 (3.9-4.3)	.11
Bilirubin (mg/dL)	0.6 (0.5-0.9)	0.7 (0.5-0.8)	.14
Aspartic aminotransferase (IU/L)	51 (33-83)	70 (46-106)	<.001
Alanine aminotransferase (IU/L)	56 (32-97)	90 (56-148)	<.001
Hemoglobin (g/dL)	13.8 (12.9-14.7)	14.2 (13.3-15.1)	<.001
Platelet count (×1000/mm^3)	157 (120-198)	150 (122-195)	0.12
Alpha-fetoprotein (ng/mL)	4 (3-6)	4 (3-6)	.80
HCV			
subtype 1 (1a/1b)	714 (79.2%)	154 (58.8%)	<.001
subtype 2 (2a/2b)	150 (16.6%)	102 (38.9%)	
others	38 (4.2%)	6 (2.3%)	

IFN = interferon; HCV = hepatitis C virus.
[a]Expressed by median (range).
[b]Expressed by median (25th percentile, 75th percentile).
[c]Mann–Whitney or chi-square test.

Follow-up of and Diagnosis of Hepatocellular Carcinoma

Follow-up of patients was made on a monthly to trimonthly basis after the initial visit. Imaging diagnosis was made 1 or more times per year with ultrasonography, computed tomography, or magnetic resonance imaging.

Statistical Analysis

Obtained clinical data were analyzed on an intention-to-treat basis. Nonparametric procedures were used for the analysis of background characteristics of the patients, including the Mann–Whitney *U*, Kruskal–Wallis, and chi-square tests.

Hepatocellular carcinogenesis and survival were calculated using the Kaplan–Meier test. The differences in carcinogenesis curves were tested using the log-rank test.[23] Independent factors associated with the appearance rate of hepatocellular carcinoma were studied using time-dependent Cox regression analysis.[24] The following 16 variables were analyzed for potential covariates for liver carcinogenesis at the initial hospital visit: age, sex, total alcohol intake, family history of liver disease, history of blood transfusion, association of diabetes, aspartic aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, albumin, bilirubin, hemoglobin, platelet count, serologic grouping of HCV, IFN administration, and effect of IFN treatment (time-dependent variable). A *P* value of less than .05 was considered significant. Statistical analysis was performed using the Statistical Package for the Social Sciences version 11.[25]

RESULTS

Demographics of Elderly Patients with or without Interferon Therapy

Table 1 summarizes the profiles and data of the 1917 elderly patients with or without IFN therapy during clinical course. The median age of the patients with IFN was younger by 3 years. Although aminotransferases were significantly higher in the treated group, albumin, bilirubin, and platelet count were not different between the 2 groups.

Hepatocarcinogenesis and Survival without Interferon Therapy

Liver cancer developed in 285 (19.5%) of 1463 elderly patients without IFN therapy. Hepatocarcinogenesis rates were 13.1% at the end of 5 years, 29.9% at 10 years, 45.5% at 15 years, and 55.1% at 20 years. Carcinogenesis rates were calculated in subgroups according to initial platelet count: high (≥150,000/mm^3), intermediate (100,000-149,000/mm^3), and low (<100,000/mm^3). Cumulative carcinogenesis rates in the subgroups of high, intermediate, and low platelet counts were 5.1%, 14.2%, and 32.1% at 5 years, 14.0%, 34.2%, and 63.4% at 10 years, and 26.1%, 57.5%, and 74.9% at 15 years, respectively (Figure 1). The carcinogenesis rate was significantly different among the 3 subgroups ($P < .0001$).

Survival in the elderly patients without IFN therapy was 92.9% at 5 years, 76.6% at 10 years, 54.3% at 15 years, and 37.2% at 20 years. Survivals in the subgroups with high, intermediate, and low platelet counts were 97.9%, 95.9%,

and 86.8% at 5 years, 90.7%, 78.6%, and 52.5% at 10 years, and 72.7%, 47.8%, and 25.0% at 15 years, respectively (Figure 2). A significant difference was observed among the 3 subgroups ($P < .0001$).

Adverse Effects and Effect of Interferon in the Elderly

Thirty-nine patients discontinued IFN therapy because of adverse effects: severe fatigue or anorexia in 10 patients (25.6%), depression in 10 patients (25.6%), hematologic disorder in 6 patients (15.4%), ophthalmic disorders in 4 patients (10.3%), and other side effects in 9 patients (23.1%). Duration of the therapy ranged from 2 weeks to 8.1 years, with a median of 24 weeks.

Among 393 patients with available judgment of IFN effect, 140 (35.6%) had a sustained virologic response, 80 (20.4%) had a biochemical response, and 173 (44.0%) had no response.

Hepatocarcinogenesis Rates in Elderly Patients with or without Interferon

During observation, hepatocellular carcinoma developed in 334 (17.4%) of 1917 patients: 285 (19.5%) in the untreated group and 49 (10.8%) in the IFN group.

Hepatocarcinogenesis rates in the untreated and IFN groups were 13.1% and 7.0% at 5 years, 29.9% and 13.9% at 10 years, and 45.5% and 33.4% at 15 years, respectively. The carcinogenesis rate in the IFN-treated group was significantly lower than in the untreated group (log-rank test, $P < .0001$).

Carcinogenesis rates also were evaluated in the subgroups with sustained virologic response (N = 140), biochemical response (N = 80), and no response (N = 173). Cumulative carcinogenesis rates were 2.5%, 1.3%, and 9.1% at 5 years, 2.5%, 11.0%, and 18.1% at 10 years, and 2.5%, 39.6%, and 41.2% at 15 years, respectively. A significant difference was found among the 4 groups, including the untreated patient group ($P < .0001$).

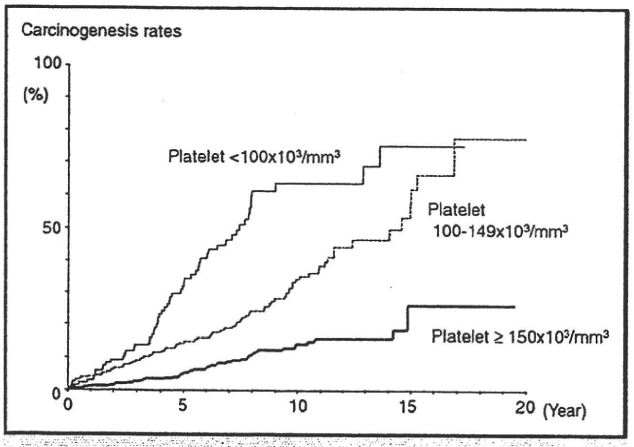

Figure 1 Hepatocarcinogenesis rates in patients without IFN therapy, according to initial platelet count. The lower the initial platelet count was, the higher the hepatocellular carcinogenesis was in the untreated cohort ($P < .0001$).

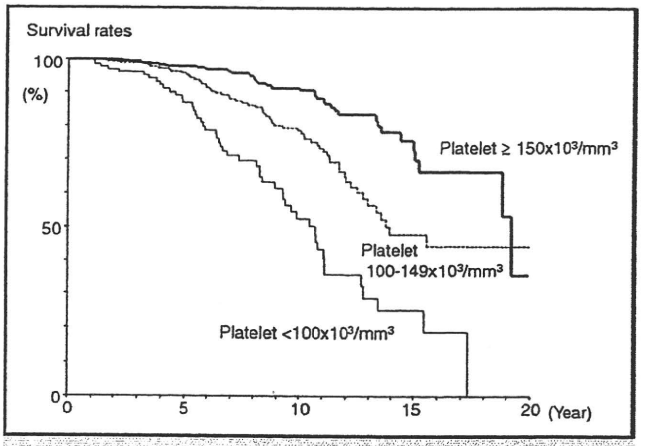

Figure 2 Cumulative survival in patients without IFN therapy, according to initial platelet count. Survival of patients with high platelet count was significantly higher than those with a low or intermediate platelet count ($P < .0001$).

Carcinogenesis rates were compared between those with or without IFN treatment in a subgroup with a high platelet count of 150,000/mm^3 or more. Cumulative carcinogenesis rates in the untreated (N = 585) and treated groups (N = 228) were 5.1% and 3.7% at 5 years, 14.0% and 13.1% at 10 years, and 26.1% and 25.9% at 15 years, respectively. The carcinogenesis rate in the IFN therapy group was slightly lower than in the untreated group, but no statistical significance was found in the high platelet subgroup ($P = .69$). Next, carcinogenesis rates were analyzed between those with or without IFN in a combined subgroup with low and intermediate platelet counts of less than 150,000 mm^3. Carcinogenesis rates in untreated (N = 459) and treated (N = 217) groups were 19.5% and 10.9% at 5 years, 43.0% and 21.6% at 10 years, and 65.3% and 39.4% at 15 years, respectively (Figure 3). The carcinogenesis rate in the group with IFN therapy was significantly lower in the untreated group ($P = .0005$).

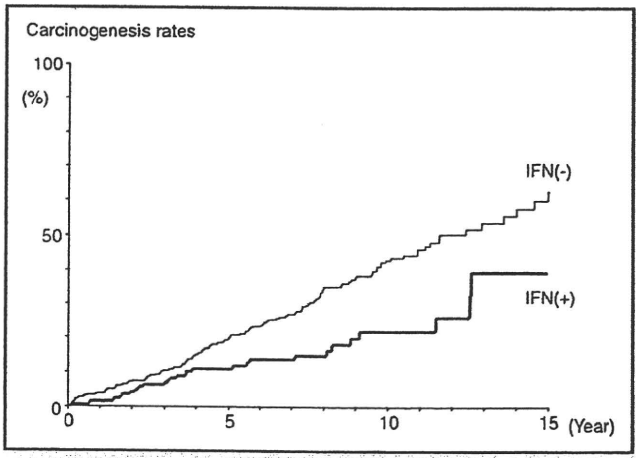

Figure 3 Hepatocarcinogenesis rates in patients with a low or intermediate platelet count. Carcinogenesis rate of patients with IFN therapy was significantly lower than those without therapy ($P = .0005$). IFN = Interferon.

Table 2 Independent Factors Associated with Hepatocellular Carcinogenesis in Elderly Patients with Hepatitis C Virus-related Chronic Liver Disease

Factors	(Category)	Hazard Ratio (95% CI)	*P*
Platelet count	1: ≥150,000/mm^3	1	
	2: 100,000-149,000/mm^3	2.42 (1.71-3.40)	<.001
	3: <100,000/mm^3	5.64 (3.88-8.22)	<.001
Alanine aminotransferase	1: <75 IU/L	1	
	2: ≥75IU/L	2.02 (1.48-2.77)	<.001
Gender	1: Female	1	
	2: Male	1.79 (1.35-2.37)	<.001
IFN	1: No therapy	1	
	2: No response	0.74 (0.44-1.25)	.26
	3: Biochemical response	0.52 (0.17-1.65)	.27
	4: Sustained virologic response	0.063 (0.009-0.449)	.006

CI = confidence interval; IFN = interferon.

Factors Affecting Hepatocellular Carcinogenesis

In the first proportional hazard analysis using IFN therapy factor as a time-dependent covariate, factors associated with carcinogenesis were explored in the entire elderly cohort. Hepatocarcinogenesis is independently associated with low platelet count ($P < .001$), high alanine aminotransferase value ($P < .001$), male sex ($P < .001$), and IFN therapy (hazard ratio = 0.67, $P = .045$).

Next, multivariate analysis was performed using factors of each IFN effect: sustained virologic response, biochemical response, no response, and no IFN therapy. Carcinogenesis was significantly associated with platelet count, male sex, alanine aminotransferase value, and sustained virologic response after IFN therapy (Table 2). Patients with low and intermediate platelet counts showed high hazard ratios and high alanine aminotransferase value; male gender showed high hazard ratios. Sustained virologic response significantly decreased the hazard ratio to 0.063 ($P = .006$).

The role of IFN treatment factor was not significant (hazard ratio 0.87, $P = .67$) in the high platelet group (≥150,000/mm^3), but it was significant (hazard ratio 0.56, $P = .035$) in the low or intermediate platelet group (<150,000/mm^3).

Survival of Elderly Patients

A total of 276 patients (14.4%) died during observation: 255 (17.4%) in the untreated group and 21 (4.6%) in the treated group. Crude survivals in the untreated and IFN groups were 92.9% and 98.7% at 5 years, 76.6% and 92.6% at 10 years, and 54.3% and 70.4% at 15 years, respectively. Survival in the IFN-treated group was significantly higher ($P < .0001$).

When a subgroup with high platelet counts (≥150,000/mm^3) was analyzed, survivals in the untreated and IFN groups were 97.9% and 99.6% at 5 years, 90.7% and 94.5% at 10 years, and 72.7% and 76.9% at 15 years, respectively. Survival was not significantly different ($P = .08$). Survival also was analyzed in a subgroup with low or intermediate platelet count (<150,000/mm^3). Cumulative survivals in the untreated and treated groups were 93.2% and 97.5% at 5 years, 70.8% and 89.9% at 10 years, and 41.2% and 64.9% at 15 years, respectively (Figure 4). Survival in the IFN therapy group was significantly higher than in the untreated group ($P = .0001$).

Factors Affecting Survival in the Elderly

Independent factors associated with survival were explored in all the elderly patients. Multivariate hazard analysis disclosed that survival is independently associated with low platelet count ($P < .001$), male sex ($P < .001$), older age ($P < .001$), and IFN therapy (hazard ratio = 0.56, $P = .041$).

In the high platelet group (≥150,000/mm^3), only gender and age were independently associated with survival. The factor of IFN therapy only showed a hazard ratio for death of 0.70 in the multivariate analysis. In the low or intermediate platelet group (<150,000/mm^3), platelet count, age,

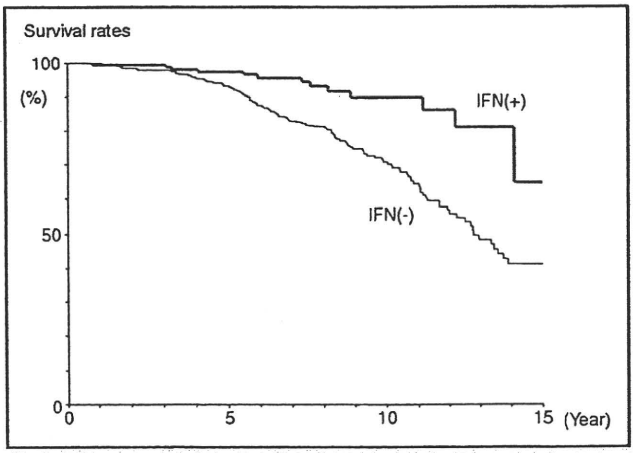

Figure 4 Cumulative survival in patients with a low or intermediate platelet count. Survival of patients with IFN therapy was significantly higher than those without therapy ($P = .0001$). IFN = Interferon.

Table 3 Independent Factors Associated with Survival Period in Elderly Patients with Hepatitis C Virus-related Chronic Liver Disease

Factors	(Category)	Hazard Ratio (95% CI)	*P*
Subgroup with High Platelet Count ($\geq$150,000/mm^3)			
Gender	1: Female	1	
	2: Male	2.81 (1.46-5.41)	.002
Age	by 1 y	1.11 (1.04-1.18)	.002
IFN	1: No	1	
	2: Yes	0.70 (0.32-1.18)	.39 (NS)
Subgroup with Low or Intermediate Platelet Count (<150,000/mm^3)			
Platelet count	1: 100,000-149,000/mm^3	1	
	2: <100,000/mm^3	3.14 (2.19-4.50)	<.001
Age	by 1 y	1.09 (1.05-1.13)	<.001
IFN	1: No	1	
	2: Yes	0.43 (0.24-0.77)	.005
Gender	1: Female	1	
	2: Male	1.56 (1.09-2.22)	.015

CI = confidence interval; IFN = interferon; NS = not significant.

IFN therapy, and sex were independently associated with hepatocellular carcinogenesis. IFN significantly decreased the hazard of death by 0.43 in the subgroup of low or intermediate platelet count ($P = .005$) (Table 3).

DISCUSSION

This retrospective study was undertaken to evaluate whether IFN therapy could decrease hepatocellular carcinogenesis and increase survival in HCV-positive elderly patients aged 60 years or more at the initial hospital visit. Because it seemed to require at least 5 years to obtain a statistical difference in carcinogenesis rates and survival between IFN-treated and untreated groups, a prospective randomized trial with untreated control patients is difficult to perform from both ethical and medical viewpoints. We therefore attempted to carry out this retrospective study to show an impact of IFN treatment with a statistical adjustment and stratification using a large number of patients under a long-term observation period.

There were significant differences in carcinogenesis and survival among patients with HCV, according to initial platelet count. Because this study dealt with all patients with HCV-related hepatitis who visited Toranomon Hospital irrespective of IFN treatment, evaluation of liver histology was performed in approximately two thirds of the patients. Platelet count has been considered a simple indicator for the progression of hepatitis, and the patients without liver biopsy were well stratified by the initial platelet count in our study. From statistics of the nationwide census for the longevity of each age group in 2003, the life expectation was 21.9 and 27.5 years for 60-year-old Japanese men and women, respectively, and 18.0 and 23.07 years for 65-year-old Japanese men and women, respectively. In view of the median age (65 years) of the untreated cohort with HCV infection, the survival of patients with high platelet counts was almost the same as that of the general population in Japan (Figure 2). Physicians should consider the longevity without IFN therapy and the cost, side effects, and risks caused by IFN for more stratified age groups of the elderly.

Although several authors have shown that effects of both IFN monotherapy[20,26,27] and IFN plus ribavirin combination therapy[28,29] were not different between elderly and younger patients with chronic HCV in regard to viral elimination and normalization of transaminase, recent reports[16,21] have shown lower virologic response rates. A possible low response rate in the elderly was closely associated with a high rate of adverse reactions,[16,20,21] and hematologic side effects seemed significant in the elderly group.[22] The low discontinuation rate (43/454, 9.5%) in the current study was partly attributable to the low rate of IFN plus ribavirin combination therapy. Horiike et al,[27] Floreani et al,[16] and Koyama et al[21] recommended IFN therapy for select patient groups with a low HCV RNA titer, non-genotype 1, or relatively young age of less than 65 years.

We previously reported a high carcinogenesis rate in elderly patients with chronic HCV who underwent IFN therapy.[30] When crude hepatocarcinogenesis rates were compared between untreated and IFN-treated groups in the current study, IFN significantly decreased the carcinogenesis rate in the elderly patients with varied severity of liver disease. As was found in the general results of patients, including the younger age group,[13] carcinogenesis in patients with sustained virologic response was significantly lower than that of patients with no response or without IFN therapy. The carcinogenesis rate was low for several years after cessation of IFN administration and increased gradually after 8 years in the group with a biochemical response (Figure 3). The cancer appearance curve of the biochemical response group implied that the normal and stable hepatitis

state in the early years contributed to suppress the process of carcinogenesis, and that reactivation of hepatitis induced the progression of hepatic oncogenesis in the later years.

Among patients with a high platelet count and mild liver disease, IFN did not decrease the rate of hepatocarcinogenesis. IFN significantly decreased the carcinogenesis rate in patients with a low or intermediate platelet count. In view of the less effective rate and high adverse reaction rate by IFN in elderly patients, IFN therapy should be considered primarily for those with a low platelet count of 150,000/mm^3 or less. Because low platelet count was closely associated with advanced disease and high risk for carcinogenesis, treatment efficacy appeared prominent in the subgroup with low and intermediate platelet counts. The best candidates for IFN therapy were those with a low platelet count, also in regard to cost-effectiveness. Because a low platelet count is closely associated with advanced stages of liver disease, IFN therapy should be avoided for elderly patients with decompensated cirrhosis or severely decreased platelet count of less than 50,000/mm^3. A sustained virologic response improves clinical symptoms in decompensated cirrhosis,[31] but IFN often induces severe complications even in young patients with decompensated cirrhosis.[32] An elderly patient with hepatitis without decompensation can be a candidate for IFN therapy if careful, close hematologic monitoring is performed. Low-dose, intermittent, long-term IFN therapy also should be considered for these patients to obtain a sustained biochemical response without creating profound and irreversible side effects. Because elderly patients generally showed some difficulties with IFN treatment, our current study demonstrated practical information about carcinogenesis and the life expectancy of elderly patients with HCV and the order of priority in management of IFN for these patients. IFN administration is preferably considered and initiated at the age of 60 years or less to reduce side effects.

CONCLUSIONS

IFN for a subgroup with low and intermediate platelet counts had significant advantages in regard to hepatocarcinogenesis and survival of elderly patients with chronic HCV.

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ORIGINAL ARTICLE

Development of hepatocellular carcinoma in elderly patients with chronic hepatitis C with or without elevated aspartate and alanine aminotransferase levels

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Abstract

Objective. Hepatocellular carcinoma (HCC) in the elderly infected with hepatitis C virus (HCV) is expected to increase globally within the next two decades. The purpose of the study was to define the natural history of elderly patients with chronic hepatitis C needs in order to prevent HCC from arising in these patients. ***Material and methods.*** Treatment-naive patients aged ≥65 years with platelet counts $>120 \times 10^3/mm^3$ were classified as 120 with aspartate and alanine aminotransferase (ASAT and ALAT) levels ≦40 IU/l (group A) and 212 with either or both levels ≥41 (group B) and followed-up for 3 years or longer without antiviral treatment. ***Results.*** Cirrhosis and HCC developed more frequently in group B than in group A ($p<0.001$ for both). In particular, of the patients aged 65–69 years at entry, cirrhosis and HCC developed more frequently in group B than in group A ($p<0.001$ and $p=0.001$, respectively). Liver-related causes of death were more common in group B than in group A (20/34 (59%) versus 1/9 (11%), $p=0.021$). HCC developed more frequently in men than in women ($p=0.033$). ***Conclusions.*** In elderly patients with chronic hepatitis C, cirrhosis and HCC develop more frequently in those with elevated transaminase levels than in those without elevated transaminase levels. Therefore, transaminase levels need to be suppressed below ≦40 IU/l, using antiviral treatments or other agents, in order to prevent cirrhosis and HCC arising in these patients. In view of rare liver-related deaths, aggressive antiviral treatment would not be necessary in the elderly with chronic hepatitis C who have normal transaminase levels.

Key Words: *Age, chronic hepatitis, cirrhosis, hepatitis C virus, hepatocellular carcinoma*

Introduction

There are an estimated 170 million people persistently infected with hepatitis C virus (HCV) worldwide, and approximately 30% of them develop serious complications during their lifetime, such as decompensated cirrhosis and hepatocellular carcinoma (HCC) [1]. The incidence of HCC in HCV carriers increases with age and is particularly high in those aged 65 years or older. Based on the shift in age-specific distribution of HCV carriers with time [2–4], HCC is expected to increase in the next 20 years, globally.

The natural history of infection with HCV is influenced by host and virological factors including age and gender [5–7], as well as viral loads and genotypes [8–10]. Thus, hepatitis proceeds slowly in HCV infections contracted by children and young women. During follow-ups carried out over 20 years, liver damage developed in a mere 3% of children who were infected with HCV during heart surgery [7], and cirrhosis emerged in only 2% of pregnant women infected with anti-D immune globulin contaminated with HCV [5].

As the average life span of human beings continues to extend, owing to improvements in sanitary

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conditions and efficient management of ailments, difficulties in the treatment of chronic hepatitis C in elderly individuals are increasingly coming to the fore. This is attributable, at least in part, to liver fibrosis accelerating in parallel with age [11], as well as less tolerability and more side effects of combined interferon (IFN) and ribavirin in these patients [6,11,12].

These constraints notwithstanding, there is a pressing need for treatment of aged individuals with antiviral agents in order to prevent the development of cirrhosis and HCC and to promote better survival with an increased quality of life. When planning antiviral treatment of the elderly, weighing its merits against untoward effects, it is essential to understand the natural history of HCV infection in these patients. However, there have been virtually no reports on the natural history of HCV infection in older adults, nor are there any solid guidelines for antiviral treatment in these patients [13].

In the 42 years from 1964 to 2005, we have followed-up 332 patients who were persistently infected with HCV and had not received any antiviral treatment. They included the 120 patients with aspartate and alanine aminotransferase (ASAT and ALAT) levels $\leq$40 IU/l (group A) and the 212 with ASAT and/or ALAT $\geq$41 (group B), and were followed-up for 3 years or longer without receiving any antiviral treatment. It is hoped that the evolution of chronic hepatitis in these patients, with special reference to the baseline transaminase levels, will shed light on how they should be treated for the prevention of cirrhosis and HCC in the coming era of global longevity.

Material and methods

Patients

During 42 years, from 1964 through 2005, 7358 patients with HCV-RNA in the serum visited the Department of Hepatology at the Toranomon Hospital in Metropolitan Tokyo. Of these patients, 843 (11.5%) were $\geq$65 years of age at presentation, and 512 (60.7% of the elderly) had not received antiviral agents or other drugs that might suppress the replication of HCV. In order to rule out cirrhosis, 180 patients with platelet counts $<120\times10^3/mm^3$ were excluded. The remaining 332 patients were classified into the 120 with ASAT and ALAT levels $\leq$40 IU/l (Group A) and the 212 with ASAT and/or ALAT levels $\geq$41 IU/l (group B); they included 22 patients (10.4%) with ASAT levels $\leq$40 IU/l and 18 (8.5%) with ALAT levels $\leq$40 IU/l. Baseline transaminase levels were determined at least twice, 2–3 months apart, in the course of 6 months. The patients were followed-up for 3 years or longer without receiving any antiviral treatment, and tested monthly for liver function, HCV-RNA and α-fetprotein (AFP) or protein induced by the absence of vitamin K or antagonist-II (PIVKA-II). Screening for cirrhosis and HCC was carried out yearly using ultrasonography and/or computed tomography. Angiography was implemented when HCC was strongly suspected by imaging modalities. During follow-ups, herbal medicine (intravenous Stronger Neo-Minophagen C (SNMC) or oral Shousaikotou) and/or ursodeoxycholic acid was given to 51 (42.5%) patients in group A and 139 (65.6%) patients in group B. Three (2.5%) patients in group A and 24 (11.2%) patients in group B, in whom IFN was started after they had been followed-up for 3 years or longer, left the study cohorts at the initiation of treatment. Informed consent was obtained from each patient who participated in this study, and the protocol conformed to the ethics guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Human Research Committee of the institution.

Markers of HCV infection

Qualitative assay for HCV-RNA was performed using polymerase chain reaction (PCR) with nested primers and the results were recorded as positive or negative, with the detection limit at 100 copies/ml. Quantification of HCV-RNA was carried out with the branched-DNA assay version 2.0 (Chiron Corp., Calif., USA), and the results were expressed in megaequivalents (MEq) per milliliter over a range from $<$0.5 to 120 MEq/ml.

Statistical analysis

Since certain data in the analysis were regarded to comply with non-Gaussian distribution, categorical variables at baseline were compared with the Fisher exact test and numerical values were analyzed with the Mann-Whitney U-test and the Kruskal-Wallis test. Cumulative rates of cirrhosis, HCC, and death were calculated using the Kaplan-Meier technique, and differences between curves were evaluated by the log-rank test. A p-value <0.05 with the two-tailed test was considered significant. All the analyses were carried out using the computer program SPSS ver.11.0 (SPSS Inc., Ill., USA).

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Results

Treatment-naive patients older than 65 years infected with HCV

During the 42 years from 1964 through 2005, the Department of Hepatology at the Toranomon Hospital in Metropolitan Tokyo admitted 332 patients aged 65 years or older with HCV who had not received any antiviral treatment, and in whom cirrhosis had not developed. In Table I we compare demographic, clinical, and virological characteristics between the 120 patients with baseline transaminase levels ≦40 IU/l and the 212 patients with levels ≧41 IU/l. ASAT and ALAT levels were higher, while platelet counts were lower in the patients with elevated transaminase levels compared with in patients without elevated transaminase levels.

When patients with baseline transaminase levels ≦40 IU/l were stratified by age, the median follow-up period was shorter in those aged 75–80 years than in those aged 65–69 or 70–74 years (4.5 versus 8.6 or 7.0 years, $p=0.011$) (Table II). Although the baseline transaminase levels were within normal limits in all of them, the median ASAT level was higher in patients aged 70–74 years than in those aged 65–70 or 75–80 years (35 versus 27 or 28 IU/l, $p=0.040$). In patients with baseline levels of both or either transaminase ≧41 IU/l, the median albumin level was lower in those aged 75–80 years than in those aged 65–69 or 70–74 years (3.9 versus 4.1 or 4.1 g /dl, $p=0.005$) (Table III).

Development of cirrhosis and HCC

Cirrhosis developed more frequently in elderly patients aged 65 years or older, with elevated transaminase levels at baseline, during follow-ups for longer than 3 years (Figure 1A). At 5 and 10 years of follow-up, cirrhosis developed in, respectively, 26% and 27% of the patients with the baseline transaminase levels ≧41 IU/l in contrast to only 4% and 13% of the patients with levels ≦40 IU/l ($p<0.001$). Likewise, HCC developed more frequently in elderly patients with elevated transaminase levels at baseline (Figure 1B). At 5 and 10 years of follow-up, HCC developed in, respectively, 22% and 26% of the patients with the baseline transaminase levels ≧41 IU/l, contrasting with only 3% and 5% of the patients with levels ≦40 IU/l ($p<0.001$).

Development of cirrhosis is compared between patients with and without elevated transaminase levels at baseline who were stratified by age (Figure 2). Cirrhosis developed more frequently in the patients with elevated transaminase levels than in those without elevated transaminase levels who were aged 65–69 years ($p<0.001$). In patients aged 70–74 years, cirrhosis tended to occur more often in those with elevated transaminase levels than in those without elevated transaminase levels during 5 years (27% versus 0%), but the difference fell short of being significant owing to the small number of patients in both groups.

Likewise, development of HCC is compared between patients with and those without elevated transaminase levels at baseline who were stratified by age (Figure 3). HCC developed more frequently in the patients with elevated transaminase levels than in those without elevated transaminase levels who were aged 65–69 years ($p=0.001$). In patients aged 70–74 and 75–80 years, HCC tended to occur more often in those with elevated transaminase levels than in those without elevated transaminase levels during 5 years (20% versus 5% and 19% versus 0%, respectively), but the difference was not significant, owing to the small number of patients in both groups.

Influence of gender on the development of cirrhosis and HCC

Figure 4 shows a comparison of the development of cirrhosis and HCC between 155 male and 177

Table I. Characteristics of patients with HCV-RNA aged 65 years or older with or without elevated transaminase (ASAT and ALAT) levels.

Features	≦40 IU/ml ($n=120$)	≧41 IU/l ($n=212$)	Differences p-value
Men	51 (42.5%)	104 (49.1%)	0.513
Follow-up (years)	7.8 (3–31.5)	8.7 (3–18.9)	0.181
ASAT (IU/l)	23 (6–40)	76 (27–496)	<0.001
ALAT (IU/l)	28 (11–40)	63 (22–411)	<0.001
Albumin (g/dl)	4.1 (2.4–4.9)	4.1 (3.2–5.3)	0.189
Platelets ($\times 10^3/mm^3$)	184 (120–343)	173 (120–313)	0.001
HCV RNA (MEq/ml)	4.5 (<0.5–120)	5.6 (<0.5–49)	0.168
HCV genotypes (1b:2a:2b:ND)	85:20:3:7	176:28:12:9	0.970

Abbreviations: HCV = hepatitis C virus; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; MEq = megaequivalents; ND = not determined. Data are expressed as the number (%) or the median with the range in parentheses.

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Table II. Characteristics of patients aged 65 years or older with HCV-RNA and without elevated baseline transaminase levels (ASAT and ALAT ≤40 IU/l) stratified by the age.

Features	65–69 years (n=79 (65.8%))	70–74 years (n=25 (20.8%))	75–80 years (n=16 (13.3%))	Differences p-value
Men	29 (36.7%)	11 (44.0%)	11 (68.8%)	0.062
Follow-up (years)	8.6 (3–31.5)	7.0 (3–12.6)	4.5 (3–17.6)	0.011
ASAT (IU/l)	27 (11–39)	35 (16–40)	28 (15–40)	0.004
ALAT (IU/l)	22 (6–40)	25 (9–40)	22 (9–37)	0.604
Albumin (g/dl)	4.1 (3.2–4.9)	4.1 (3.0–4.4)	4.0 (2.4–4.5)	0.247
Platelets ($\times 10^3$/mm^3)	193 (120–298)	177 (120–343)	182 (120–263)	0.408
HCV RNA (MEq/ml)	4.2 (<0.5–34.6)	6.5 (<0.5–120)	4.0 (<0.5–17.1)	0.181
HCV genotypes (1b:2a:2b:ND)	51:19:2:4	21:1:1:1	13:0:0:2	0.074

Abbreviations: HCV = hepatitis C virus; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; MEq = megaequivalents; ND = not determined. Data are expressed as the number (%) or the median with the range in parentheses.

female patients aged 65 years or older. Cirrhosis tended to occur more frequently in male than in female patients. There were marked gender differences in the development of HCC. At 5 and 10 years of follow-up, HCC occurred more frequently in men than in women (18% and 25% versus 9% and 9%, respectively, p=0.033).

Complications and death in patients with the baseline transaminase levels ≦40 IU/l and ≧41IU/l

Of the 120 patients with baseline transaminase levels ≦40 IU/l, 33 (27.5%) developed complications during follow-up (hypertension in 9 (27%), diabetes in 7 (21%), both complications in 1 (3%), pulmonary disease in 4 (12%), heart disease in 4 (12%), and other illnesses in the remaining 8 (24%)). At 5, 10, and 15 years of follow-up, respectively, death occurred more frequently in the patients with complications than in those without complications (10%, 18%, and 45% versus 0%, 5%, and 5%, p=0.015) (Figure 5).

Among 9 of the 120 (7.5%) patients who died, liver disease was the cause of death in only one. Of the remaining 8 (89%) patients, 4 died of heart failure or infarction, and one each of pneumonia, cerebral hemorrhage, renal insufficiency, and decrepitude. Death was more frequent in the patients aged ≥70 years than in those aged <70 years at presentation (p=0.006) (Figure 6).

Complications and death in patients with the baseline transaminase levels ≧41 IU/l

Of the 212 patients with baseline tranasaminase levels ≧41 IU/l, 83 (39.2%) developed complications during follow-up (hypertension in 18 (22%), diabetes in 23 (28%), both complications in 10 (12%), extrahepatic malignancies in 12 (15%), and other diseases in the remaining 20 (24%)). There were no differences in the frequency of death between the patients with and those without complications, however (Figure 7).

Among 34 of the 212 (14.0%) patients who died, liver disease was the most frequent cause of death and occurred in 20 (59%); the frequency was higher than that (11% (1/9)) in the patients with transaminase levels ≦40 IU/l at baseline (p=0.021). There were no differences in the frequency of death among

Table III. Characteristics of patients with HCV-RNA aged 65 years or older and with elevated baseline transaminase levels (ASAT and/or ALAT ≥41 IU/l) stratified by the age.

Features	65–69 years (n=140 (66.0%))	70–74 years (n=48 (22.6%))	75–80 years (n=24 (11.3%))	Differences p-value
Men	63 (45.0%)	25 (52.1%)	16 (66.7%)	0.707
Follow-up (years)	9.0 (3–18.9)	8.4 (3–17.2)	7.7 (3–14.7)	0.061
ALAT (IU/l)	82 (28–496)	74 (27–440)	64 (30–269)	0.959
ASAT (IU/l)	67 (22–411)	67 (34–309)	71 (35–172)	0.201
Albumin (g/dl)	4.1 (3.2–5.3)	4.1 (3.4–4.6)	3.9 (3.4–4.7)	0.005
Platelets ($\times 10^3$/cm^3)	171 (120–313)	180 (120–289)	157 (120–263)	0.398
HCV RNA (MEq/ml)	5.9 (<0.5–44.8)	5.6 (<0.5–30.0)	3.0 (<0.5–49.0)	0.251
HCV genotypes (1b:2a:2b:ND)	121:19:8:6	37:7:4:1	18:2:0:2	0.294

Abbreviations: HCV = hepatitis C virus; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; MEq = megaequivalents; ND = not determined.

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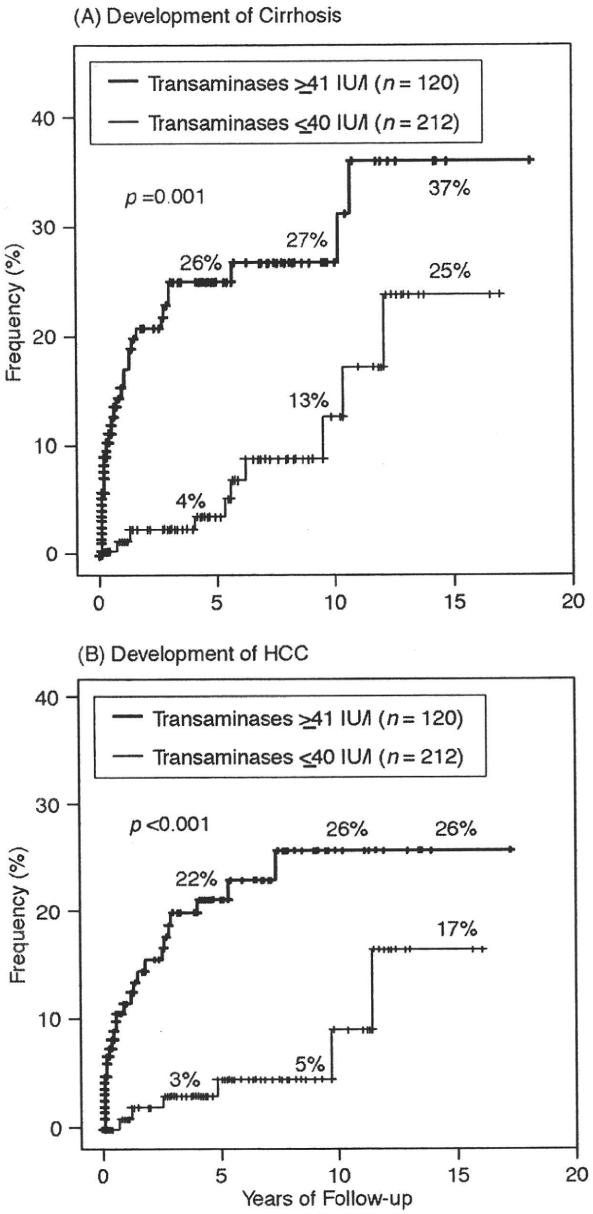

Figure 1. Development of cirrhosis (A) and HCC (hepatocelllular carcinoma) (B) in patients over 65 years of age with chronic hepatitis C who were followed-up without receiving antiviral treatment. Patients with and without elevated baseline transaminase levels are compared.

the patients in distinct age groups who had elevated baseline transaminase levels at baseline (Figure 8).

Discussion

The World Health Organization defines elderly individuals as those aged ≥65 years. In general, IFN is indicated for patients under 65 years of age, in view of frequent side effects and safety precautions. HCC develops increasingly with age and in the majority after 65 years, and in Japan approximately

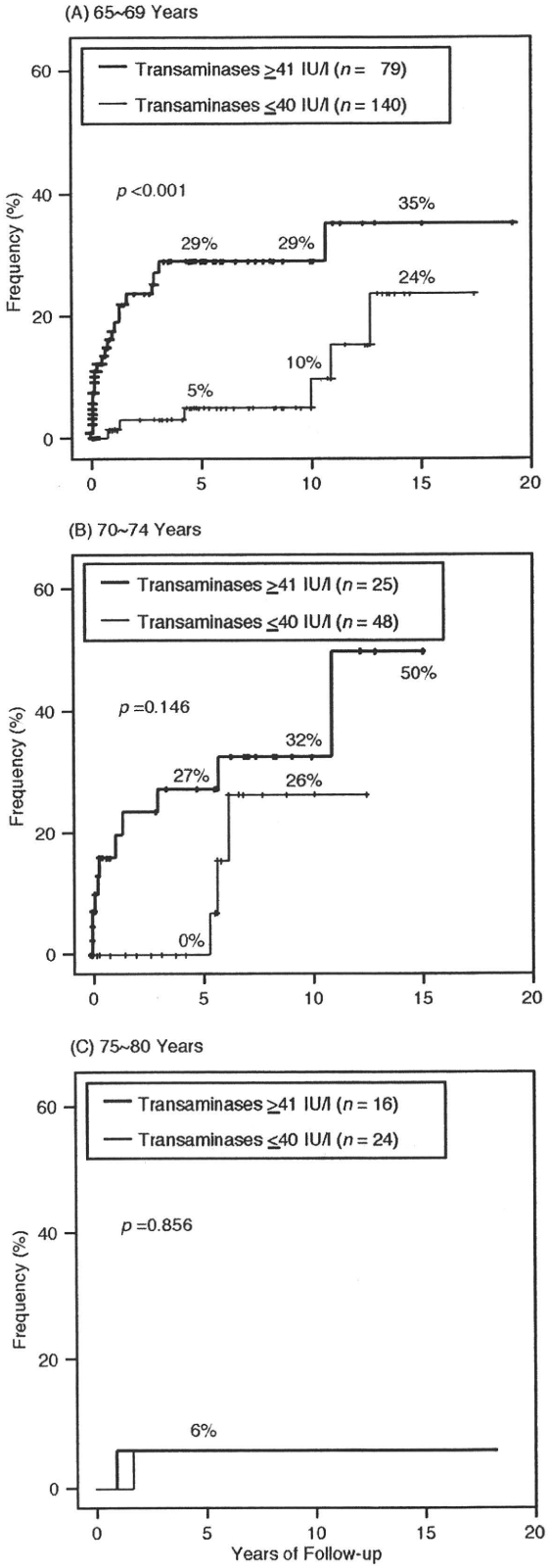

Figure 2. Development of cirrhosis in patients of more than 65 years of age with chronic hepatitis C who were followed-up without receiving antiviral treatment. Patients in different age groups are compared between those with and those without elevated transaminase levels.

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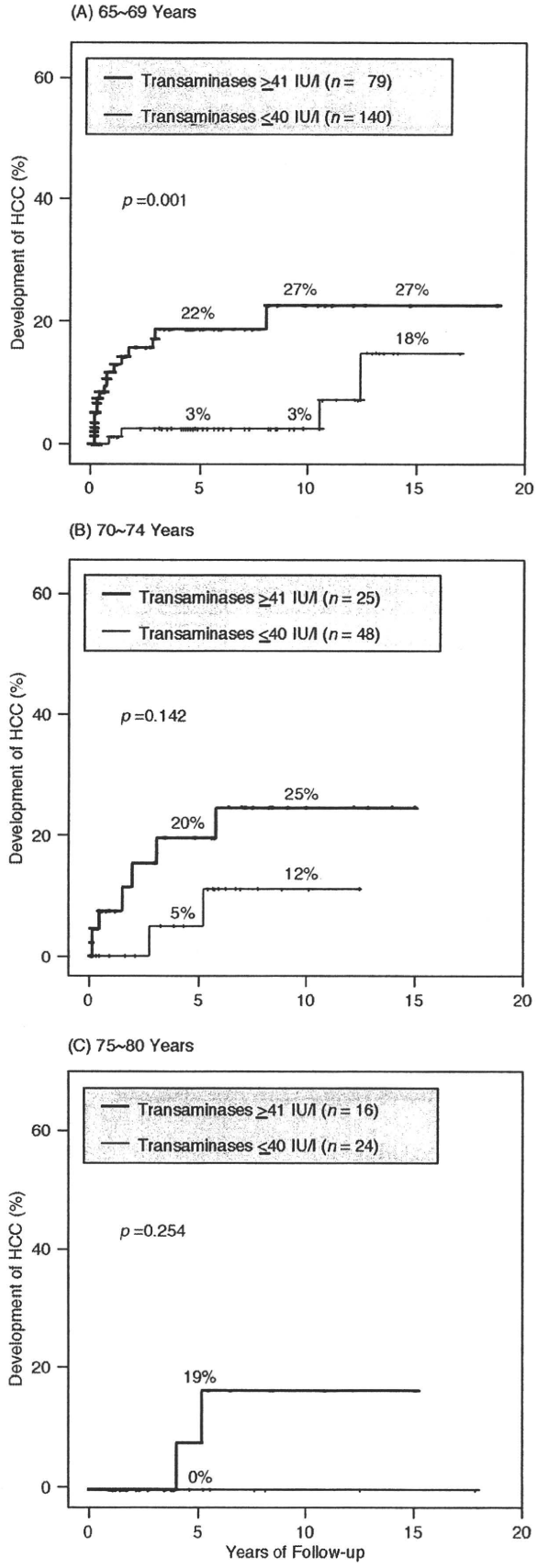

Figure 3 (*Continued*)

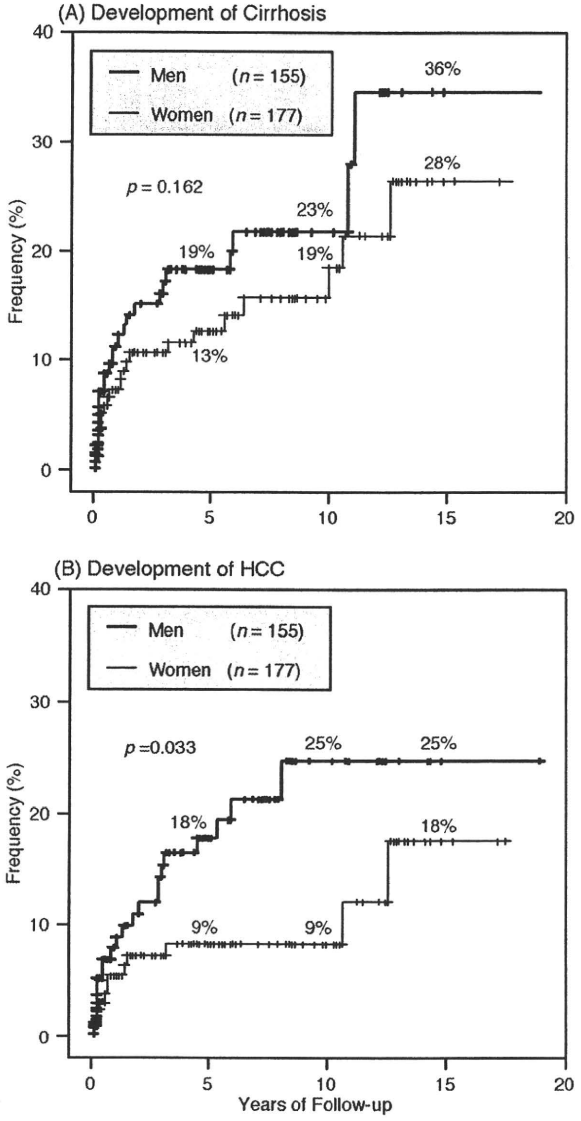

Figure 4. Development of cirrhosis (A) and HCC (hepatocelllular carcinoma) (B) in patients over 65 years of age with chronic hepatitis C who were followed-up without receiving antiviral treatment. Male and female patients are compared.

30,000 patients infected with HCV die yearly [14]. Furthermore, HCC is steadily increasing in the United States, and the incidence is expected to double or triple in the next two decades [15]. Hence, HCV carriers aged 65 years or older should be given IFN treatment, which is proven to be efficacious in preventing the development of HCC [16,17]. Previously, we have evaluated the efficacy and safety of IFN monotherapy in patients aged 65 years or older [18]. Of the 84 patients studied, the sustained virological response was reached in 30 (36%), while

Figure 3. Development of hepaptocelluar carcinoma (HCC) in patients over 65 years of age with chronic hepatitis C who were followed-up without receiving antiviral treatment. Patients in different age groups are compared between those with and those without elevated transaminase levels.

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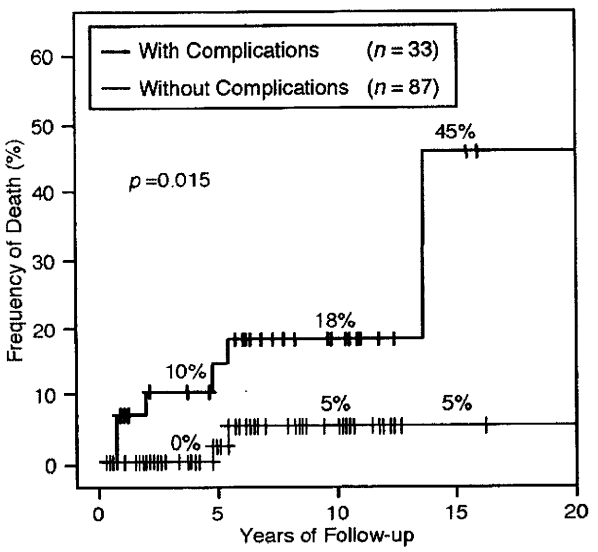

Figure 5. Deceased patients without elevated baseline transaminase levels (ASAT and ALAT <40 IU/l). Patients with and without complications other than liver disease are compared.

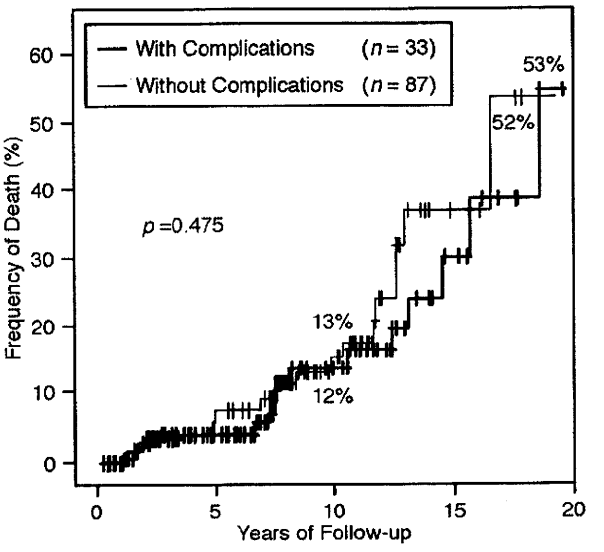

Figure 7. Deceased patients without elevated baseline transaminase levels (ASAT and ALAT <40 IU/l). Patients with and without complications other than liver disease are compared.

IFN was discontinued owing to adverse events in 11 (13%). Remarkably, the sustained virological response to combined IFN and ribavirin was comparable between the 66 patients aged ≥60 years and the 154 aged <60 years (31.8% versus 38.3%), although ribavirin had to be discontinued more frequently in the older patients (33.3% versus 20.8%, $p<0.05$) [19].

HCV spread widely in Japan around the end of World War II, at least 20 years earlier than in the other countries [4,14]. As a consequence, patients given combined IFN and ribavirin are 10–15 years older than those in Western countries [20–22]. Throughout the world, there are increasing numbers of individuals who are infected with HCV and entering the elder years. By the year 2010, the number of the elderly infected with HCV is estimated to account for 0.48 (54%) of the entire 0.89 million infected in Japan, and that in the United States for 0.78 (22%) of the 3.61 million [2–4]. These numbers will continue to increase for some time thereafter. As sequellae to this, cirrhosis and HCC will continue to increase, demanding higher medical costs. In the USA already, HCV-related

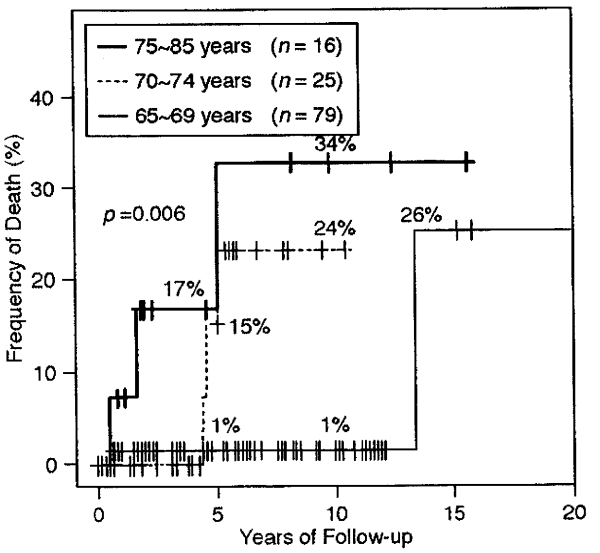

Figure 6. Deceased patients with elevated baseline transaminase levels (ASAT and/or ALAT >41 IU/l). Patients in the different age groups are compared.

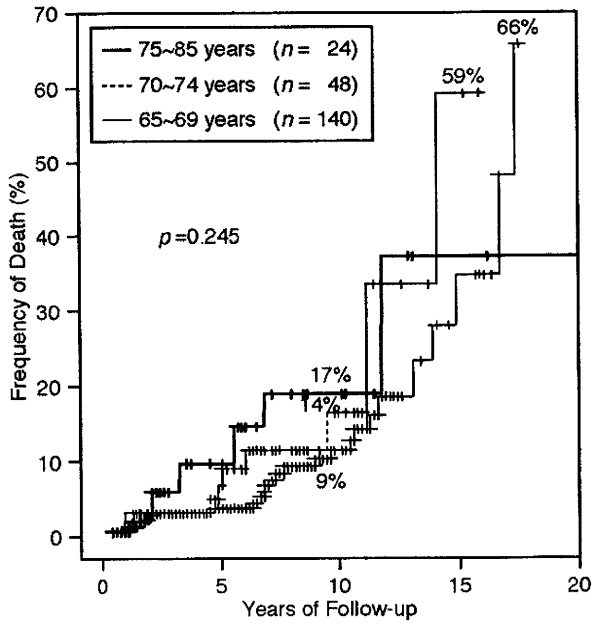

Figure 8. Deceased patients with elevated baseline transaminase levels (ASAT and/or ALAT >41 IU/l). Patients in the different age groups are compared.

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end-stage liver disease is the leading cause of orthotopic liver transplantation [23]. This background demands that immediate measures should be taken to prevent fibrosis developing in the elderly with chronic hepatitis C by initiating the appropriate treatment; pegylated IFN combined with ribavirin can eliminate HCV efficiently [24,25].

Management of antiviral treatment in the elderly, however, is not without difficulties. Discontinuation of therapy or dose reduction was required frequently in the Japanese patients older than 60 years with chronic hepatitis C [21]. It is obvious that antiviral treatment needs to be administered with caution in aged patients with chronic hepatitis C, with the indication restricted to those who are likely to derive benefit from it. Early virological response at 12 weeks of treatment is predictive of sustained virological response [26]. The influence of HCV genotypes on the response to combined therapy, which increases with age [27], would have to be taken into consideration, also. In the Japanese patients infected with HCV genotype 1b, substitutions of amino acids at positions 70 and 91 are associated with a better response to combined treatment [28]. In view of the more frequent and serious side effects in elderly patients, these predictors would need to be taken into account when deciding whether to continue or discontinue combined treatment with IFN and ribavirin in elderly patients with chronic hepatitis C.

In order to plan the treatment of elderly patients, the natural history of HCV infection in these patients needs to be elucidated, which has not been done as yet. In the present study, we have followed-up treatment-naive patients aged ≥ 65 years without antiviral treatment for more than 3 years. None of them had cirrhosis at baseline. They were stratified by baseline transaminase levels $\leqq 40$ IU/l (group A ($n=120$)) and $\geqq 41$ IU/l (group B ($n=212$)) and classified further into the three age groups, 65–69, 70–74, and 75–85 years. Cirrhosis and HCC developed more frequently in the patients in group B than those in group A ($p<0.001$ for both). Of the patients aged 65–69 years at entry, in particular, cirrhosis and HCC developed more frequently in group B than in group A ($p<0.001$ and $p=0.001$, respectively). Liver-related causes of death were more common in group B than in group A (20/34 (59%) versus 1/9 (11%), $p<0.05$), and HCC developed more frequently in men than in women ($p=0.021$).

Despite the progression of fibrosis that is accelerated with age [6], liver-related deaths were infrequent in patients with normal baseline transaminase levels and much less often than in those with elevated baseline transaminase levels (1/120 (0.8%) versus 20/212 (9.4%), $p=0.002$). Development of cirrhosis or HCC was no different between patients in groups A and B who were aged 70 years or older at entry. Taken altogether, elderly patients with elevated transaminase levels who are younger than 70 years would be the best candidates for antiviral treatment. They would need to be treated, even when side effects appear, by modifying the doses of IFN and ribavirin. In contrast, antiviral treatment may not be necessary for elderly patients with normal ALAT levels, or can be discontinued in these patients when side effects emerge.

There has been some controversy over antiviral treatment for elderly patients with chronic hepatitis C, and no specific guidelines have been drawn up so far [29]. The sustained virological response to antiviral treatment in aged patients is reported to be either poorer than [30–32] or comparable with that in younger patients [19,33]. The difference is most likely ascribed to careful selection of the aged patients who would benefit from treatment [13]. Based on the natural history of elderly patients with chronic hepatitis C described herein, those with elevated transaminase levels would need treatment to prevent progression to cirrhosis and HCC, while others with normal levels may not require treatment. It is to be hoped that the results in this study might be of help in planning a reasonable treatment strategy towards the longevity, without development of cirrhosis or HCC, in elderly patients with chronic hepatitis C, whose numbers are expected to increase progressively in the foreseeable future.

Acknowledgements

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Hyperplastic Nodular Hepatic Lesions Following End-to-side Portacaval Shunting in Childhood

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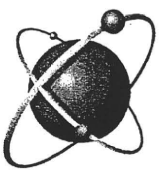

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□ CASE REPORT □

Hyperplastic Nodular Hepatic Lesions Following End-to-side Portacaval Shunting in Childhood

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Abstract

We describe a 48-year-old man with nodular intrahepatic lesions accompanied by communication between the inferior vena cava and portal systems as well as absence of intrahepatic portal veins. After infection with malaria in childhood, end-to-side portacaval shunting had been performed to treat upper gastrointestinal bleeding at the age of 15 years. A biopsy specimen obtained under ultrasonographic guidance showed hyperplastic nodules suggestive of focal nodular hyperplasia. The estradiol concentration in the blood was elevated (55 pg/ml). This case suggests that portacaval shunting may be associated with hyperplastic liver nodules through hyperestrogenemia and abnormal hepatic hemodynamics.

Key words: portacaval anastomosis, focal nodular hyperplasia, hyperestrogenemia

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Introduction

End-to-side portacaval anastomosis, termed an Eck fistula (1, 2), is an operation performed to treat life-threatening portal hypertension by creating a major shunt between the inferior vena cava (IVC) and the portal trunk. The structural relationship between portal and systemic veins after portacaval shunting is similar to that seen in congenital absence of the portal vein (CAPV), which often is associated with hyperplastic liver lesions. Development of such lesions following a portacaval shunt procedure has been reported only in patients with type I glycogen storage disease (GSD-I). The present case appears to be the first occurrence of benign hyperplastic liver lesions to follow portosystemic shunting in a patient with no other condition predisposing to hepatic neoplasia.

Case Report

A 48-year-old Japanese man was referred to our institution because of nodular intrahepatic lesions recently detected ultrasonographically at another hospital. He was infected with malaria (from his uncle) in childhood and received medication. No further details regarding his medication were available. Splenectomy was performed when the patient was 5 years old. At 15 years old hematemesis occurred, most likely a result of portal hypertension. A shunt operation was performed, and a blood transfusion was given. Earlier abdominal ultrasonography, performed 13 months before referral to our hospital, had shown no nodular lesion in the liver.

On admission to our hospital, his performance status was excellent. No symptoms of malaria were evident. The liver was not palpable. A healed midline abdominal scar was noted. The patient's history disclosed only minimal alcohol intake. Serologic and molecular tests for hepatitis B and C viruses (HBV and HCV) indicated past infection by both viruses [HB surface antigen negative, HB core antibody positive, HCV antibody positive, HCV-RNA negative]. Serum chemistry data showed mild elevations of aspartate aminotransferase (AST, 42 U/L; normal, 13 to 33), gamma-glutamyl transpeptidase (γ-GTP, 81 U/L; normal, 10 to 47),

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