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Analysis of factors interfering with the acceptance of interferon therapy by HCV-infected patients

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

PI

Summary

Background: Interferon (IFN) therapy, an antiviral agent, contributes to the prevention of occurrence of hepatocellular carcinoma (HCC) and to improvement in long-term prognosis. However, IFN therapy is not well-implemented in Japan. The present study was conducted to analyze factors preventing the implementation of IFN therapy.

Material/Methods: Questionnaires were sent to patients with hepatitis C virus (HCV)-related liver disease who were treated at 7 clinics (by non liver-specialists) and 1 hospital (by liver specialists) and by their attending physicians.

Results: Of 139 patients for whom attending physicians recommended IFN therapy, 92 (66.2%) agreed to receive the treatment. The proportions of patients who agreed to receive IFN therapy were 74 (86.0%) out of 86 hospital patients and 18 (34%) out of 53 clinic patients. In logistic regression analysis, the adjusted odds ratios on treatment facilities, sex and complications were 18.06, 3.65, and 3.63 respectively, indicating that there were significant differences. Female patients more than male patients declined IFN therapy because of worries over the adverse reactions of IFN therapy.

Conclusions: Multivariate analysis showed that factors contributing to the risk that a patient would not consent to receive IFN therapy included a) treatment facilities, b) sex, and c) the presence or absence of complications. It is also essential to devise measures to create cooperation between hospitals and clinics, and to improve communication between physicians and patients.

key words: **hepatitis C virus • interferon therapy • chronic hepatitis C • hepatocellular carcinoma • liver specialist • non liver-specialist**

Abbreviations: **anti-HCV** – anti-bodies to HCV; **HCC** – hepatocellular carcinoma; **HCV** – hepatitis C virus; **IFN** – Interferon

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Background

Hepatocellular carcinoma (HCC) is the third most common cause of death from cancer in men and the sixth most common cause in women [1]. An increase in the number of cases of HCC has occurred in the United States over the past two decades [2]. The age-specific incidence of this cancer has progressively shifted toward younger people. Similarly, the number of deaths in Japan from HCC keeps increasing. This trend is expected to continue until 2015 [3]. In Japan, ~80% of HCCs are caused by hepatitis C virus (HCV) and ~10% by hepatitis B virus (HBV). The increase in the number of HCC patients due to HCV contributes to the increase in the deaths in Japan from HCC.

It is presumed that between 1 and 2 million Japanese people are chronically infected with HCV [3]. Because many such people are unaware that they are infected, carriers may develop liver cirrhosis and HCC, and this poses a serious problem. In April 2002, the Ministry of Health, Labour and Welfare began targeting area residents for hepatitis virus screening as part of urgent comprehensive measures for identifying hepatitis C and other infections. Since 2002, antibodies to HCV (anti-HCV) and HBs antigens have been tested in Japanese individuals who receive a basic health check up. This is part of the Elderly Health Project whose goal is to re-test them every 5 years between ages 40 and 70.

The national compliance rate for this health check during 4 years from 2002 to 2005 was about 27% (~5.1 million people). The HCV infection rate at that time was 0.9% (~47,000 people). However, only 6,160 HCV carriers in fact received treatment at secondary medical facilities, while 16% (969/6,160) of carriers were treated with interferon (IFN) at secondary medical facilities during the 4 years. These statistics suggest that not many patients or residents are actually treated with IFN despite the fact that IFN can get rid of HCV [4]. Currently, creation of a network for post-health screening treatment has been in progress.

IFN therapy for chronic hepatitis C is the only treatment for completely eliminating HCV. In recent years, the standard therapy has been the combination of pegylated interferon (Peg-IFN) and ribavirin. Following 1-year administration of this combination, the treatment was found to be markedly effective in~50 to 60% of all HCV-infected patients, including those with conventionally intractable genotype 1b • high titer [5]. It has been demonstrated that IFN therapy contributes to the prevention of occurrence of HCC and to improvement in long-term prognosis [6–9].

Why is IFN therapy for HCV carriers in Japan not used more widely? Reasons remain unclear because no systematic investigation has been conducted.

In our previous study, we sent questionnaires to both 254 pairs of HCV carriers and their attending physicians in different areas in Japan in which we discussed the future state of medical care in which IFN therapy would be used more widely [10]. There was a great difference among types of medical facilities in the proportions of patients who opted to receive IFN therapy. Whereas 78.2% of patients of liver specialists agreed to IFN therapy, the proportion was only 15.7% for patients of non liver-specialists.

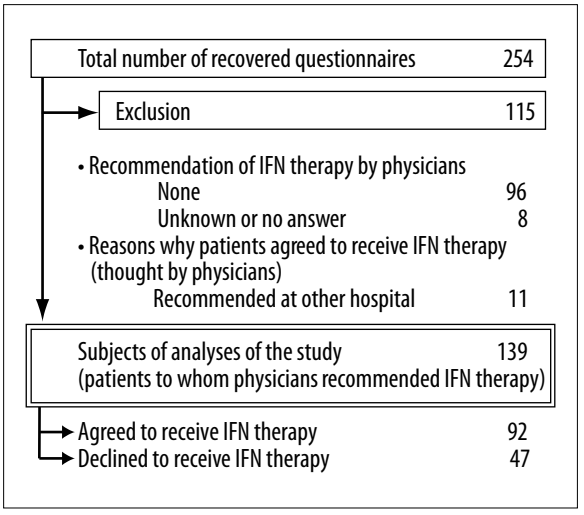

Figure 1. Diagram of 139 subjects of the study.

In the present study, patients who were recommended to receive IFN therapy were defined as "patients who ought to receive IFN therapy." Then, we looked for factors that caused patients who ought to receive IFN therapy to not receive it. That is, we looked for factors interfering with the introduction of IFN therapy. The geographical area where our investigation was conducted was one where we have been conducting successive epidemiological investigations on liver diseases and extrahepatic manifestations since 1990 [11–17].

Material and Methods

Subjects

Between October 1, 2005 and February 28, 2006, unregistered questionnaires were sent to HCV carriers who had been treated at a key hospital in A City, Fukuoka Prefecture and all clinics in H Town in A City and their attending physicians, and 254 pairs of answers were recovered. Subject medical organizations were 7 clinics without liver specialists and 1 hospital where many liver specialists authorized by the Japan Association for the Study of the Liver work full time. We mailed questionnaires directly to these 8 medical organizations. A database for the results of our investigation was compiled at the Office of Pharmaceutical Industry Research (OPIR)/Japan Pharmaceutical Manufacturers Association (JPMA).

The 254 patients were divided into groups depending on whether or not their physicians recommended any of the following IFN therapy: IFN monotherapy, Peg-IFNα-2a monotherapy, IFNα-2b plus ribavirin, and Peg-IFNα-2b plus ribavirin. As shown in Figure 1, 139 patients to whom physicians recommended IFN therapy were selected for the analysis of factors influencing the decision of patients whether or not to receive IFN therapy. Excluded from our analyses were 96 patients to whom physicians did not recommend IFN therapy, and 8 patients for whom it was unclear whether or not physicians recommended IFN therapy, or who did not respond to the questionnaire. Also excluded were 11 patients who received IFN therapy after recommendations from other hospitals. Of 139 patients analyzed, 92 consented to receive IFN therapy and 47 did not.

Table 1. Items of investigation by questionnaires sent to both physicians and patients.

1. Patients' background
(1) Patients' attributes (age, sex, joining the patient advocacy group for liver disease)
(2) Diagnosis of liver diseases and complications
(3) Nutritional instruction for liver diseases (received, not received)
(4) Health foods and folk medicines (taken, not taken)
(5) Treatment other than IFN therapy (treated, not treated)
2. IFN therapy
(1) Explanation of IFN therapy (given, not given). If yes, when
(2) Implementation of IFN therapy (received, not received)
(3) Frequency of IFN therapy (*)
(4) The nearest place where IFN therapy was given (*)
(5) Reasons why patients decided to receive IFN therapy (*)
(6) The latest therapeutic effects of IFN therapy
(7) Reasons why IFN therapy was discontinued (*)
3. Factors for which IFN therapy was not performed
(1) IFN therapy was recommended (yes, no)
(2) Reasons why IFN therapy was recommended
Reasons why IFN therapy was not recommended (*)
(3) Did patients decline IFN therapy? (yes, no)
(4) Reasons why patients declined IFN therapy
4. Comments (write what you think about liver diseases)

(*) Questions asked to physicians only.

The investigation was conducted in accordance with the "ethical guidelines on epidemiological studies" by the Ministry of Education and Science and the Ministry of Health, Labour and Welfare and observed the spirit of the Helsinki Declaration. Physicians at study facilities explained to patients the content and significance of the study and obtained consent in accordance with rules at each facility.

Items of investigation

Unregistered questionnaires asked patients and their attending physicians to respond to the following items.

1) Patients' background, 2) IFN therapy, and 3) factors determining the decision to not implement IFN therapy.

Items of investigation are listed in Table 1.

Statistical analysis

Crude odds ratios and adjusted odds ratios were calculated for factors possibly related to consenting to IFN therapy. Adjusted odds ratios were calculated using logistic regression analysis. Candidate factors for logistic regression analysis were selected by using a strategy that was recommended by Hosmer, DW, et al. [18], and secondary interactions among the selected factors were also assessed. Selection of factors for the final model was performed in a stepwise method, and the significance level for entering or removing of factors into or from regression models were both 0.15. The fitting of models was assessed using the Hosmer-Lemeshow test.

We tabulated reasons why patients declined IFN therapy, and therapeutic effects in patients who received IFN therapy.

All statistical analyses were conducted using SAS for Windows Version 8.2 (SAS Institute, Cary, NC, USA). The level of statistical significance was defined as 0.05.

PI

Results

Patients' background

Table 2 lists clinical information for patients who were recommended to receive IFN therapy. Physicians recommended IFN therapy to 139 patients; 53 at clinics (non liver-specialists) and 86 at a hospital (liver specialists). For patients older than 60, 36 were recommended at clinics (67.9%) and 55 at a hospital (64.0%). The number of patients who joined the patient advocacy group for liver disease was zero at clinics and 13 (15.1%) at a hospital. The number of patients who were female were 30 (56.6%) at clinics and 45 (52.3%) at a hospital. The number of patients with concomitant medical complications were 36 (67.9%) at clinics and 65 (75.6%) at a hospital. Patients in the two groups were well-matched for baseline characteristics.

Univariate analysis

Of 139 subjects of analyses to whom physicians recommended IFN therapy, 92 (66.2%) agreed to receive the therapy (Table 2). Whereas 74 of 86 hospital patients (86.0%) agreed to receive IFN therapy, only 18 of 53 clinic patients (34.0%) did so.

In univariate analyses (Table 3), the crude odds ratio of treatment facilities (clinic/hospital) was calculated as 11.99, demonstrating a significant difference in the proportion agreeing to receive IFN therapy between clinic patients and hospital patients. As for other factors, the crude odds ratio for sex (female/male) was 1.96 and that for joining the Liver Society (or not) was 0.14, suggesting that the associations between these factors and the decision to receive IFN therapy were not statistically significant.

Multivariate analysis

According to multivariate analysis, three factors, treatment facilities (clinic/hospital), sex (female/male) and complications (yes/no), were identified as factors that influenced patients' decisions to receive IFN therapy. The adjusted odds ratios for these 3 factors were 18.06, 3.65 and 3.63, respectively, and each was statistically significant. Among all of the selected factors, the adjusted odds ratios were increased over the crude odds ratios. Factors of sex and complications were not statistically significant in the crude odds ratios but significant following multivariate adjustment.

Table 2. Clinical information of 139 patients to whom IFN therapy was recommended.

		Total n=139 (%)		Clinic (Non liver-specialist) n=53 (%)		Hospital (Liver specialist) n=86 (%)	
IFN therapy	Accepted	92	(66.2)	18	(34.0)	74	(86.0)
	Not accepted	47	(33.8)	35	(66.0)	12	(14.0)
Treatment facilities	Hospital (liver-specialist)	86	(61.9)				
	Clinic (non liver-specialist)	53	(38.1)				
Age	20–29 years old	2	(1.4)	0	(0.0)	2	(2.3)
	30–39	3	(2.2)	0	(0.0)	3	(3.5)
	40–49	10	(7.2)	4	(7.5)	6	(7.0)
	50–59	33	(23.7)	13	(24.5)	20	(23.3)
	60–69	44	(31.7)	14	(26.4)	30	(34.9)
	70–79	45	(32.4)	22	(41.5)	23	(26.7)
	80 years or older	2	(1.4)	0	(0.0)	2	(2.3)
Sex	Male	63	(45.3)	22	(41.5)	41	(47.7)
	Female	75	(54.0)	30	(56.6)	45	(52.3)
	No answer	1	(0.7)	1	(1.9)	0	(0.0)
Diagnosis of liver diseases (choose one)	Chronic hepatitis C alone	103	(74.1)	34	(64.2)	69	(80.2)
	Other than chronic hepatitis C alone	36	(25.9)	19	(35.8)	17	(19.8)
	No answer	0	(0.0)	0	(0.0)	0	(0.0)
Diagnosis of liver diseases (choose all applicable)	Chronic hepatitis C	117	(84.2)	41	(77.4)	76	(88.4)
	HCV-related liver cirrhosis	22	(15.8)	10	(18.9)	12	(14.0)
	HCC type C	7	(5.0)	4	(7.5)	3	(3.5)
	Asymptomatic HCV carrier	1	(0.7)	1	(1.9)	0	(0.0)
	History of HCV infection	3	(2.2)	2	(3.8)	1	(1.2)
	Others	7	(5.0)	4	(7.5)	3	(3.5)
	Uncertain	0	(0.0)	0	(0.0)	0	(0.0)
	No answer	0	(0.0)	0	(0.0)	0	(0.0)
Concomitant medical complications	No	36	(25.9)	15	(28.3)	21	(24.4)
	Yes	101	(72.7)	36	(67.9)	65	(75.6)
	Hypertension	68	(48.9)	27	(50.9)	41	(47.7)
	Diabetes mellitus	28	(20.1)	11	(20.8)	17	(19.8)
	Heart diseases	10	(7.2)	3	(5.7)	7	(8.1)
	Cerebrovascular diseases	4	(2.9)	1	(1.9)	3	(3.5)
	Thyroid diseases	7	(5.0)	1	(1.9)	6	(7.0)
	Rheumatism	0	(0.0)	0	(0.0)	0	(0.0)
	Stomatitis	2	(1.4)	0	(0.0)	2	(2.3)
	Others	33	(23.7)	7	(13.2)	26	(30.2)
	No answer	2	(1.4)	2	(3.8)	0	(0.0)
Patient advocacy group for liver disease	Joined	13	(9.4)	0	(0.0)	13	(15.1)
	Not joined	126	(90.6)	53	(100.0)	73	(84.9)

HCC – Hepatocellular carcinoma.

Table 3. Results of univariate analysis (crude odds ratio).

		Number of patients		Crude odds ratio (95% confidence intervals)		P value
		Not accepted	Accepted			
Treatment facilities	Hospital	12	74	1.00		
	Clinic	35	18	11.99	(5.21–27.60)	<0.0001
Age	20–59	16	32	1.00		
	60–69	12	32	0.75	(0.31–1.84)	0.5286
	70 years or older	19	28	1.36	(0.59–3.13)	0.4742
Sex	Male	16	47	1.00		
	Female	30	45	1.96	(0.94–4.07)	0.0718
	No answer	1	0			
Diagnosis of liver diseases	Chronic hepatitis C alone	33	70	1.00		
	Other than chronic hepatitis C alone	14	22	1.35	(0.61–2.97)	0.4553
Concomitant medical complications	No	10	26	1.00		
	Yes	37	64	1.50	(0.65–3.46)	
	No answer	0	2			0.3383
Patient advocacy group for liver disease	Joined	46	80	1.00		
	Not joined	1	12	0.14	(0.65–3.46)	0.0677

Table 4. Acknowledgement by patients who did not agree to receive IFN therapy upon recommendation.

	Patients who did not agree to receive IFN therapy		Treatment facilities				Sex						Complications			
			Clinic (non liver-specialist)		Hospital (liver specialist)		Male		Female		No answer		No		Yes	
	n=47 (%)		n=35 (%)		n=12 (%)		n=16 (%)		n=30 (%)		n=1 (%)		n=10 (%)		n=37 (%)	
To recommendation by physicians of IFN therapy																
Patients acknowledged it	30	(63.8)	20	(57.1)	10	(83.3)	11	(68.8)	18	(60.0)	1	(100.0)	8	(80.0)	22	(59.5)
Patients did not acknowledge it	13	(27.7)	13	(37.1)	0	(0.0)	5	(31.3)	8	(26.7)	0	(0.0)	2	(20.0)	11	(29.7)
Uncertain or no answer	4	(8.5)	2	(5.7)	2	(16.7)	0	(0.0)	4	(13.3)	0	(0.0)	0	(0.0)	4	(10.8)

The Hosmer-Lemeshow goodness-of-fit test indicated that the model fits (P=0.6025).

Reasons why patients declined IFN therapy

Of 47 patients who declined IFN therapy despite recommendation by their physicians, 30 (11 males, 18 female and 1 no answer) acknowledged that "IFN therapy was recommended to them by physicians" (Table 4).

Table 5 lists 17 reasons used by patients to decline IFN therapy. Of 29 patients (11 males and 18 females) who declined IFN therapy, 2 (18.2%) out of 11 males and 6 (33.3%) out of 18 females mentioned "worries over adverse reactions" as the biggest reason for declining. A higher proportion of female patients worried over adverse reactions than the proportion of male patients who did. Ten reasons including "didn't want other people to know about my illness" were not selected as the most accurate reason for declining IFN therapy (Table 5).

Therapeutic effects of IFN

Of 92 patients who agreed to receive IFN therapy upon recommendation by their physician, 28 could not be eval-

Table 5. Reasons why patients who acknowledged that physicians recommended IFN therapy but patients did not agree to receive the therapy (the reason expressing their feelings most accurately).

	Patients who declined IFN therapy despite acknowledging recommendation of physicians	Treatment facilities		Sex			Complications	
		Clinic (non liver-specialist)	Hospital (liver-specialist)	Male	Female	No answer	No	Yes
	n=30 (%)	n=20 (%)	n=10 (%)	n=11 (%)	n=18 (%)	n=1 (%)	n=8 (%)	n=22 (%)
Worries over adverse reactions	8 (26.7)	6 (30.0)	2 (20.0)	2 (18.2)	6 (33.3)	–	4 (50.0)	4 (18.2)
High cost	2 (6.7)	2 (10.0)	–	–	1 (5.6)	1 (100)	–	2 (9.1)
Seemed to be unnecessary because of being asymptomatic	2 (6.7)	1 (5.0)	1 (10.0)	2 (18.2)	–	–	–	2 (9.1)
Was busy	2 (6.7)	2 (10.0)	–	2 (18.2)	–	–	–	2 (9.1)
Was anxious	2 (6.7)	1 (5.0)	1 (10.0)	1 (9.1)	1 (5.6)	–	–	2 (9.1)
Didn't want other people to know about my illness	–	–	–	–	–	–	–	–
Seemed to be unsuitable because of old age	1 (3.3)	–	1 (10.0)	–	1 (5.6)	–	–	1 (4.5)
Seemed to be not urgent	2 (6.7)	1 (5.0)	1 (10.0)	2 (18.2)	–	–	–	2 (9.1)
Was reluctant to go to other hospitals or clinics	–	–	–	–	–	–	–	–
Was satisfied with current treatment	–	–	–	–	–	–	–	–
Family objection	–	–	–	–	–	–	–	–
Seemed to be unsuitable because of the presence of other illnesses	–	–	–	–	–	–	–	–
Seemed to be bothersome to go to clinics more often	–	–	–	–	–	–	–	–
Seemed to be ineffective	–	–	–	–	–	–	–	–
Did not like injection	–	–	–	–	–	–	–	–
Explanation by physicians was insufficient	–	–	–	–	–	–	–	–
Could not understand the explanation by physicians	–	–	–	–	–	–	–	–
Others	3 (10.0)	3 (15.0)	–	–	3 (16.7)	–	3 (37.5)	–
No answer	8 (26.7)	4 (20.0)	4 (40.0)	2 (18.2)	6 (33.3)	–	1 (12.5)	7 (31.8)

uated for the effect of IFN because the therapy was in progress. Therapeutic effects of IFN for the remaining 64 patients are as follows (Table 6). "Sustained virological response (SVR) (negative HCV RNA and normal transaminase in tests conducted 6 months after the completion of IFN therapy)" was found for 46.9% (30/64) of the patients; "biological response (BR) (positive HCV RNA and normal transaminase in tests conducted 6 months after the completion of IFN therapy)" for 14.1% (9/64); "no response (NR)" for 34.4% (22/64); and "Unclear or no answer" for 4.7% (3/64).

Of 64 patients in whom therapeutic effects of IFN could be evaluated, 18 were treated at clinics (non liver-specialists) and 46 at a hospital (liver specialists). For these two groups, IFN therapy was evaluated as SVR in 44.4% (8/18) and 47.8% (22/46) of patients. This shows that effects of IFN therapy were comparable in the two groups despite

Table 6. Therapeutic effects of IFN to patients who agreed to receive IFN therapy upon recommendation by their physicians (excluding patients in whom the therapy is in progress).

	Patients who agreed to receive IFN therapy (excluding patients who could not be evaluated)	Treatment facilities	
		Clinic (non liver-specialist)	Hospital (liver specialist)
	n=64 (%)	n=18 (%)	n=46 (%)
SVR	30 (46.9)	8 (44.4)	22 (47.8)
BR	9 (14.1)	2 (11.1)	7 (15.2)
NR	22 (34.4)	7 (38.9)	15 (32.6)
Unclear or no answer	3 (4.7)	1 (5.6)	2 (4.3)

SVR – sustained virological response; BR – biological response; NR – no response.

their having attended different treatment facilities (clinics vs hospital).

Discussion

We have reported studies done in an HCV hyperendemic area [10–17]. In 1990, 10% (739 people) of the adult population (7,389) in the area were selected randomly, of whom 509 people were tested for liver disease. The positive rates of anti-HCV, HCV RNA and HBs antigen were, respectively, 23.6%, 17.9% and 2.6% [11].

Findings concerning the area obtained so far are as follows. Medical activities are regarded as the original source of HCV dissemination in the area [12]. Many HCV carriers die of HCC or cirrhosis [13]. Follow up from 1990 to 2002 found that the yearly onset rate of HCC from chronic hepatitis C was 1.7% and that of HCC from cirrhosis was 6.7% [14]. Nineteen percent of HCV carriers were under the care of liver specialists and 75% of residents with a history of IFN therapy were treated by liver specialists [15]. HCV carriers had extrahepatic manifestations including lichen planus and diabetes mellitus more frequently than non-carriers [16,17].

Telephone interviews were conducted to determine the reasons why some carriers who knew the facts did not participate in screenings or declined to receive treatment. Reasons included high medical cost, being asymptomatic, secrecy from families, and being busy [15].

In our previous reports of the same area [10], according to responses by physicians to questionnaires, 59.1% (150/254) of patients were recommended IFN therapy by physicians and 40.6% (103/254) of patients received IFN therapy. The proportions of these patients receiving IFN therapy were 78.2% for patients of liver specialists and 15.7% for patients of non liver-specialists, revealing that the two differed by approximately 5 fold. The difference was due to the intensity of the effort and the strength of the explanations or recommendations given by physicians to patients. It was also found that liver specialists offered to patients information on new therapies, influencing the decision by patients to receive IFN therapy. Liver specialists also explained and recommended IFN therapy to patients even though the patients were elderly with complications [10].

In the present paper, factors were studied statistically that influenced the decision by patients with chronic hepatitis C whether or not to receive IFN therapy after it was recommended by their physician. We could collect unbiased answers from groups that have relatively homogenous medical environments and living customs, as many medical facilities in the subject area were cooperative. Of 139 patients to whom physicians recommended IFN therapy, 92 (66.2%) agreed to receive IFN therapy. Whereas 74 (86.0%) of 86 hospital patients (treated by liver specialists) agreed to receive IFN therapy, only 18 (34.0%) of 53 clinic patients (treated by non liver-specialists) did so.

Multivariate analysis demonstrated that treatment facilities, sex and the presence or absence of complications were factors associated with the risk that patients would decline IFN therapy. In other words, age (elderly) and stages of liver diseases which physicians answered as factors for which IFN therapy was not recommended did not influence the decision by patients. Analysis suggested that differences in sex influenced the decision by patients.

The most frequently mentioned reason for not receiving IFN therapy even though physicians recommended it and patients acknowledged the recommendation was "worries over adverse reactions." A higher proportion of females than males worried about adverse reactions (male: 18.2%, female: 33.3%), as shown in Table 5. Although the risk of HCC in males was higher than that in females, treatment of HCC in elderly females has become an issue because of HCC patients' aging [19]. It has been reported concerning IFN therapy for female patients that IFN monotherapy for females over 40 years old was not markedly effective [20], and caution should be exercised for hemolytic anemia as an adverse reaction of ribavirin [21]. It may be necessary for physicians to explain and recommend IFN therapy to female patients while keeping in mind that females are more anxious about the therapy than are males.

It is understandable that it is difficult for non-specialists to explain well to patients about diseases and treatments outside their specialties. However, there was no difference between treatment facilities in therapeutic effects of IFN therapy in patients who agreed to receive the therapy upon recommendation by physicians. In other words, therapeutic effects were not affected greatly whether attending phy-

sicians were liver specialists or not. Therefore, it is essential, in order to facilitate patients' decision to receive IFN therapy, for physicians to strive to explain it as thoroughly as possible.

CONCLUSIONS

It is important, in order to facilitate patients decisions to receive IFN therapy, to improve communication between physicians and patients. It is also important for physicians and patients to strive to establish trust between themselves. It is hoped that specialists and non-specialists in all areas will hold discussions to create cooperation between hospitals and clinics.

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