Effectiveness of Interferon Therapy for Reducing the Incidence of Hepatocellular Carcinoma among Patients with Type C Chronic Hepatitis

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Study purpose: To evaluate the effect of interferon treatment for reducing the incidence of hepatocellular carcinoma among patients with type C chronic hepatitis.

Methods: Retrospective cohort study was conducted on 923 patients with type C chronic hepatitis, who were identified through databases of Osaka Medical Center for Cancer and Cardiovascular Diseases. Two hundred and twenty-four of those had undergone interferon treatment, while the other 699 patients had not. Kaplan-Meier method and the proportional hazards model were used for statistical analysis.

Results: Five-years’ cumulative incidence of hepatocellular carcinoma was 2.2% among the interferon treated patients, while 9.5% among the interferon untreated. Difference between the 2 curves of the cumulative incidence was statistically significant (p=0.0015). After adjustment for possible confounders, hazard rate ratio of hepatocellular carcinoma was 0.31 in the interferon treated group, significantly lower than that in the untreated (p=0.015). Hazard rate ratio for death from causes other than hepatocellular carcinoma and liver diseases was also lower among the interferon treated group than that among the untreated, although not significant.

Conclusions: Interferon treatment is suggested to reduce the risk of hepatocellular carcinoma among patients with type C chronic hepatitis, and not to increase the risk for death from causes other than hepatocellular carcinoma and liver diseases. J Epidemiol, 2000 ; 10 : 234-240.

Interferon, hepatitis C virus, chronic hepatitis, hepatocellular carcinoma

INTRODUCTION

Liver cancer ranks third among all cancer deaths in Japan, following stomach and lung cancers. The major histological type of liver cancer is hepatocellular carcinoma (HCC), which accounts for 90% of all liver cancer in Osaka, where the age-standardized mortality rate of liver cancer is higher than in any other prefectures in Japan. Hepatitis C virus (HCV) is the major cause of chronic liver disease and HCC. More than 75% of HCC patients were positive for antibody to hepatitis C virus (HCV-Ab) in Japan. In 1992, Japanese health insurance approved interferon (IFN) therapy for chronic active hepatitis caused by HCV. Since then, IFN has prevailed as a standard treatment for type C chronic active hepatitis in Japan. Recently there have been published several reports showing reductions in the incidence of HCC among type C chronic hepatitis or liver cirrhosis patients treated with IFN. However, the number of HCC incidence was generally not large enough to get a reliable estimate for the risk reduction, and the quality of follow-up was generally not so good from the epidemiological point of view. Survival and causes of death were not fully investigated in those studies. We, therefore, conducted a retrospective cohort study of patients with type C chronic hepatitis to evaluate the effect of IFN treatment for reducing the incidence of HCC, taking the above-mentioned shortcomings. Not only the development of HCC but also survival rates and causes of death were compared between the IFN treated group and the IFN untreated group.
STUDY SUBJECTS AND METHODS

Study subjects:

Study subjects were collected from two sources. One was a file of chronic liver disease patients being kept in the Section for Liver Cancer Screening of Osaka Medical Center for Cancer and Cardiovascular Diseases (OMCC), where outpatients diagnosed with chronic hepatitis or with liver cirrhosis and fit to pre-arranged criteria were registered for an evaluation program of effectiveness for periodic check-up for HCC with ultrasonography and serum α-fetoprotein (AFP) measurement. There were identified 1,114 patients positive for HCV-Ab but negative for hepatitis B surface antigen (HBsAg) during the period of registration from May 1987 to March 1995 in this file. Two hundred and seventy-one patients of them were diagnosed with liver cirrhosis at the registration; therefore, they were not included in the present study. Medical records for the remaining 843 patients were scrutinized and identified that 144 patients had a history of IFN treatment for type C chronic active hepatitis, while 699 patients had never been treated with IFN. In 6 patients of the former, however, starting date on IFN treatment could not be determined, and then their data were omitted. Another source of the study subjects was a file of type C chronic active hepatitis patients treated with IFN at OMCC during the same period as the former source. Eighty-six of those were patients who had not been registered in the Section for Liver Cancer Screening of OMCC. Our study subjects were, finally, composed of 224 patients treated with IFN and 699 patients without IFN treatment.

Follow-up:

The method of clinical follow-up for detection of HCC was not necessarily uniform among the study subjects. Six hundred and twenty patients in the study group for the evaluation program of effectiveness for periodic check-up for HCC were recommended and urged to undergo ultrasonography and serum AFP measurement every 3 or 6 months. Meanwhile, 217 patients in the control group for that evaluation program and fit to pre-arranged criteria were registered for an evaluation program for periodic check-up of HCC. Observation started on the first date of IFN treatment for the IFN treated group. As for the IFN untreated group, it began on the registration date of the evaluation program for periodic check-up of HCC. Observation for incidence of HCC was closed at the date of HCC diagnosis, death or the end of December 1997; whichever came first. For patients who were lost to follow-up, the last confirmed dates of living were used for closing observation for survival.

The chi-square test was used for comparisons of baseline data between the IFN treated group and the untreated group. The Kaplan-Meier method was employed for calculating cumulative incidence rates of HCC and cumulative survival rates. The logrank test was applied to test the difference in the survival curves, while the Cox proportional hazards model was used to estimate hazard rate ratios for HCC among the IFN treated group as compared with the IFN untreated group. Sex (male / female), age (years old), serum AFP (ng/ml; 20 and over <abnormal>, vs. less <normal>), alanine aminotransaminase (ALT) (IU; quartile -57, -94, -153, over 153) and platelet count (×10⁴/mm³; quartile -13, -15, -20, over 20) at baseline were adjusted for estimating hazard rate ratios for HCC. P-values less than 0.05 were judged as statistically significant. Statistical package software, STATA was used for statistical analyses.

RESULTS

Table 1 presents the baseline characteristics between the IFN treated group and the IFN untreated group. The proportion of males in the IFN treated group was higher than that in the IFN untreated group. The IFN treated group was younger in comparison with the IFN untreated group. Percentage of those with elevated serum AFP levels was not different significantly between the two groups, if missing data was omitted. There existed higher proportion of patients with higher serum ALT levels and lower platelet counts in the IFN treated group than the IFN untreated group.

Table 2 shows outcomes of the follow-up study according to IFN treatment. Mean follow-up period was 54.9 months for the IFN treated group and 70.4 months for the IFN untreated group. During the follow-up period, HCC was developed in 106 patients, 3 of whom were found first through collating with the Osaka Cancer Registry’s file. Five patients (2.2%) developed HCC in the IFN treated group, while 101 patients (14.4%) developed HCC in the IFN untreated group. As for the vital status of the study subjects at the end of December 1997, 4 deaths (1.8%) in the IFN treated group and 84 deaths (12.0%) in the IFN untreated group were confirmed. Only 3 patients were unknown for vital status. Among the IFN treated group, no death from HCC was observed, although one person died from the other liver disease. In contrast, among the IFN untreated group, 34 deaths from HCC and 11 deaths from...
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Table 1. Baseline characteristics of IFN* treated group and untreated group.

|                | IFN* treated group | IFN untreated group | P-value |
|----------------|--------------------|---------------------|---------|
|                | n = 224 (%)        | n = 699 (%)         |         |
| Sex            |                    |                     |         |
| Male           | 157 (70.1)         | 392 (56.1)          | 0.000   |
| Female         | 67 (29.9)          | 307 (43.9)          |         |
| Age distribution |                  |                     |         |
| <53            | 115 (51.3)         | 140 (20.0)          | 0.000   |
| <58            | 49 (21.9)          | 181 (25.9)          |         |
| <63            | 47 (21.0)          | 206 (29.5)          |         |
| ≥64-           | 13 (5.8)           | 172 (24.6)          |         |
| AFP* (ng/ml)   |                    |                     |         |
| <20            | 172 (83.1)         | 568 (83.5)          | 0.882   |
| ≥20            | 35 (16.9)          | 112 (16.5)          |         |
| Unknown        | 17                 | 19                  |         |
| ALT (*U. L.)   |                    |                     |         |
| <57            | 23 (10.3)          | 218 (31.1)          | 0.000   |
| <94            | 48 (21.4)          | 174 (24.9)          |         |
| <153           | 68 (30.4)          | 164 (23.5)          |         |
| ≥154           | 85 (37.9)          | 143 (20.5)          |         |
| Platelet count (×10^12/mm^3) |                  |                     |         |
| >13            | 51 (23.4)          | 164 (25.0)          |         |
| >16            | 63 (28.9)          | 132 (20.1)          | 0.000   |
| >20            | 59 (27.1)          | 172 (26.2)          |         |
| ≥20            | 45 (20.6)          | 189 (28.7)          |         |
| Unknown        | 6                  | 42                  |         |

*: Interferon  
†: α-fetoprotein  
‡: Alanine aminotransaminase

Table 2. Outcome of follow-up study according to IFN* treatment.

|                | IFN* treated group | IFN untreated group | P-value |
|----------------|--------------------|---------------------|---------|
|                | n = 224 (%)        | n = 699 (%)         |         |
| Development of HCC† | 5 (2.2)            | 101 (14.4)          |         |
| Alive          | 218 (97.3)         | 614 (85.7)          |         |
| Dead           | 4 (1.8)            | 84 (12.0)           |         |
| Causes of death |                    |                     |         |
| HCC†           | 0                  | 34                  |         |
| Other liver diseases | 1                 | 11                  |         |
| Other causes   | 3                  | 33                  |         |
| Unknown        | 0                  | 6                   |         |
| Unknown for vital status | 2 (0.9)       | 1 (0.1)             |         |
| Follow-up period in months, mean | 54.9  | 70.4  |         |
| <range>        | <9-119>            | <1-127>             |         |

*: Interferon  
†: Hepatocellular carcinoma

Figure 1 shows Kaplan-Meier’s estimates of cumulative incidence of HCC for the 2 groups. Since the mean follow-up period for the IFN treated group was relatively short (54.9 months), the estimates were only depicted until 5-years. Five-years’ cumulative incidence of HCC was 2.2% (95% confidence interval <CI>: 0.0-4.4%) for IFN group, while 9.5% (95% CI: 7.1-11.9%) for IFN untreated group. The difference between the 2 curves was statistically significant (Logrank test: p=0.0015).

The Cox proportional hazards model was used to estimate hazard rate ratios for HCC in the IFN group as compared with the IFN untreated group. Sex-and age-adjusted hazard rate ratio was 0.32 (95% CI: 0.13-0.80), significantly lower than the unity. Further adjustment for AFP, ALT, and platelet count showed a still statistically significant lower hazard rate ratio: 0.31 (95% CI: 0.12-0.80) (Model 1 and 2 in Table 3, respectively). Hazard rate ratios for other risk factors of HCC than the IFN treatment, i.e., sex, age, platelet count, serum ALT and AFP measurements were also shown in Table 3. Male sex, elderly age, elevated AFP levels, higher ALT measurements, and decreased platelet counts were all shown to be significant or marginally significant risk factors for HCC after adjustment.
Figure 1. Comparison of cumulative incidence of hepatocellular carcinoma between the interferon treated group and the interferon untreated group.

DISCUSSION

During the last 10 years, the age-standardized incidence rate (per 100,000, standardized to the world population) of liver cancer in Osaka has increased more than twice, from 13.2 among males and 5.2 among females in 1979-1982 to 46.7 and 11.5 in 1988-1992, respectively. Although the biological mechanisms of HCV-related hepatocarcinogenesis remain obscure, most of the increase can be explained by the high HCV-prevalent Japanese generations reaching the ages of fifties and sixties, where HCC is common. It seems, therefore, very important to prevent HCC development among HCV carriers.

Table 5 summarized the results dealing with the effect of IFN treatment on reducing the incidence of HCC among type C chronic hepatitis or cirrhosis patients. Except for one study conducted in Italy for HCV-related cirrhosis, study results in Table 5 showed a reducing effect of HCC through IFN treatment for type C chronic active hepatitis or cirrhosis. Our present study also indicated a beneficial effect of IFN for type C hepatitis patients; that is, the hazard rate ratio for HCC was 0.31 in the IFN treated group as compared with that in the IFN untreated group after adjustment for sex, age, serum AFP, ALT and platelet counts. Risk factors for development of HCC were also elucidated after adjustment for IFN treatment. Those findings on risk factors for HCC were well consistent with other studies, including ones by the authors.

Survival of patients who underwent IFN treatment also showed a favorable effect of IFN. This indicated that IFN treatment did not significantly increase risk of death from causes other than HCC and liver diseases. At the same time, however, this showed a possible difference regarding the prospect of longevity between the two groups, i.e., bias toward a better survival for IFN treated group at enrollment. Several limitations of this study should be discussed.

This study was not a randomized controlled study, but a retrospective cohort study. Even though we adjusted possible confounders with proportional hazard model as much as we could, other possible confounders such as HCV-genotype, amount of HCV-RNA and degree of fibrosis of the liver could not be controlled because data on these factors could not be collected. Furthermore, unknown risk factors of HCC might have been distributed unevenly between the two groups. Although it seems unlikely that such uncontrolled confounders would reverse the results completely, it is possible that these factors might have overestimated the beneficial effect by IFN treatment.

Clinical follow-ups for detection of HCC were not necessarily uniform among the study subjects. In fact, proportion of participants in the screening evaluation program at OMCC was 40.2% for the IFN treated group and 75.8% for the IFN untreated group. To examine the effect of detection bias, we restricted the study subjects to all participants in the screening evaluation program as a subcategory analysis. As a result, sim-
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Table 3. Risk factors for the development of HCC* among the study subjects.

|                           | No. of cases developed HCC | Hazard ratio | 95% CI    | P-value |
|---------------------------|----------------------------|--------------|-----------|---------|
| Model 1                   |                            |              |           |         |
| Sex                       |                            |              |           |         |
| Female                    | 30                         | 1.00         |           |         |
| Male                      | 76                         | 2.12         | 1.38-3.24 | 0.001   |
| Age                       |                            |              |           |         |
| +1 year old               | 106                        | 1.06         | 1.03-1.09 | 0.000   |
| IFN² treatment            |                            |              |           |         |
| No                        | 101                        | 1.00         |           |         |
| Yes                       | 5                          | 0.32         | 0.13-0.81 | 0.016   |
| Model 2                   |                            |              |           |         |
| Sex                       |                            |              |           |         |
| Female                    | 27                         | 1.00         |           |         |
| Male                      | 70                         | 2.43         | 1.53-3.87 | 0.000   |
| Age                       |                            |              |           |         |
| +1 year old               | 97                         | 1.06         | 1.02-1.10 | 0.001   |
| AFP* (ng/ml)              |                            |              |           |         |
| <20                       | 50                         | 1.00         |           |         |
| ≥20                       | 47                         | 2.85         | 1.81-4.49 | 0.000   |
| ALT§ (I.U.)               |                            |              |           |         |
| -57                       | 7                          | 1.00         |           |         |
| -94                       | 10                         | 2.22         | 0.93-5.32 | 0.074   |
| -153                      | 33                         | 2.50         | 1.08-5.78 | 0.033   |
| 154-                      | 37                         | 2.11         | 0.89-4.98 | 0.090   |
| Platelet (∗10³/mm³)       |                            |              |           |         |
| -13                       | 54                         | 1.00         |           |         |
| -16                       | 21                         | 0.61         | 0.36-1.03 | 0.065   |
| -20                       | 12                         | 0.26         | 0.13-0.49 | 0.000   |
| >20                       | 10                         | 0.28         | 0.14-0.58 | 0.001   |
| IFN³ treatment            |                            |              |           |         |
| No                        | 92                         | 1.00         |           |         |
| Yes                       | 5                          | 0.31         | 0.12-0.80 | 0.015   |

*: Hepatocellular carcinoma
†*: Interferon
‡*: α-fetoprotein
§*: Alanine aminotransaminase

Table 4. Hazard rate ratio for death among IFN* treated group compared with untreated group.

|                                | Age-, sex-adjusted hazard rate ratio | Multi-variate adjusted hazard rate ratio | 95% CI      | P-value |
|--------------------------------|--------------------------------------|------------------------------------------|-------------|---------|
| All death                      | 0.53                                 | 0.52                                     | 0.16-1.72   | 0.28    |
| Death from other reasons       |                                      |                                          |             |         |
| than HCC and liver diseases    | 0.86                                 | 0.89                                     | 0.20-4.10   | 0.89    |
| (a)                            |                                      |                                          |             |         |
| Death from other reasons       | 0.80                                 | 0.82                                     | 0.18-3.71   | 0.79    |
| than HCC and liver diseases    |                                      |                                          |             |         |
| (b)                            |                                      |                                          |             |         |

*: Interferon
†*: Adjusted for sex, age, α-fetoprotein, alanine aminotransaminase, platelet count
‡*: Hepatocellular carcinoma
†*: Unknown causes of death were regarded as deaths from liver diseases
†*: Unknown causes of death were regarded as censored
Table 5. Summary of reports on effectiveness of interferon therapy for prevention of HCC* among type C hepatitis patients.

| Authors Place of study | Study design | IFN* treated | Study subjects | No. of cases developed HCC* | Follow-up period (month) | Hazard rate ratio (95% CI) for IFN* treatment + vs. - (Adjusted factors) | Follow-up methods for HCC* and vital status (% of unknown vital status) | Analysis of survival and causes of death |
|------------------------|-------------|--------------|----------------|-----------------------------|---------------------------|-------------------------------------------------|-------------------------------------------------|----------------------------------------|
| Present study Japan    | Retrospective cohort study | + 224 Chronic active hepatitis, type C 699 Chronic hepatitis, type C | 5 | 54.9 | 0.31 (0.12-0.80) (sex, age, serum AFP, ALT, platelet count) | Clinical follow-up (Collaboration with population-based cancer registry) | Referring to resident registration (0.3%) | Fully described |
| Imai et al. Japan (5)  | Retrospective cohort study | + 419 Chronic active hepatitis, type C 144 Chronic active hepatitis or cirrhosis, type C | 28 | Median 47.6 | 0.53 (0.28-0.97) (age, sex, serum AFP, ALT, platelet count, histologic staging score, histologic activity score) | Clinical follow-up (Collaboration with population-based cancer registry) | (Not described) | Not described |
| Ikeda et al. Japan (6) | Retrospective cohort study | + 1,191 Chronic hepatitis, type C 452 Chronic hepatitis, type C | 28 | Median 61.2 | 0.67 (0.40-1.14) (age, sex, γ-glutamyl transpeptidase histologic staging) | Clinical follow-up (10.3% of the original cohort were excluded because of no-follow-up or less than 1 year of follow-up) | % of drop-outs (IFN*: 4.4%, IFN†: 12.3%) | Partly described (survival only) |
| Yoshida et al. Japan (7) | Retrospective cohort study | + 2,400 Chronic hepatitis, Cirrhosis, type C 89 490 Chronic hepatitis, Cirrhosis, type C | 89 | Median 51.6 | 0.52 (0.36-0.74) (age, sex, stage of fibrosis) | Clinical follow-up (Not described) | 10.3% of the original cohort were excluded because of no-follow-up or less than 1 year of follow-up | Not conducted |
| Benvegnu et al. Italy (8) | Retrospective cohort study | + 88 HCV-related cirrhosis 101 HCV-related cirrhosis | 5 | Mean 71.9 | 0.14 (0.05-0.38) (albumin, duration of cirrhosis, γ-glutamyl transpeptidase prothrombin time) | Clinical follow-up (Not described) | (Not described) | Partly described |
| Bruno et al. Italy (9) | Prospective cohort study | + 83 HCV-related cirrhosis 80 HCV-related cirrhosis | Data not shown | 2.03 (0.77-5.37) (sex, age, genotype 1b alcohol abuse) | Clinical follow-up (Not described) | (Not described) | Not described |
| Nishiguchi et al. Japan (10) | Randomized trial | + 45 HCV-related chronic active with cirrhosis 45 HCV-related chronic active with cirrhosis | 2 | Mean 52.8 | 0.07 (0.009-0.53) (sex, age, ALT, albumin, platelet count) | Clinical follow-up (Not described) | (Partly described) | (causes of death only) |

* : Hepatocellular carcinoma
† : Interferon
‡ : α-fetoprotein
§ : Alanine aminotransaminase
ilar hazard rate ratio was obtained (0.37 for IFN treatment after multi-variate adjustment). We suppose that the record linkage to the Osaka Cancer Registry and confirmation of vital status and causes of death among the study subjects would have played significant roles for reducing possible detection bias in this study.

The number of study subjects, in particular the number of patients who underwent IFN treatment, were still rather small. Besides, the observation periods were relatively short. Although deaths related to IFN treatment were not observed, it seems that our study did not have enough statistical power to dismiss serious side effects with IFN treatment.

Despite those limitations, this study indicated that IFN therapy for type C chronic hepatitis had promising effects on prevention for HCC. Large-scale and well-designed clinical follow-up studies will be necessary to confirm effectiveness of IFN therapy for reducing the incidence of HCC among type C chronic hepatitis patients. Sub-classification analyses should be also conducted to examine heterogeneity of the effectiveness. Accumulations of those data will be useful for establishing effective treatment of type C chronic hepatitis and prevention of HCC, under the circumstances that IFN treatment for type C chronic hepatitis has already been accepted as a standard remedy.

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