

Effects of Long-Term Postoperative Interferon- α Therapy on Intrahepatic Recurrence after Resection of Hepatitis C Virus–Related Hepatocellular Carcinoma

A Randomized, Controlled Trial

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Background: Interferon therapy decreases the incidence of hepatocellular carcinoma in patients with chronic hepatitis C.

Objective: To evaluate effects of interferon- α on recurrence after resection of hepatitis C virus–related hepatocellular carcinoma.

Design: Randomized, controlled trial.

Setting: University hospital, medical center, and affiliated hospital in Osaka, Japan.

Patients: 30 men were randomly allocated after resection to the interferon- α group ($n = 15$) or the control group ($n = 15$).

Intervention: Patients in the interferon- α group received interferon- α , 6 MIU intramuscularly daily for 2 weeks, then three times weekly for 14 weeks, and finally twice weekly for 88 weeks.

Measurements: Recurrence rates after resection.

Results: Recurrent tumors were detected in 5 patients in the interferon- α group and in 12 control patients. The recurrence rate was significantly lower in the interferon- α group than in the control group ($P = 0.037$).

Conclusion: Postoperative interferon- α therapy appears to decrease recurrence after resection of hepatitis C virus–related hepatocellular carcinoma.

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Hepatitis C virus (HCV) is an important cause of hepatocellular carcinoma in many areas of the world (1). The recurrence rate at 5 years after resection of HCV-related hepatocellular carcinoma has been reported as 70% to 80% (2–4). Recurrences after resection of hepatocellular carcinoma may be either metastases from the primary carcinoma or new foci of carcinomas (multicentric occurrence) (4–8). Chronic active hepatitis is a risk factor for recurrence, including multicentric carcinogenesis, after resection (4, 7, 8). In addition, the recurrence rate after the resection of HCV-related hepatocellular carcinoma is higher in patients with HCV viremia than in those without viremia (4). Interferon treatment decreases the incidence of hepatocellular carcinoma in patients with chronic hepatitis C (9–16). We conducted a randomized, controlled trial to evaluate whether postoperative therapy with interferon- α would decrease the incidence of recurrence after resection of HCV-related hepatocellular carcinoma.

METHODS

Patients and Trial Profile

Between November 1993 and March 1997, 112 HCV-positive patients underwent resection for hepato-

cellular carcinoma at Osaka City University Hospital or Osaka City General Hospital, Osaka, Japan. Seventy-seven patients met the eligibility criteria: 1) single tumors less than 5 cm in maximum diameter on preoperative imaging; 2) detectable HCV RNA without hepatitis B surface antigen or HIV antibodies; 3) chronic hepatitis C or a Child–Pugh score of A or B for compensated cirrhosis (17); and 4) no severe thrombocytopenia (platelet count $< 50 \times 10^9$ cells/L). Before resection, 31 of the 77 eligible patients gave written informed consent to participate in the trial; however, one patient was later excluded because resection was not curative. Forty-six patients declined to participate because they were unwilling or unable to agree to twice-weekly hospital visits for 2 years or were concerned about widely publicized side effects of interferon use. A curative operation was defined as complete resection of all macroscopically evident tumor tissue. Specifically, no tumors could be detected in the remnant liver on computed tomography performed 3 to 4 weeks after resection. In the one patient excluded from the trial after resection, a residual tumor was found on computed tomography 3 weeks after resection. In all, 30 patients

were enrolled and randomly allocated to the interferon- α group ($n = 15$) or a control group ($n = 15$). Randomization was done by using a random-numbers table, and patient assignments were withheld from the investigators. During the trial, no patient in the control group received any type of treatment; no patient in the interferon group received chemotherapy or any treatment other than interferon- α . This study was done in accordance with the Helsinki Declaration and was approved by the ethics committees of our institutions.

Interferon- α Treatment

Patients received 6 MIU of interferon- α (human lymphoblastoid interferon, Sumiferon, Sumitomo Pharmaceuticals, Osaka, Japan) intramuscularly every day for 2 weeks, then 3 times weekly for 14 weeks, and finally twice weekly for 88 weeks (total dose, 1572 MIU). Interferon- α therapy was started 5 to 15 weeks (mean, 9 weeks) after resection. In 1 of the 15 patients in the interferon- α group, treatment was delayed until 7 months after resection at the patient's request. Laboratory tests were done at least once monthly during interferon- α therapy and at least once every 3 months thereafter for evaluation of the response to therapy and identification of side effects of interferon- α . Serum HCV RNA was detected by using a method reported previously (9), and viral load was measured by using a branched-DNA probe assay (Quantiplex HCV-RNA, Chiron Corp., Emeryville, California).

Response to Interferon- α Therapy

A complete response was defined as the absence of serum HCV RNA (virologic remission) and serum alanine aminotransferase (ALT) activity within the reference range (≤ 750 nkat/L [≤ 45 U/L]) for at least 6 months after interferon- α therapy (biochemical remission) (9). A biochemical response was defined as a decrease in serum ALT activity to within the reference range but with persistently detectable serum HCV RNA. Nonresponse was defined as persistence of HCV RNA and no decrease in ALT activity.

Detection of Recurrence

Serum concentrations of α -fetoprotein and protein induced by vitamin K absence and antagonist II were measured within 2 months of resection and every 3 months thereafter. Ultrasonography, computed tomog-

raphy, magnetic resonance imaging, or some combination of these tests was done within 2 months after the operation and every 3 months thereafter. These examinations were done until the detection of recurrence or until the trial end point (final examination). When tumor recurrence was suspected on the basis of tumor markers, imaging, or both, angiography, ultrasonography-guided biopsy, or both were done to establish a definitive diagnosis. The radiologists who were responsible for diagnosis of tumor recurrences had no contact with the patients and had no information about the trial.

Statistical Analysis

Time to recurrence was measured from the time of resection to the detection of a recurrent tumor. The recurrence rates (including data on patients who could not complete interferon- α therapy) were calculated by using the Kaplan–Meier method, and significance of between-group differences was assessed by using the log-rank test. All analyses were done by using SAS statistical software, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

The funding sources had no role in the collection, analysis, and interpretation of the data or in the decision to submit the paper for publication.

RESULTS

Most baseline variables were similar in the two groups, as were the operative procedures (Table). The patients who declined participation and the patients who were enrolled were similar with regard to most variables.

Interferon- α could not be administered to one patient because of premature ventricular contractions. Data on this patient were included in the interferon- α group for all analyses. Interferon- α administration could not be completed in 3 patients because of depression ($n = 1$, at 17 days), severe general fatigue ($n = 1$, at 11 months), and renal abscess ($n = 1$, at 10 months; this patient also had a recurrence detected in the same month). In 4 patients with recurrence, interferon- α administration was stopped prematurely to allow treatment of the tumor. In the interferon- α group, 2 patients were complete responders, 6 patients were biochemical responders only, and 7 patients were nonresponders. Among the control patients, postoperative serum ALT

Table. Patient Demographic and Clinical Characteristics*

Characteristic	Interferon- α Group (n = 15)	Control Group (n = 15)	Other Eligible Patients (n = 46)
Mean age \pm SD, y	61.9 \pm 5.8	60.0 \pm 4.8	62.3 \pm 5.0
Men, n (%)	15 (100)	15 (100)	43 (93)
Alcohol abuse, n (%)	4 (27)	5 (33)	13 (28)
Child-Pugh score A, n (%)	11 (73)	12 (80)	34 (74)
Albumin level, g/L†	36 (33, 43)	36 (33, 41)	36 (33, 41)
ALT activity, nkat/L [U/L]†	1750 (750, 2183) [105 (45, 131)]	1433 (967, 2517) [86 (58, 151)]	1350 (700, 2483) [81 (42, 149)]
Platelet count, $\times 10^9$ cells/L†	147 (75, 231)	112 (61, 209)	118 (64, 208)
α -Fetoprotein level \geq 100 μ g/L, n (%)	4 (27)	4 (27)	13 (28)
Tumor size, cm†	2.5 (1.9, 3.5)	2.6 (2.4, 3.5)	2.5 (1.5, 4.2)
Differentiation of tumor, n (%)			
Good	1 (7)	2 (13)	6 (13)
Moderate	11 (73)	11 (73)	31 (67)
Poor	3 (20)	2 (13)	9 (20)
Histologic activity index, n (%)‡			
Grade 1	4 (27)	1 (7)	5 (11)
Grade 2	6 (40)	7 (47)	29 (63)
Grade 3	5 (33)	7 (47)	12 (26)
Cirrhosis, n (%)	7 (47)	8 (53)	25 (54)
HCV genotype, n (%)			
1a	0 (0)	0 (0)	0 (0)
1b	12 (80)	10 (67)	37 (80)
2a	3 (20)	4 (27)	4 (9)
2b	0 (0)	1 (7)	2 (4)
Unknown	0 (0)	0 (0)	3 (7)
High viral load (\geq 1.0 mEq/mL), n (%)	7 (47)	8 (53)	NT
Anatomical resection, n (%)	8 (53)	7 (47)	19 (41)

* Unless otherwise specified, values are the number (percentage) of patients. ALT = alanine aminotransferase; HCV = hepatitis C virus; NT = not tested.

† Values are the median (10th, 90th percentiles).

‡ The histologic activity index with modifications (19) was used for evaluation of the severity of active hepatitis and the degree of fibrosis in noncancerous hepatic tissue.

activity (except immediately after resection) was greater than the reference range, and serum HCV RNA was detected at the follow-up appointments.

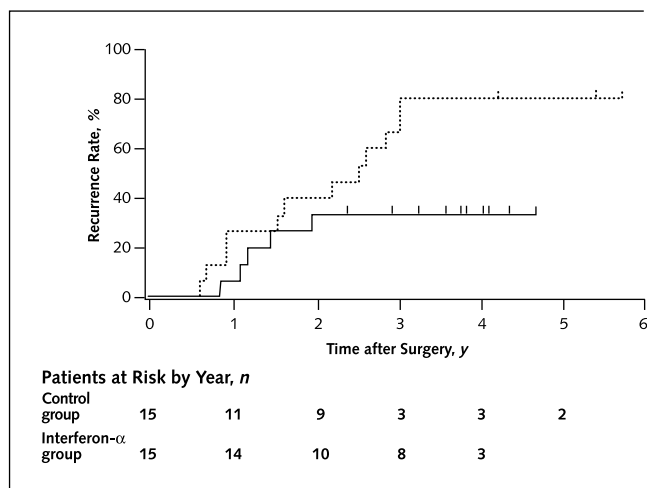
The median follow-up period (from the operation to the detection of recurrence or to the study end point) was 1087 days (25th and 75th percentiles, 514 and 1376 days) for patients receiving interferon- α and 897 days (25th and 75th percentiles, 439 and 1105 days) for the controls. In all patients, examinations for detection of recurrence were done according to schedule. All patients without recurrence were still alive at the end of this trial. Recurrent tumors were detected in 5 patients (including the patient who could not tolerate interferon- α therapy) in the interferon- α group and in 12 control patients. In the interferon- α group, recurrence was definitively diagnosed in 3 patients by using angiography and in 2 patients by using angiography and biopsy. In the control group, definitive diagnoses were made in 8 patients by using angiography, in 3 patients by using biopsy, and in 1 patient by using both methods. No recurrence was detected in either of the 2 complete re-

sponders in the interferon- α group. One of the 6 biochemical responders and 4 of the 7 nonresponders had recurrent tumors. The recurrence rates increased along similar curves in the two groups in the 2 years after resection; thereafter, 6 controls but no patient receiving interferon- α had recurrence (Figure). The recurrence rate was significantly lower in the interferon- α group than in the control group ($P = 0.037$).

DISCUSSION

Persistent active hepatitis is a risk factor for development of hepatocellular carcinoma, indicating that treatment of active hepatitis may be important in the management of patients with HCV-related hepatocellular carcinoma (4). In our study, absence of interferon- α therapy was a risk factor for recurrence. Although for the first 2 years of follow-up the recurrence rate increased for the two groups in similar curves, the recurrence rate in the interferon- α group did not increase after that time. This finding suggests that patients in the interferon- α group had been truly cured. Recurrent tumors detected

Figure. Recurrence rates in the interferon- α (solid line) and control (dotted line) groups.



Tick marks show censoring times. All censored patients were alive without recurrence of hepatocellular carcinoma at the end of this trial. The recurrence rate was significantly lower in the interferon- α group than in the control group according to the log-rank test ($P = 0.037$).

within 2 years of the operation were likely to be either metastases from the primary carcinoma or carcinoma that appeared before or during interferon- α therapy but had gone undetected at the operation. Our findings indicate that interferon- α therapy does not suppress carcinoma itself. On the other hand, recurrences that appear more than 2 years after resection are likely to have arisen because of new carcinogenesis. Recurrence was detected in 1 of 8 patients with a biochemical remission (including the 2 complete responders) and in 4 of the 7 non-responders. Recently, several investigators have shown that hepatocellular carcinoma is less likely to develop in patients in whom interferon- α decreases ALT activity to within the reference range, even if HCV is not eradicated, probably because of decreased hepatocyte necrosis and liver fibrosis (9, 11, 12, 14–16). Thus, eradication of HCV may not be necessary for reduced risk for recurrence; a decrease in ALT activity due to interferon- α therapy may prevent carcinogenesis after resection.

In previous studies, 24% to 36% of patients with cirrhosis (11, 18) and 51% of patients without cirrhosis (14) had biochemical remission after interferon- α therapy. In our study, biochemical remission was observed in 8 (53%) of 15 patients in the interferon- α group. The high dose of interferon- α given over a long administration period may have contributed to the high re-

sponse rate in our trial. If decreases in ALT activity due to interferon- α help to prevent recurrences, perhaps the dose and the total amount of interferon can be reduced, decreasing the incidence of side effects.

In this study, other covariates, including a low platelet count ($<100 \times 10^9$ cells/L) and a high histologic activity index grade (≥ 3) (19) were not significant factors according to the log-rank test ($P > 0.2$ for the platelet count and $P > 0.2$ for the grade). The P value of the difference in the recurrence rate between groups was affected little, if at all, after adjustment for these factors. There has been no report, to our knowledge, indicating that these are risk factors for recurrence in patients with hepatitis C viremia, although persistent active hepatitis is a risk factor for recurrence in patients infected with hepatitis B virus, HCV, or both (20). These factors may have contributed to the low recurrence rate in the interferon- α group. The number of patients in this study was too few to allow a clear conclusion to be reached.

Postoperative interferon- α therapy appears to decrease the incidence of recurrence after resection of HCV-related hepatocellular carcinoma. The similarities between the larger group of eligible patients and the smaller group of enrolled patients suggest that findings in our treated group can be extended to such patients in general. Patients with early-stage hepatocellular carcinoma and satisfactory liver function may be candidates for postoperative interferon- α therapy because the clinicopathologic findings of our eligible patients were similar to those of the enrolled patients.

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