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Long-term Effects of Postoperative Interferon Therapy for Patients with Hepatitis C Virus-related Hepatocellular Carcinoma

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Background: We reviewed the long-term effects of postoperative interferon (IFN) therapy on hepatitis C virus-related hepatocellular carcinoma (HCC). **Methods:** A total of 202 patients aged 65 years or less with hepatitis C virus-related HCC who had no histopathologic evidence of portal or hepatic vein invasion or intrahepatic metastasis underwent curative resection from 1990 to 1999. Tumors were 50 mm or less in greatest dimension, and of the simple nodular type macroscopically. Of these patients, 20 underwent postoperative IFN therapy (IFN group) and 182 served as controls (non-IFN group). Statistical analysis was made of the background factors and cumulative survival and disease-free survival rates in the IFN and non-IFN groups. **Results:** There were no significant differences between the IFN group and non-IFN group in age, gender, resected tumor size, number of tumors, gross type, degree of differentiation, non-cancerous liver parenchyma, or preoperative indocyanine green retention rate at 15 minutes. The 5- and 10-year survival rates were 100 and 69.8% in the IFN group and 69.3 and 16.8% in the non-IFN group, respectively (p=0.0005). The 5-year disease-free survival rate was 57.0 and 28.8% in the IFN group and non-IFN group, respectively (p=0.0083). Multivariate analysis showed that postoperative IFN therapy was an independent prognostic factor of both survival and disease-free survival (p=0.0004, p=0.0031). However, by the 10th postoperative year the disease-free survival rate showed nearly identical rates. **Conclusions:** These results suggest the possibility that postoperative IFN therapy for hepatitis C virus-related HCC has the dual effect of delaying postoperative occult recurrence of HCC and controlling multicentric carcinogenesis. However, IFN therapy could not provide perfect long-term control of intrahepatic recurrence of HCC.

Key words: hepatocellular carcinoma, chronic hepatitis C, carcinogenesis, hepatectomy, interferon-alpha

Introduction

Most cases of HCC in Japan are associated with chronic hepatopathy caused by hepatitis B or C virus, and the characteristics have been clarified previously[1)-3)]. Even if curative resection of HCC is achieved, the underlying hepatopathy may cause new carcinogenesis or multicentric carcinogenesis. Removing the hepatitis virus is therefore considered one way of preventing carcinogenesis. Recently, IFN therapy after curative operation or ablation of HCC is used to prevent intrahepatic recurrence. However, there have been few reports of the long-term effects of postoperative IFN therapy. In the present study, we studied the long-term effects of postoperative IFN therapy on hepatitis C virus-related HCC.

Materials and Methods

1. Patients

We studied 202 patients who underwent hepatectomy for HCC at our institute from 1990 to 1999 and met the following six criteria; aged 65 years or less, greatest tumor dimension of the resected specimens 50 mm or less, of the simple nodular type macroscopically, no histopathologic evidence of portal or hepatic vein invasion or intrahepatic metastasis, curative resection, hepatitis C virus antibody

Table 1 Postoperative interferon therapy after resection of hepatitis C virus-related hepatocellular carcinoma

Age (yrs)	Gender	Resected tumor size (mm)	Gross type	Degree of Differentiation	Non-cancerous liver parenchyma	ICG R_{15} (%)	ALT (KU)	HCV-RNA	Genotype	Response
56	M	20	SN	Moderately	CH	12	80	ND	ND	SVR
53	M	15	SNIM	Well	LC	29	140	+	2a	SVR
64	M	35	SN	Moderately	CH	8	81	ND	1b	SVR
61	M	18	SN	Moderately	CH	15	94	+	2a	SVR
65	M	10	SNIM	Well	LC	20	98	+	1b	SVR
59	M	35	SN	Moderately	CH	14	155	+	2a	SVR
60	F	29	SN	Moderately	LC	20	108	+	ND	BR
61	M	31	SN	Moderately	CH	25	89	+	1b	BR
60	M	40	SN	Moderately	LC	35	76	+	1b	BR
65	F	13	SN	Well	LC	26	177	+	1b	BR
57	F	10	SNIM	Moderately	LC	23	155	+	ND	NR
49	M	19	SN	Moderately	LC	24	87	+	ND	NR
59	M	21	SNIM	Moderately	LC	9	147	+	2b	NR
64	M	30	SN	Moderately	CH	12	51	+	1b	NR
58	M	15	SNIM	Well	LC	36	116	ND	2a	NR
62	M	32	SN	Moderately	CH	12	66	+	2a	NR
59	M	17	SN	Moderately	CH	13	158	+	2a	NR
64	F	23	SN	Moderately	CH	15	89	+	1b	NR
56	M	18	SN	Moderately	CH	16	142	+	1b	NR
59	M	45	SN	Moderately	LC	24	31	+	1b	NR

ICG R_{15}: indocyanine green retention at 15 minutes. ALT: alanine aminotransferase. HCV-RNA: hepatitis C virus-ribonucleic acid. M: male. F: female. SN: simple nodular type. SNIM: simple nodular type with indistinct margin. CH: chronic hepatitis. LC: liver cirrhosis. ND: not done. SVR: sustained viral response. BR: biochemical remission. NR: no response.

positive. Postoperative follow-up term was 9-17 years. Postoperative IFN therapy was performed in 20 of these patients (16 men, 4 women; age range, 49-65 years; mean age, 59.55 ± 4.10 years) after obtaining informed consent. The greatest tumor dimension of the resected HCC ranged from 10 to 45 mm (mean 2.38 ± 1.02 cm). There were 14 cases of solitary and 6 cases of multiple HCC. With regard to gross type of the resected tumor, 5 cases were of the simple nodular type with indistinct margins and 15 cases were of the simple nodular type. The degree of differentiation was well differentiated in 4 and moderately differentiated in 16 cases. The non-cancerous liver parenchyma was cirrhotic in 10 and non-cirrhotic in 10 cases. Preoperative indocyanine green retention rate at 15 minutes (ICG R_{15}) ranged from 9 to 36% (mean 18.15 ± 8.71%) (Table 1).

2. Efficacy of postoperative IFN therapy

The efficacy of postoperative IFN therapy was evaluated on the basis of hepatitis C virus-ribonucleic acid (HCV-RNA) and alanine aminotransferase (ALT) in serum after 6 months. We defined the following three types; sustained viral response (SVR) with negative HCV-RNA and normal ALT in serum, biochemical remission (BR) with positive HCV-RNA and normal ALT in serum, and no response (NR) with positive HCV-RNA and abnormal ALT in serum. SVR was achieved in 6, BR in 4, and NR in 10 cases (Table 1). We used recombination IFN-alpha. The patients were readmitted after hepatectomy and given 10,000,000 units of IFN-alpha 2 b (Intron, Schering-Plough Co., NJ, USA) intramuscularly daily for 2 weeks, followed by three times weekly for 22 weeks at the outpatient department, or 6,000,000 units of IFN-alpha 2a (Canferon, Takeda Co., Osaka, Japan) intramuscularly daily for 2 weeks, followed by three times weekly for 22 weeks at the outpatient department. We started the postoperative IFN therapy from 3 months to 2 years after operation (mean 1.05 ± 0.62 years). Abdominal ultrasound (US) and abdominal computed tomography (CT) were performed before and during IFN therapy at 3-month intervals to check for HCC recurrence.

3. Examination items

We investigated the background factors and cu-

Table 2 Background factors of postoperative interferon therapy

Factor	IFN group (n=20)	non-IFN group (n=182)	p-value
Age (yrs)	59.55 ± 4.10	58.82 ± 5.21	0.5448
Gender (male : female)	16 : 4	145 : 37	0.9722
Resected tumor size (mean ± SD mm)	23.8 ± 10.2	23.9 ± 10.0	0.9292
Number of tumors			
single	14 (70%)	124 (68.1%)	
multiple	6 (30%)	58 (31.9%)	0.8647
Gross type			
simple nodular type with indistinct margin	5 (25%)	24 (13.2%)	
simple nodular type	15 (75%)	158 (86.8%)	0.1527
Degree of differentiation			
well	4 (20%)	56 (30.8%)	
moderately or poorly	16 (80%)	126 (69.2%)	0.2772
Non-cancerous liver parenchyma			
liver cirrhosis	10 (50%)	117 (64.3%)	
chronic hepatitis	10 (50%)	65 (35.7%)	0.2094
Preoperative ICG R_{15} (mean ± SD %)	18.15 ± 8.71	17.35 ± 9.15	0.7081

IFN: interferon therapy, ICG R_{15}: indocyanine green retention at 15 minutes, SD: standard deviation.

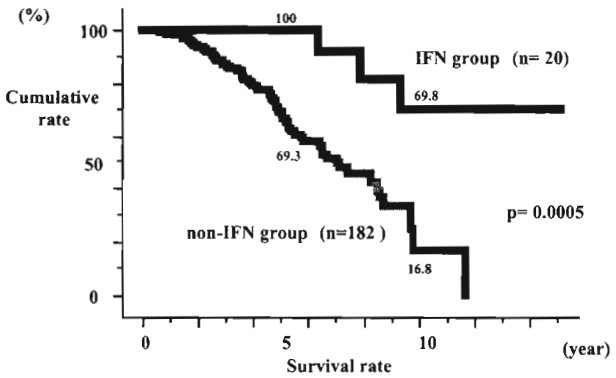

Fig. 1 Cumulative survival rate
The 5- and 10-year cumulative survival rates showed a statistically significant difference (p = 0.0005) between the groups, with 100 and 69.8% in the IFN group and 69.3 and 16.8% in the non-IFN group.

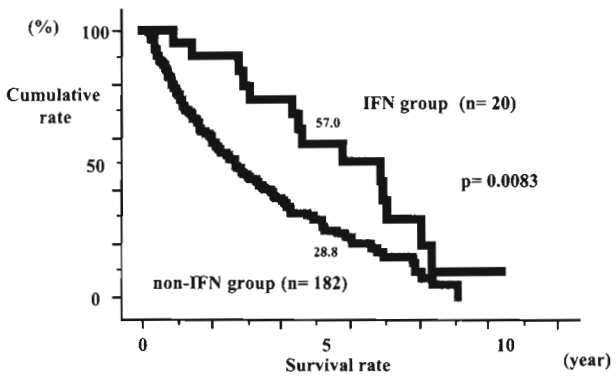

Fig. 2 Disease-free survival rate
There was a statistically significant difference (p = 0.0083) in 5-year disease-free survival rate between the groups, with 57.0 and 28.8% in the IFN group and non-IFN group.

mulative survival and disease-free survival rates in the IFN group and non-IFN group, and cumulative survival and disease-free survival rates by therapy effect in the IFN group. Additionally, we analyzed prognostic factors for survival and disease-free survival. Background factors were age, male: female ratio, resected tumor size, number of tumors, gross type of the resected tumor, degree of differentiation, presence of cirrhosis in non-cancerous parts of the liver, preoperative ICG-R_{15}.

4. Data analysis

Statistical analysis between two background groups was done by chi-square test. Survival was calculated with the Kaplan-Meier method and evaluated by log-rank test. Multivariate analysis was done using the Cox proportional hazard regression model. A p value less than 0.05 was considered to indicate a statistically significant difference. Values were expressed as means ± standard deviation.

Results

There were no significant differences in background factors, age, male: female ratio, resected tumor size, number of tumors, gross type of the resected tumor, degree of differentiation, presence of cirrhosis in non-cancerous parts of the liver, or preoperative ICG-R_{15} between the IFN group and the

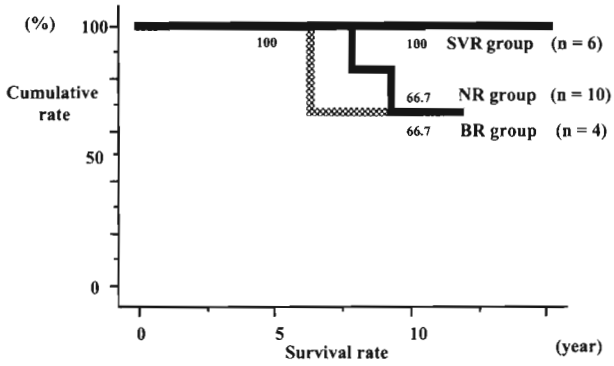

Fig. 3 Cumulative survival rate by therapy effect in the IFN group
The 10-year cumulative survival rate by therapy effect in the IFN group was 100, 66.7, and 66.7% in the SVR group, NR group, and BR group.

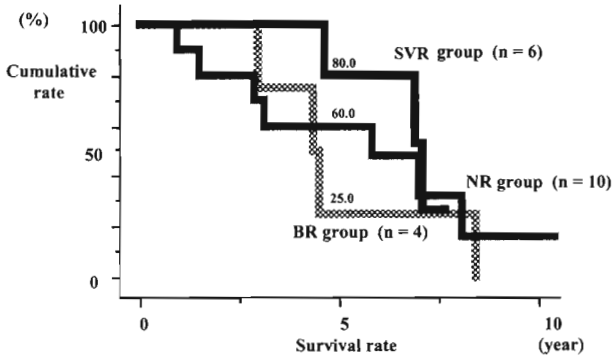

Fig. 4 Disease-free survival rate by therapy effect in the IFN group
The 5-year disease-free survival rate by therapy effect in the IFN group was 80.0, 60.0, and 25.0% in the SVR group, NR group, and BR group.

Table 3 Univariate analysis of survival rate

Variables	Category	Survival rates after hepatectomy		p-value
		3-year	5-year	
Age (yrs)	≧60 (n=107)	82.6	67.9	0.2147
	<60 (n=95)	95.3	78.3	
Gender	male (n=161)	89.6	75.6	0.2732
	female (n=41)	86.1	62.8	
Resected tumor size (mm)	≦20 (n=90)	91.3	79.7	0.0481
	>20 (n=112)	86.7	67.1	
Number of tumors	single (n=138)	89.2	77.3	0.1431
	multiple (n=64)	88.4	66.4	
Gross type	simple nodular type with indistinct margin (n=29)	88.5	79.6	0.1844
	simple nodular type (n=173)	89.0	71.8	
Degree of differentiation	well (n=60)	94.3	82.2	0.2104
	moderately or poorly (n=142)	86.6	69.1	
Non-cancerous liver parenchyma	liver cirrhosis (n=127)	87.7	70.1	0.2856
	non-liver cirrhosis (n=75)	91.2	79.4	
Preoperative ICG R_{15} (%)	≦20 (n=145)	89.2	77.3	0.0487
	>20 (n=57)	88.2	63.9	
Interferon therapy	IFN (n=20)	100	100	0.0005
	non-IFN (n=182)	87.4	69.3	

ICG R_{15}: indocyanine green retention at 15 minutes, IFN: interferon therapy.

non-IFN group (Table 2).

The 5- and 10-year cumulative survival rates showed a statistically significant difference ($p = 0.0005$) between the groups, with 100 and 69.8% in the IFN group and 69.3 and 16.8% in the non-IFN group, respectively (Fig. 1).

There was a statistically significant difference ($p=0.0083$) in 5-year disease-free survival rate between the groups, with 57.0 and 28.8% in the IFN group and non-IFN group, respectively (Fig. 2).

The 10-year cumulative survival rate by therapy effect in the IFN group was 100, 66.7, and 66.7% in the SVR group, NR group, and BR group, respectively (Fig. 3). The 5-year disease-free survival rate by therapy effect in the IFN group was 80.0, 60.0, and 25.0% in the SVR group, NR group, and BR group, respectively (Fig. 4).

In univariate analysis of survival rate, patients with tumors 20 mm or less in greatest dimension, low preoperative ICG-R_{15} levels and those treated with IFN therapy showed improved survival rates (Table 3). In multivariate analysis of survival rate, low preoperative ICG-R_{15} levels and IFN therapy were revealed to be independent factors associated

Table 4 Multivariate analysis of survival rate

Variables	Wald χ^2	p-value	Hazard ratio
Preoperative ICG R_{15} (%)			
≦20 (n=145)	12.353	0.0004	0.366
>20 (n=57)			
Interferon therapy			
IFN (n=20)	12.746	0.0004	10.415
non-IFN (n=182)			

ICG R_{15}: indocyanine green retention at 15 minutes, IFN: interferon therapy.

Table 5 Univariate analysis of disease-free survival rate

Variables	Category	Survival rates after hepatectomy		p-value
		3-year	5-year	
Age (yrs)	≧60 (n=107)	48.3	23.9	0.4419
	<60 (n=95)	51.3	39.3	
Gender	male (n=161)	50.1	33.7	0.1635
	female (n=41)	49.2	26.4	
Resected tumor size (mm)	≦20 (n=90)	67.3	51.4	<0.0001
	>20 (n=112)	35.0	15.6	
Number of tumors	single (n=138)	55.2	40.4	0.0062
	multiple (n=64)	39.8	17.0	
Gross type	simple nodular type with indistinct margin (n=29)	69.4	47.3	0.2117
	simple nodular type (n=173)	46.3	29.5	
Degree of differentiation	well (n=60)	59.8	45.6	0.0400
	moderately or poorly (n=142)	45.5	26.7	
Non-cancerous liver parenchyma	liver cirrhosis (n=127)	47.5	29.0	0.0551
	non-liver cirrhosis (n=75)	54.1	38.8	
Preoperative ICG R_{15} (%)	≦20 (n=145)	50.1	32.5	0.4354
	>20 (n=57)	49.2	32.1	
Interferon therapy	IFN (n=20)	79.4	57.0	0.0083
	non-IFN (n=182)	45.9	28.8	

ICG R_{15}: indocyanine green retention at 15 minutes, IFN: interferon therapy.

with improved survival rate (Table 4).

In univariate analysis of disease-free survival rate, patients with tumors 20 mm or less in greatest dimension, those with single tumors, those with well differentiated HCC, and those treated with IFN therapy showed improved disease-free survival rates (Table 5). In multivariate analysis of disease-free survival rate, tumors 20 mm or less in greatest dimension, single tumors, low preoperative ICG-R_{15} levels and IFN therapy were revealed to be independent factors associated with improved disease-free survival rate (Table 6).

Discussion

IFN therapy for hepatitis C virus antibody positive patients has previously been reported to be effective in inhibiting oncogenesis and improving liver function[4]. Inhibition of the development of HCC has been reported in groups in which transaminase normalized or HCV-RNA became negative after IFN therapy[5)6)]. Ikeda et al. have reported that IFN after hepatectomy or percutaneous ethanol injection therapy for hepatitis C virus-related HCC prevented recurrence[7]. Kubo et al. conducted a randomized controlled trial of postoperative IFN therapy for hepatitis C virus-related HCC and reported a significant reduction in recurrence rate in the IFN group[8]. Lower postoperative recurrence rates of hepatitis C virus-related HCC have been reported in patients who underwent preoperative IFN therapy[9].

On the other hand, there have also been numerous reports on the antitumor effect of IFN therapy.

Table 6 Multivariate analysis of disease-free survival rate

Variables	Wald χ^2	p-value	Hazard ratio
Resected tumor size (mm)			
≦20 (n=90)	14.404	0.0001	0.452
>20 (n=112)			
Number of tumors			
single (n=138)	4.562	0.0327	1.545
multiple (n=64)			
Preoperative ICG R_{15} (%)			
≦20 (n=145)	4.040	0.0444	0.645
>20 (n=57)			
Interferon therapy			
IFN (n=20)	8.771	0.0031	2.500
non-IFN (n=182)			

ICG R_{15}: indocyanine green retention at 15 minutes, IFN: interferon therapy.

Direct basic research includes reports on expression of cancer antigens[10], cell cycle delay[11], and cell damaging action[12], and indirect research includes NK cell activation[13], macrophage activation[14], and T-cell activation[15]. A recent study has reported high doses of IFN to control highly-metastatic human HCC dose-dependently through inhibition of angiogenesis[16]. Single administration of IFN-alpha has been reported to be effective in reducing the size of unresectable HCC in clinical cases[17]. There have also been reports indicating no antitumor effect by single administration alone[18].

Some studies report a high antitumor effect when IFN-alpha was combined with 5-fluorouracil (5-FU), such as elevated intracellular concentrations of 5-FU intermediary metabolites by IFN-alpha[19] and increased tumor cell apoptosis[20]. The treatment has also been reported to be effective in clinical HCC cases with low AFP levels[21]. In addition, several studies have reported efficacy by combination chemotherapy with IFN, 5-FU and other anticancer agents. In far-advanced HCC with tumor emboli in the main portal trunk and distant metastasis, improved outcomes have been reported with combined therapy with cisplatin[22], cisplatin and methotrexate[23], and cisplatin and doxorubicin[24]. Recently, Sakon et al. have reported that combined intraarterial 5-fluouracil and subcutaneous IFN-alpha therapy for advanced HCC with tumor thrombi in the major portal branches has a highly important antitumor effect[25]. These reports suggest that, in addition to preventing multicentric carcinogenesis, IFN therapy is useful for its antitumor effect on HCC itself.

Our present study was consistent with these reports, showing a significantly better 10-year cumulative survival rate in the IFN group (69.8%) than in the non-IFN group (16.8%). With regard to disease-free survival rate, although cases of recurrence were seen in the IFN group, there was a significant difference in 5-year disease-free survival rates, with 57.0 and 28.8% in the IFN group and non-IFN group, respectively. In addition, postoperative IFN therapy was revealed to be an independent factor for improvement of both survival and disease-free survival rates. Interestingly, however, by the 10th postoperative year disease-free survival showed nearly identical curves and rates, a result which differed from our original objective of preventing multicentric carcinogenesis by eliminating the hepatitis C virus. This strongly suggests that postoperative IFN therapy for hepatitis C virus-related HCC is not only effective in controlling multicentric carcinogenesis by eliminating the hepatitis C virus as an antiviral agent as described above[4-9], but also has an antitumor effect of delaying postoperative recurrence of occult carcinoma.

However, with regard to the cumulative survival rate by long-term therapy effect in the IFN group, the 10-year survival rate was 100% in the SVR group, showing good results in the SVR group. With regard to the disease-free survival rate by therapy

effect in the IFN group, the 5-year disease-free survival rate was 80.0% in the SVR group. This suggests that, if the hepatitis C virus can be completely eliminated, multicentric carcinogenesis can be effectively controlled.

In conclusion, these results indicate that postoperative IFN therapy for hepatitis C virus-related HCC can significantly improve survival and disease-free survival rates, strongly suggesting the possibility that it has the dual effect of delaying postoperative recurrence of HCC and controlling multicentric carcinogenesis.

Even if curative resection of HCC is achieved, recurrence in the remnant liver is common. Future research should focus on how to control multicentric carcinogenesis and recurrence. Postoperative IFN therapy for hepatitis C virus-related HCC was found to be an effective adjuvant therapy that significantly improved survival and disease-free survival rates, although further study with a greater number of patients is necessary.

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C型肝炎ウイルス陽性肝細胞癌に対する術後インターフェロン療法の長期予後について

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C型肝炎ウイルス陽性肝細胞癌に対する術後インターフェロン（IFN）療法の長期予後について検討した．1990～1999年の間に，手術時年齢65歳以下，腫瘍最大径50 mm以下，切除標本肉眼型が単純結節型または境界不明瞭型，病理組織上の門脈肝静脈浸潤と肝内転移を認めない，治癒切除，と以上の項目を満たした202例を対象とした．その中で術後IFN療法を行った20例とコントロール群の182例において，両群間の背景，術後累積生存率，無再発生存率について検討した．背景では，年齢，性別，切除腫瘍径，腫瘍個数，切除標本肉眼型，病理組織学的分化度，非癌肝組織，術前ICGR15分値では両群間に有意差はなかった．術後累積生存率では，5年/10年がIFN群で100/69.8%，non-IFN群で69.3/16.8%であり，有意差をもってIFN群が良好であった．無再発生存率でも5年でIFN群が57.0%，non-IFN群が28.8%で両群間に有意差を認めた．多変量解析においては術後生存，無再発生存ともに術後IFN療法施行の有無が予後因子として抽出された．しかしながら，術後10年までに無再発生存率はIFN，non-IFN群ともほぼ同等の結果となった．C型肝炎ウイルス陽性肝細胞癌に対する術後IFN療法は肝細胞癌術後のoccult carcinomaの顕正化を遅延させる抗腫瘍効果と，ウイルス排除からの多中心性発癌再発抑制効果の2面性を兼ね備えている可能性がある．しかしながら，長期予後において術後IFN療法は肝細胞癌の残肝再発を完全に抑制することはできなかった．