Criteria Grid
Best Practices and Interventions for the Prevention and Awareness of Hepatitis C

Best Practice/Intervention:	Miyake Y. et al. (2010) Meta-analysis: interferon-alpha prevents the recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma. *Journal of Viral Hepatitis*, 17(4):287-292.
Date of Review:	June 15, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other: Hepatocellular carcinoma** **Level:** **Group** ☒ **Individual** ☐ **Other:** **Target Population: HCV infected patients received curative therapy for hepatocellular carcinoma** **Setting: Health care setting/Clinic** ☒ **Home** ☐ **Other:** **Country of Origin: Japan** **Language:** **English** ☒ **French** ☐ **Other:**

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research? ***Please go to Comments section****.*	☒	☐	☐	Meta-analysis; to identify if interferon-alpha treatment prevents the recurrence of hepatocellular carcinoma in patients chronically infected with hepatitis C virus
The best practice/intervention shows evidence of "scale up" ability	☐	☐	☒	
The best practice/intervention shows evidence of transferability	☐	☐	☒	
The best practice/intervention shows evidence of adaptation	☐	☐	☒	

Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	
	YES	**NO**	**N/A**	**COMMENTS**
Are the best practices/methodology/results described applicable in developed countries?	☐	☐	☒	All studies included in meta-analysis were originated in Japan.
Are the best practices/methodology/results described applicable in developing countries?	☐	☐	☒	
The best practice/intervention has utilized a program evaluation process	☐	☒	☐	
Consultation and feedback with community has taken place	☐	☒	☐	
The best practice/intervention is sensitive to gender issues	☐	☐	☒	No specific study included in analysis was specified to be sensitive to gender issues.
The best practice/intervention is sensitive to multicultural and marginalized populations	☐	☐	☒	
The best practice/intervention is easily accessed/available electronically	☐	☒	☐	Purchase required for full access from http://onlinelibrary.wiley.com/
Is there evidence of a cost effective analysis? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
How is the best practice/intervention funded? ***Please go to Comments section***	☐	☒	☐	The article was no funded.
Is the best practice/intervention dependent on external funds?	☐	☒	☐	
Other relevant criteria: _____	☐	☐	☐	- IFN-alpha treatment after curative treatment of HCC may be effective in preventing HCC recurrence

				- Higher SVR rate in population treated with IFN-alpha are associated with better preventive effect of IFN-alpha treatment on HCC recurrence

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Meta-analysis: interferon-alpha prevents the recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma

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SUMMARY. Various clinical studies have indicated that interferon (IFN)-alpha treatment prevents the development of hepatocellular carcinoma (HCC) in people chronically infected with hepatitis C virus. However, it has been controversial whether IFN-alpha treatment prevents HCC recurrence. The aim of this study was to identify the preventive effect of IFN-alpha treatment after curative therapy of primary tumours within the Milan criteria (three or fewer nodules 3 cm or less in diameter or a single nodule of 5 cm or less) on HCC recurrence. We conducted a meta-analysis of five trials including 355 patients (167 patients received IFN-alpha treatment after curative therapy of primary tumours) and estimated relative risks (RRs) and 95% confidence intervals (CIs) for the effect of IFN-alpha on HCC recurrence according to the DerSimonian and Laird method. IFN-alpha treatment after curative therapy of primary tumours significantly prevented HCC recurrence (RR 0.33; 95%CI 0.19–0.58, $P < 0.0001$) without a significant heterogeneity ($Q = 4.52$, $P = 0.34$). An evaluation using the Begg method suggested no evidence of publication bias. Sub-group analyses revealed that IFN-alpha treatment reduced HCC recurrence in two studies achieving sustained virologic response (SVR) rates >30% (RR 0.20; 95%CI 0.05–0.81, $P = 0.02$) and in three studies achieving SVR rates ≤30% (RR 0.44; 95%CI 0.23–0.84, $P = 0.01$). In conclusion, IFN-alpha treatment after curative treatment of primary tumour within Milan criteria may be effective for the prevention of HCC recurrence, and higher SVR rate may be associated with better preventive effect of IFN-alpha treatment on HCC recurrence.

Keywords: hepatitis C, hepatocellular carcinoma, interferon, Milan criteria, prevention, recurrence.

INTRODUCTION

Worldwide, liver cancer is the sixth most common cancer (626 000 cases or 5.7% of new cancer cases in 2002) and the number of deaths is almost the same (598 000) because of the very poor prognosis [1]. Hepatocellular carcinoma (HCC) accounts for between 85% and 90% of primary liver cancer [2]. Hepatitis B virus and hepatitis C virus (HCV) infections are estimated to be causally associated with over 80% of HCC in the world [3].

Abbreviations: CIs, confidence intervals; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; NRCT, non-randomized controlled trials; RCTs, randomized controlled trials; RRs, relative risks; SVR, sustained virologic response.

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About 170 million people (3% of the world's population) are chronically infected with HCV and 3–4 million are newly infected each year in the world [3]. Up to about 20% of chronically infected people develop liver cirrhosis over a 20–25-year period, and about 3–4% of peoples with liver cirrhosis develop HCC per year [3].

To date, various clinical studies have indicated that interferon (IFN)-alpha treatment prevents the development of HCC in people chronically infected with HCV [4–7]. On the contrary, estimation of preventive effect of IFN-alpha treatment after curative treatment of primary tumours on HCC recurrence has yet to be fully implemented.

The recurrence rate at 5 years after resection of primary tumours is reported 80% in HCV-related HCC [8,9]. HCC recurrence is considered because of metastases from primary tumour or multi-centric carcinogenesis. Recently, patients who met the Milan criteria (three or fewer nodules 3 cm or less in diameter or a single nodule of 5 cm or less) [10] were

reported to show lower recurrent rate after resection of primary tumours than others [11]. In patients who did not meet the Milan criteria, tumour-related factors (tumour size, tumour number, microscopic vascular invasion) were mainly associated with the recurrence. However, in patients who met the Milan criteria, not only tumour-related factors but also liver function factors (albumin, bilirubin, histological cirrhosis) did. It is expected that IFN-alpha treatment improves liver function in patients with chronic hepatitis C [12]. Thus, IFN-alpha treatment may reduce recurrent rate of HCC in patients who met the Milan criteria. In this study, we performed a meta-analysis on the basis of published data in order to identify the preventive effect of IFN-alpha treatment after the curative therapy of primary HCC within Milan criteria on the recurrence of HCC.

METHODS

Endpoint

The primary endpoint was to identify the effect of IFN-alpha administration after curative treatment of primary tumours within Milan criteria on HCC recurrence by performing a meta-analysis of randomized controlled trials (RCTs) and non-randomized controlled trials (NRCT).

Literature search

We searched PubMed for the medical literature published by using the following keywords: *interferon*, *hepatocellular carcinoma*, *hepatitis C*, *recurrence*. We limited our search to original, English-language articles published between May, 1991 and January, 2009. Studies were included if they met all of the following criteria: (1) clinical trial comparing patients treated with IFN-alpha (total dose ≥216 MU) and untreated patients after curative treatment (resection, percutaneous ablation) of primary HCC within Milan criteria (three or fewer nodules 3 cm or less in diameter or a single nodule of 5 cm or less), (2) providing sufficient information of IFN-alpha treatment schedule, follow-up and outcomes, (3) assessing HCC recurrence as an outcome measure of IFN-alpha treatment's effect. Articles published in language other than English, or trials including patients whose primary HCC was treated with palliative treatment (transarterial chemoembolization, systemic chemotherapy, radiation) were excluded from this analysis.

Data collection

Two investigators (Y. Miyake, Y. Iwasaki) trained in hepatology independently reviewed the included studies by using a standardized protocol and data collection form. Discrepancies among reviewers were solved with discussion. We collected data on patient characteristics, treatment of primary HCC, IFN-alpha treatment and outcomes.

Statistical analysis

Crude rates of HCC recurrence after curative treatment of primary tumours were assessed as the measures of IFN-alpha's potential effect. We calculated pooled relative risks (RR) and 95% confidence intervals (CIs) for HCC recurrence according to the DerSimonian and Laird method [13]. The quantitative heterogeneity was evaluated by a chi-square test-based Q statistic, and trials with a P-value less than 0.1 were defined as heterogeneous. In addition, the Begg method was performed to test a potential publication bias [14].

We performed subgroup analysis to explore the effect of potential sources of variability on observed treatment effects. We investigated the impacts of the following plausible effect modifier on treatment outcomes: rates of sustained virologic response (SVR) in population treated with IFN-alpha after curative treatment of primary tumours (≤30% *vs* >30%). SVR was defined as the sustained absence of serum HCV RNA for more than 24 weeks after completion of IFN-alpha treatment.

RESULTS

Features of five studies

Literature searches of PubMed using the four keywords yielded 104 studies published between May, 1991 and January, 2009. Of the 104 studies, 94 did not fulfil the inclusion criteria (21 in language other than English, 29 review articles, 3 case-reports, total dose of IFN-alpha <216 MU in one study, primary HCC treated with palliative treatment in one study, primary HCC over Milan criteria in three studies, 36 concerning something other than preventive effect of IFN-alpha on HCC recurrence). Ten studies [15–24] fulfilled the inclusion criteria. However, of the 10 studies, 4 were reported by Kubo and colleagues [17,20–22], 2 were reported by Kudo and colleague [18,23] and 2 were reported by Jeong *et al.* [19,24]. So, one study each [17–19] was selected from these researchers. Thus, five studies [15–19] were selected finally. The main features of the five studies are shown in Table 1. All studies were performed in Japan and reported as full papers. Two studies [16,17] were RCT, and the remaining three [15,18,19] were NRCT. The sample size of each study varied, ranging from 30 to 127 patients. A total of 355 patients participated in these five studies, among which 273 (77%) were males. Primary HCC was treated with resection in one study [17] and with percutaneous ablation in two studies [16,18]. In the remaining two studies, primary HCC was treated with either resection or percutaneous ablation [15,19]. After curative treatment of primary HCC, 167 patients received IFN-alpha treatment

Table 1 Five clinical trials assessing the effect of IFN-alpha on HCC recurrence

Study (reference)	Year	Study design	Sample size (*n*)	Male (%)	Age (years)
Suou [15]	2001	NRCT	T 18	83	61
			C 22	82	62
Shiratori [16]	2003	RCT	T 49	71	61
			C 25	68	63
Kubo [17]	2005	RCT	T 15	100	62
			C 15	100	60
Kudo [18]	2007	NRCT	T 43	77	65
			C 84	71	66
Jeong [19]	2007	NRCT	T 42	86	62
			C 42	69	63

Primary HCC size (cm)	Solitary HCC (%)	Treatment for primary HCC, resection/ablation (*n*/*n*)	Basal cirrhosis (%)
T 2.0	T 100	11/7	T NR
C 2.1	C 100	14/8	C NR
T 2.2	T 65	0/49	T 100
C 2.3	C 64	0/25	C 100
T 2.5	T 100	15/0	T 47
C 2.6	C 100	15/0	C 53
T 1.8	T 95	0/43	T NR
C 1.5	C 92	0/84	C NR
T 2.0	T 71	24/18	T 17
C 1.5	C 86	22/20	C 17

IFN regimens	IFN duration	SVR (%)	Follow-up (years)	HCC recurrence (%)
α or α-2b; 6 MU daily for 2 weeks and thrice a week for 22 weeks	24 weeks	33	T 4.0 C 4.1	T 28 C 82
α; 6 MU thrice a week	48 weeks	29	T 5.0 C 5.0	T 80 C 92
α; 6 MU daily for 2 weeks, thrice a week for 14 weeks and twice a week for 88 weeks	104 weeks	13	T 5.0 C 4.1	T 60 C 87
α-2b; 3 MU twice a week or pegylated IFN-α-2a; 90 μg once 1–2 weeks	Median 4.7 (1.0–7.1) years	5	T 5.1 C 4.9	T 56 C 71
α; 6 MU daily for 2 weeks and thrice a week for 22 weeks	24 weeks	69	T 2.7 C 2.6	T 48 C 71

IFN, interferon; HCC, hepatocellular carcinoma; RCT, randomized controlled trial; NRCT, non-randomized controlled trial; wk, week; yr, year; SVR, sustained virological response; T, treated; C, controls; NR, not reported; MU, million unit.

as adjuvant therapy. In one study [18], pegylated IFN-alpha-2a of 90 μg or IFN-alpha-2b of 3 MU was administered. In the remaining four studies [15–17,19], IFN-alpha or IFN-alpha-2b of 3–6 MU was administered. The duration of IFN-alpha treatment ranged from 24 weeks to 4.7 years. SVR rate in patients treated with IFN-alpha ranged from 5% to 69%. HCC recurrence rate in control group of each study ranged from 71% to 92%.

IFN-alpha as adjuvant therapy

The effect of IFN-alpha on the HCC recurrence is shown in Fig. 1. IFN-alpha seemingly decreased the recurrent rate of HCC in three studies [16–18], and a statistically significant decrease was observed in two studies [15,19]. The pooled estimate of the preventive effect on HCC recurrence was significantly in favour of IFN-alpha administration after the

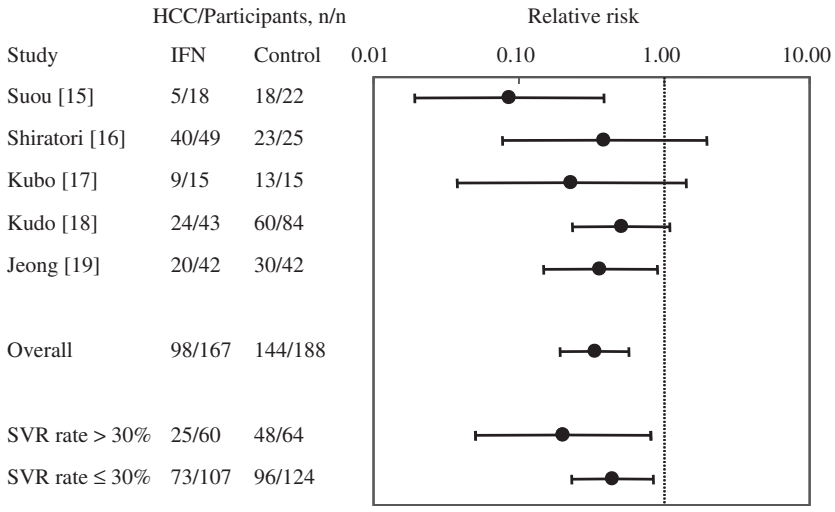

Fig. 1 Meta-analysis of the five IFN-alpha studies for the prevention of hepatocellular carcinoma recurrence. Relative risk and 95% confidence intervals for each study are plotted on the graph.

curative treatment of primary HCC within Milan criteria (RR 0.33; 95%CI 0.19–0.58, $P < 0.0001$) without a significant heterogeneity ($Q = 4.52$, $P = 0.34$). An evaluation using the Begg method suggested no evidence of publication bias statistically ($z = -0.98$, $P = 0.33$).

SVR rate and HCC recurrence

The pooled estimate from two studies [15,19] showed that IFN-alpha treatment reduced HCC recurrence in population achieving SVR rate greater than 30% (RR 0.20; 95%CI 0.05–0.81, $P = 0.02$) without a significant heterogeneity ($Q = 2.64$, $P = 0.10$). On the contrary, IFN-alpha treatment also prevented HCC recurrence in population achieving SVR rate of 30% or less (RR 0.44; 95%CI 0.23–0.84, $P = 0.01$) without a significant heterogeneity ($Q = 0.64$, $P = 0.73$) [16–18].

DISCUSSION

In order to prevent HCC recurrence after curative treatment of early HCC, suppression of multi-centric carcinogenesis is considered important. In general, more than 70% of HCV-related HCC develop in cirrhotic or pre-cirrhotic liver [25,26]. Annual incidence of HCC in HCV-related cirrhotic or pre-cirrhotic liver is reported as 4–8%, and IFN-alpha treatment is estimated to reduce approximately 50% of annual incidence of HCC in chronic hepatitis C with cirrhotic or pre-cirrhotic liver, if SVR rate of approximately 30% is achieved [7]. Preventive effect of IFN-alpha on HCC development is considered because of anti-necroinflammatory effect and suppression of viral replication. Furthermore, SVR leads to the regression of histological fibrosis, even in cirrhotic liver [27]. In this study, IFN-alpha treatment after curative treatment of primary tumour within Milan criteria showed preventive effect on HCC recurrence. In the prevention of HCC recurrence, the anti-necroinflammatory effect and suppression of viral replication by IFN-alpha is considered effective.

In this study, two NRCT [15,19] showed the significant reductions of HCC recurrence by IFN-alpha treatment after curative treatment of primary tumour within Milan criteria and might strongly influence the result of this meta-analysis. Thus, the meta-analysis on the other three trials has been performed [16–18], and the pooled estimate of the preventive effect on HCC recurrence was significantly in favour of IFN-alpha administration after the curative treatment of primary HCC within Milan criteria (RR 0.44; 95%CI 0.23–0.84, $P = 0.01$) without a significant heterogeneity ($Q = 0.64$, $P = 0.73$). An evaluation using the Begg method suggested no evidence of publication bias statistically ($z = -1.57$, $P = 0.12$).

A previous large-cohort study [7] revealed that not only SVR but also sustained biochemical response (sustained normal alanine aminotransferase levels for more than 24 weeks after completion of IFN-alpha treatment) and response with mildly elevated alanine aminotransferase levels less than two times the upper limit of normal for more than 24 weeks after completion of IFN-alpha treatment led to prevention of HCC development. In this study, preventive effect of IFN-alpha treatment on HCC recurrence was accepted not only in two studies achieving SVR rates >30% but also in three studies achieving SVR rates ≤30% although higher SVR rate might be associated with the better preventive effect. Reduced transaminase levels after curative treatment of primary tumour may be effective for the prevention of HCC recurrence.

In chronic hepatitis C, response to IFN-alpha treatment is associated with incidence of HCC, and achieving SVR reduces incidence of HCC largely [6,7]. In order to effectively reduce incidence of HCC, higher SVR rate is necessary. SVR rate is associated with genotype and serum HCV RNA levels. In 1990s, IFN-alpha monotherapy for 48 weeks resulted in SVR rate of lower than 10% in patients with both genotype 1

and high HCV RNA loads [28,29]. Recently, combination treatment of pegylated-IFN-alpha and ribavirin for 48 weeks presents SVR rate of 40–50% in patients with both genotype 1 and high HCV RNA loads [30]. Approval of this combination treatment is expected to improve incidence of HCC. On the contrary, preventive effect of this combination treatment on HCC recurrence has not reported as yet. Henceforth, preventive effect of this combination treatment on HCC recurrence would be investigated.

In this study, preventive effect of IFN-alpha treatment after curative treatment of primary tumours over Milan criteria on HCC recurrence was not investigated. In order to prevent HCC recurrence after curative treatment of primary tumours over Milan criteria, anticancer therapy for undetectable residual tumours during primary treatment is considered more important. Experimentally, IFN-alpha has been reported to express anticancer effect in a dose-dependent manner by induction of apoptosis and blockage of cell cycle at the S phase in human HCC cell lines [31]. Clinically, one RCT shows partial response rate of 7% by IFN-alpha monotherapy in HCV-related inoperable HCC [32]. IFN-alpha treatment may have some degree of preventive effect on HCC recurrence after curative treatment of primary tumour over Milan criteria; however this effect has been controversial. Further studies are required.

Interferon-beta has been used also for the treatment of chronic hepatitis C and reported to be effective especially for patients with low HCV RNA loads [33,34]. A previous RCT [35] showed that IFN-beta treatment after curative treatment of primary tumour prevented HCC recurrence in patients chronically infected with HCV; however the sample size of the study was small. Further RCTs are required in order to confirm preventive effect of IFN-beta after curative treatment of primary tumour on HCC recurrence.

This meta-analysis suggests that IFN-alpha treatment after curative treatment of primary tumour within Milan criteria may be effective for the prevention of HCC recurrence and that higher SVR rate in population treated with IFN-alpha may be associated with better preventive effect of IFN-alpha treatment on HCC recurrence. Henceforth, preventive effect of combination treatment of pegylated-IFN-alpha and ribavirin, which presents higher SVR rate than IFN-alpha monotherapy, on HCC recurrence would be investigated.

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