Original Article
Effect of interferon therapy on outcomes after hepatic resection for hepatitis C virus-related hepatocellular carcinoma: a meta-analysis

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Received October 12, 2015; Accepted January 27, 2016; Epub February 15, 2016; Published February 29, 2016

Abstract: Aim: To investigate the efficacy and safety of Interferon (IFN) therapy for hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) after hepatic resection. Methods: A literature search of Pubmed, Embase and Cochrane Collaboration’s database, were searched to identify eligible studies until July 2015. Randomized controlled trials (RCTs) and non-randomized controlled trials (NRCTs) were collected, if they evaluated the outcomes of IFN therapy after resection for HCV-related HCC. Major outcomes include early recurrence, overall mortality and 1-, 2-, 3-, 5-survival rates. A meta-analysis was conducted using risk ratio (RRs) and 95% confidence interval (95% CIs) as the effect sizes. Results: Overall, 658 papers were initially retrieved, of which 6 RCTs or NRCTs were included. They included a total of 959 subjects. Compared to patients without IFN therapy, the recurrence rates of HCC-related HCV in patients with IFN therapy were not significantly different [RR=0.94; 95% CI=0.71 to 1.24, P=0.66]. The overall mortality were significantly lower in patients with IFN therapy than in those without IFN therapy [RR=0.64; 95% CI=0.51 to 0.80; P=0.0001]. The 1- and 2-year survival rates were statistically similar between patients with and without IFN therapy after resection for HCV-related HCC [three trials, RR=1.01, 95% CI=0.92 to 1.09, P=0.90; three trials, RR=0.97, 95% CI=0.86 to 1.10, P=0.65]. By contrast, the 3- and 5-year survival rates were significantly higher in patients with IFN therapy than in those without IFN therapy [six trials, RR=1.09, 95% CI=1.00 to 1.18, P=0.04; six trials, RR=1.37, 95% CI=1.24 to 1.51, P<0.00001]. Conclusion: Adjuvant IFN therapy may significantly reduce the mortality of patients with HCV-related HCC and improve the 3- and 5- survival rates (>2 years) of patients after resection treatment.

Keywords: Interferon, hepatic resection, hepatitis C virus, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver, which ranks the sixth among the malignant tumors in incidence [1]. The global incidence of HCC has continuously increased, with Asian countries accounting for almost 80% of victims worldwide [2, 3]. Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the leading causes of HCC.

Current strategies for treating HCC include liver transplantation, liver resection and local ablative therapy [4]. Among these, liver resection is a potentially curative treatment option for HCC patients with preserved liver function [5]. With the advances in surgical techniques and perioperative management, the short-term outcome of surgery has dramatically improved over the last decade. However, the long-term outcome remains guarded because of the frequent locoregional tumor recurrence and concomitant hepatic decompensation [6].

Interferons (IFNs) are common antiviral drugs which not only have the property of suppressing the replication of HCV, but also possessing a variety of biological properties, including antiviral, immunomodulatory, antiproliferative, and antiangiogenic effects [7, 8]. IFNs might prevent from the tumor recurrence and improve the survival of HCV-related HCC. However, several clinical trials on the influence of IFNs in the
management of HCC are still unclear. Additionally, a few meta-analyses have been conducted to evaluate the efficacy and safety of IFN therapy in patients with HCC. However, they were limited by selection bias of study population and treatment method and significant heterogeneity among studies [9-12].

The aim of our study was to confirm the potential effect of IFN therapy on HCV-related HCC after surgical resection by using currently available randomized controlled trials (RCTs) and non-randomized controlled trials (NRCTs).

Materials and methods

Selection of studies

A computerized literature search was conducted on the following databases up to June 19, 2015: Pubmed, Embase, Collaboration’s database. The free text used for search purposes was ‘hepatic resection OR liver resection OR surgery OR hepatectomy’ AND ‘interferon’ AND ‘hepatitis C virus OR HCV’ AND ‘hepatocellular carcinoma OR liver cancer’. The search was done without any restriction on language or publication year, and was conducted on human subject. All searched literatures were retrieved, and their references were checked as well for other relevant publications. Review papers were also searched to find additional eligible studies. For papers with overlapping data or on the same population, only the most recent or the ones with the largest group of subject data-set were included in this analysis. To identify potentially eligible articles, the title and abstract of each one identified by the literature search were assessed.

The following inclusion criteria were used for the paper selection: (1) the study design should be RCT or NRCT; (2) the participants should have primary HCC associated with HCV; (3) all eligible patients received IFN therapy after hepatic resection regardless of previous IFN treatment; (4) early recurrence rate, mortality and 1-, 2-, 3-, 5-survival rate and/or side effects were compared between patients with and without IFN therapy. Accordingly, the major reasons for exclusion were also used: (1) letters, reviews and duplicated literatures; (2) HBV-related HCC; (3) rather than surgery; (4) studies with no clear outcomes of recurrence, mortality and cumulative probability of survival.

Data extraction

From each of the eligible papers, the following data were extracted: publication data (first author, publication year, and country of population studied), design type, patients characteristics (patients number, mean age and sex ratio),
tumor characteristics (tumor number, tumor size), therapy protocols (IFN type, median follow-up time).

**Study quality assessment and level of evidence**

The methodological qualities of the included trials were assessed independently by two investigators (Liu YT and Zhang YJ) in accordance with the Cochrane Collaboration’s tool for assessing risk of bias [13].

**Statistical analysis**

Data were processed in accordance with the Cochrane Handbook. Intervention effects were expressed as risk ratios (RRs) with corresponding 95% confidence intervals (95% CIs). Z-test determined the significance of the pooled RRs and P<0.05 was considered as statistically significant. The random or fixed effects model was used for significantly heterogeneous or insignificantly heterogeneous data, respectively, as appropriate. Heterogeneity among studies was examined by chi-square test and P test (P>50% and/or P<0.1, significant heterogeneity; P<50% insignificant heterogeneity) [14]. Subgroup analyses were used to examine the influence of various sources of patients and different study types. All the statistical analyses were performed using Review Manager 5.3 software (Cochrane collaboration, Oxford, UK).

**Results**

**Search results and study characteristics**

A total of 658 papers were initially searched, among which, six articles were selected for the present meta-analysis after reading the abstracts and full texts. The detailed steps of the literature search are shown in Figure 1.

In total, three RCTs [15, 16, 19] and three NRCTs [17, 18, 20] were eligible for this study. Sample sizes ranged from 30 to 379. The longest follow-up time was 45.0 months and the shortest follow-up time was 84.0 months. The characteristics of all included studies were listed in Table 1.

**Risk of bias**

All studies reported baseline circumstances of cases and showed a good comparability. Risk of bias evaluation was mainly from the following categories: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. The judgments about each risk of bias items for each included study are shown in Figure 2.

**Recurrence rates for hepatocellular carcinoma**

Six studies including 959 cases [15-20] compared the IFN group and the control group with regard to the recurrence rates of HCV-related HCC. The results was P=0.002 (<0.1), P=73%, which indicated that there was a significant heterogeneity among studies. Therefore, we used a random-effect model. The results (RR=0.94; 95% CI=0.71 to 1.24, P=0.66) indicated that there was no difference between the IFN group after hepatic resection and the control group. The subgroup analysis suggested no significant associations in Japanese or in non-Japanese (Figure 3).
IFN therapy for HCV-related HCC

Overall mortality for hepatocellular carcinoma

Five studies including 910 patients [15-19] were performed in the comparison between IFN group and control group in the mortality of HCC. The results of heterogeneity was $P=0.10$, $I^2=48\%$ (<50%), which indicated there was no significant heterogeneity. So we conducted the present meta-analysis with a fixed-effect model. The results (RR=0.64; 95% CI=0.51 to 0.80; $P=0.0001$) suggested that IFN therapy might decrease the mortality of HCV-related HCC. The subgroup results with respect to ethnicity (RR=0.59; 95% CI=0.45 to 0.77; $P<0.0001$ for Japanese; and RR=0.80; 95%

Adverse effects of IFN

All included papers except one trial [17] reported data on adverse effects. The most common side effects of IFN therapy are high fever, depression, general fatigue and malaise, hepatotoxicity and hyperthyroidism, which occurred in almost every patient. Less common adverse effects include thrombocytopenia [16, 18-20], renal abscess [15], hyperthyroidism [16], hepatic encephalopathy [18] and skin eruption [20].

Sensitivity analysis

In order to compare the difference and confirm the stability and liability of the meta-analysis, we sequentially omitted individual eligible studies. Then, we reanalyzed the data of the remaining studies. The statistical significance of the results were not materially changed (data were not shown), indicating our results are comparatively stable and credible.

Discussion

The present meta-analysis evaluates the efficacy and safety of IFN therapy for HCV-related HCC who underwent surgical resection. The results indicate a significant benefit of IFN
treatment on overall mortality and 3-, 5-year survival rate. But the effect of IFN on recurrence and 1, 2-year survival rate between IFN group and control group are not significant. In order to exclude bias stratified by the source of patients, we performed subgroup analysis on recurrence rate and mortality. Patients were divided into two groups including Japanese and non-Japanese. On recurrence rate aspect, both in Japanese and non-Japanese, the subgroup analysis results are similar to the overall results. On mortality, there is significant difference in Japanese but insignificant correlation in non-Japanese.
The effects of IFN on HCC are affected by several factors, including antitumor, antiviral, anti-angiogenic and modulatory inflammatory factors or hepatic stellate cells in the tumor microenvironment [21]. IFN is currently the standard therapy for HCV-infection and has also been proven to inhibit HCC development in HCV patients through clearance of HCV RNA, improv-
IFN therapy for HCV-related HCC

...ing the degree of inflammation and preventing worsening of compensated cirrhosis [22]. Unquestionable, the recurrence of postoperative HCC has become the most important difficulty to improve the prognosis of patients [23, 24]. A meta-analysis of Singal AK et al. [25] found that patients underwent liver resection or ablation therapy for HCV-related HCC, the recurrence rate of sustaining virological responders who achieving IFN treatment was significantly lower than non-responders. Non-responders comparing to control groups without IFN treatment, the recurrence rate between the two groups was not statistically significant. In the report from China [26], there was no significant difference existing between IFN and control groups in a forest plot, which is consistent with our results. However, the meta-analyses conducting by Xu JB et al. [12] and Zhang W et al. [21] suggested a significant difference. Reportedly, the risk factors of tumor recurrence after surgical treatment include tumor location, tumor size, multi-nodular tumor and insufficient safety margin [27]. In contrast, Eastern Cooperative Oncology Group performance score, tumor size, microvascular invasion and tumor number were independent prognostic factors for overall survival [19]. Studies shown that, IFN therapy could reduce mortality in patients with HCC, and accordingly improving overall survival. Probably due to the following reasons: IFN helps relieve the inflammatory activity in the liver and improve liver function. Meanwhile, the improving of liver function provides a good condition for the following treatment of tumor recurrence. Though antiproliferative effect of IFN fails to prevent tumor recurrence, it suppresses tumor growth and reduce the severity of the tumor recurrence [28, 39].

Some limitations existing in this meta-analysis should be talked over. First of all, six trials included three NRCTs. In general, NRCTs are identified to result in incorrect associations because of the lack of reliability and precision. Second, the results failed to analyze the correlation between IFN therapy group and control group on early recurrence rate (≤2 years) and late recurrence rate (>2 years) of HCC proposed by Llovet et al [30]. Third, the treatment of most patients in this paper is surgery, but one study [19] did not list the curative treatments in detail and included ablation treatment, although making up a very small percentage of the total. Forth, the regimen of IFN therapy varied widely in the studies. The interval between previous therapies and IFN administration was not mentioned in most of the articles, which might be the potential factor that affects the efficacy. Lastly, four studies brought into Japanese populations, which might lead to bias. Further studies should include data from other ethnicities.

Acknowledgements

This study was funded by a grant from Science and Technology of Liaoning Province, China (No. 2013GS210102).

Disclosure of conflict of interest

None.

Authors’ contributions

Zhang Yanjun and Liu Yiting contributed equally to this work including designing and drafting the manuscript, performing the literature search and selection, data extraction, quality assessment and statistical analyses. Yu Xiaosong gave the critical comments.

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IFN therapy for HCV-related HCC


