

## Strategy for improving survival and reducing recurrence of HCV-related hepatocellular carcinoma

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Received: June 2, 2013 Revised: August 2, 2013

Accepted: August 8, 2013

Published online: October 7, 2013

### Abstract

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related death in the world. With advances in imaging diagnostics, accompanied by better understanding of high-risk patients, HCC is now frequently detected at an early stage; however, the prognosis remains poor. The recurrence rate after treatment of HCC is higher than that associated with cancers of other organs. This may be because of the high incidence of intrahepatic distant recurrence and multicentric recurrence, especially with hepatitis C virus (HCV)-related hepatocellular carcinoma. The Barcelona Clinic Liver Cancer (BCLC) classification has recently emerged as the standard classification system for the clinical management of patients with HCC. According to the BCLC staging system, curative therapies (resection, transplantation, transcatheter arterial chemoembolization, percutaneous ethanol injection therapy, percutaneous microwave coagulation therapy and percutaneous radiofrequency ablation) can improve survival in HCC patients diagnosed at an early stage and offer a potential long-term cure. However, treatment strategies for recurrent disease are not mentioned in the BCLC classification. The strategy for recurrence may differ according to the recurrence pattern, *i.e.*, intrahepatic distant recurrence *vs* multicentric

recurrence. In this article, we review recurrent HCC and the therapeutic strategies for reducing recurrent HCC, especially HCV-related HCC.

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**Key words:** Hepatocellular carcinoma; Intrahepatic distant recurrence; Multicentric recurrence; Hepatitis C virus; Interferon; Arterial chemotherapy

**Core tip:** Recent advances in treatment modalities have improved the survival rate of patients with hepatocellular carcinoma (HCC). However, long-term outcomes of patients with HCC remain unsatisfactory because of the high incidence of distant intrahepatic recurrence, multicentric recurrence and low survival rates. In particular, hepatitis C virus-related hepatocellular carcinoma has a much higher recurrence rate than other cancers. In this article, we describe the prognosis of recurrent HCC and the therapeutic strategies for reducing recurrent HCC.

Ishikawa T. Strategy for improving survival and reducing recurrence of HCV-related hepatocellular carcinoma. *World J Gastroenterol* 2013; 19(37): 6127-6130 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v19/i37/6127.htm> DOI: <http://dx.doi.org/10.3748/wjg.v19.i37.6127>

### INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer mortality in the world<sup>[1,2]</sup>. It is estimated that HCC is responsible for more than 600000 deaths annually worldwide<sup>[3]</sup>.

Recent advances in treatment modalities have improved the survival rate of patients with HCC<sup>[4,5]</sup>. However, long-term outcomes for patients with HCC remain unsatisfactory because of the high incidence of intrahepatic distant recurrence, multicentric recurrence and low

survival rates.

In many cases, surgical options for HCC are limited because of complicating hepatic cirrhosis; furthermore, HCC is associated with a 5-year recurrence rate of approximately 80% after radical treatment, which is much higher than that of other gastrointestinal carcinomas, resulting from its tendency to multicentric carcinogenesis secondary to chronic liver disease, or intrahepatic distant recurrence<sup>[6,7]</sup>.

Typically, recurrence rates in HCC follow a 2-peak distribution. Early recurrence usually occurs within 2 years after resection, and is most closely related to cancer metastasis, while late recurrence mainly results from *de novo* tumors as a consequence of the carcinogenic cirrhotic environment<sup>[7]</sup>. Therefore, a treatment strategy with a focus on recurrence is necessary.

In recent years, the Barcelona Clinic Liver Cancer (BCLC) classification has emerged as the standard classification system for the clinical management of patients with HCC<sup>[8]</sup>. However, in the recommendations regarding topical therapy for the treatment of early stage HCC, the BCLC guidelines do not mention a strategy for reducing recurrence. Togo *et al*<sup>[9]</sup> recommended a strategy based on the differentiation between recurrence types, *i.e.*, intrahepatic distant recurrences *vs* multicentric recurrence. Transcatheter arterial infusion (TAI) with platinum agents may be effective as adjuvant therapy for the prevention of residual liver recurrence after hepatectomy, probably by suppression of the development of intrahepatic micrometastasis, rather than multicentric carcinogenesis. Furthermore, antiviral treatment, including interferon (IFN), is recommended for preventing multicentric recurrence. We discuss a possible strategy for reducing the recurrence of hepatitis C virus (HCV)-related HCC in terms of our clinical data.

## PREVENTIVE TREATMENT STRATEGY PRIOR TO DEVELOPMENT OF RECURRENT MULTIPLE HEPATOCELLULAR CARCINOMA TO MAINTAIN RESIDUAL HEPATIC FUNCTION

IFN therapy may be useful in the prevention of recurrence of HCC secondary to chronic viral hepatitis after radical treatment by inhibiting multicentric carcinogenesis, while chemotherapy based on TAI is recommended to inhibit intrahepatic metastasis.

It is widely recognized that HCV infection is a major cause of liver cirrhosis and HCC in Japan and other countries. According to the Liver Cancer Study Group of Japan, 67.7% of Japanese patients with HCC are HCV antibody-positive<sup>[10]</sup>.

We evaluated the treatment response and functional hepatic reserve in patients who received combination

therapy with PEG-IFN  $\alpha$ -2b and ribavirin (RBV) after radical treatment of HCV-related HCC<sup>[11]</sup>.

This study comprised 54 patients with primary HCV-related HCC (stage I / II) whose survival rate, meta-chronous recurrence rate and hepatic functional reserve were assessed. Among these patients, 29 received combination therapy with PEG-IFN  $\alpha$ -2b and RBV after treatment of HCC (secondary IFN treatment group), and the other 25 did not receive IFN, including PEG-IFN  $\alpha$ -2b and RBV (non-secondary treatment group). The 1- and 3-year cumulative survival rates were 100.0% and 90.2% in the secondary IFN treatment group, and 96.0% and 61.2% in the non-secondary treatment group, respectively, showing a significant difference between the groups. Multivariate analysis identified secondary IFN treatment as a significant factor related to prognosis. In the PEG-IFN  $\alpha$ -2b/RBV group, serum albumin levels decreased transiently but increased thereafter, indicating improvement in hepatic functional reserve. These results show that combination therapy with IFN, including PEG-IFN  $\alpha$ -2b and RBV, following treatment of HCC, contributes to improvement in hepatic functional reserve and increases treatment options in the case of recurrence.

## TREATMENT STRATEGIES FOR INTRAHEPATIC METASTASIS

For intrahepatic metastasis, on the other hand, it is essential to select treatment not only for overt lesions, but also for micrometastasis. Hence, combination therapy, including intra-arterial treatment, such as transcatheter arterial chemoembolization (TACE), is required for initial treatment or treatment of recurrence.

### *Efficacy of platinum-containing drugs in transhepatic arterial infusion*

After treatment of HCC, the remaining liver is still in a state of precarcinogenesis. The protective effect of chemotherapy against recurrence in the remaining liver is demonstrated by its efficacy in patients with a high probability of intrahepatic metastasis, and thus, a high recurrence rate.

Although it is well-established that more effective chemotherapy, performed preoperatively in patients with intrahepatic micrometastasis or with the possibility of intraoperative tumor spread, may prevent tumor recurrence in the residual liver and further improve prognosis, few reports have described such cases. Systemic chemotherapy is generally not effective in most cases of HCC. Further, chemotherapy often impairs liver function in cases complicated by cirrhosis. At present, systemic chemotherapy with cytotoxic anticancer agents is only used infrequently in the treatment of HCC. Compared with systemic chemotherapy, hepatic arterial infusion (HAI) chemotherapy has the advantages of increasing the local concentration of chemotherapeutic agents to levels that are adequate to kill cancer cells without damaging healthy

liver tissue, and of reducing systemic side effects.

### Treatment strategy and problems with TACE

In Japan, TACE, which is recommended for inoperable patients in whom local puncture therapy is not indicated according to the guidelines for the management of liver cancer, plays a central role in the treatment of recurrent advanced multiple HCC<sup>[12,13]</sup>.

TACE is primarily performed as chemolipiodolization, using anticancer drugs mixed with lipiodol<sup>[14,15]</sup>. There have also been several retrospective reports of TACE with anthracyclines *vs* platinum compounds, suggesting the utility of platinum compounds<sup>[16,17]</sup>. However, no single effective drug has been identified, because no prospective comparative studies have been performed, and various anticancer drugs, including epirubicin, cisplatin, mitomycin C and doxorubicin, have been used with intercenter variance.

Kaibori *et al*<sup>[18]</sup> previously recommended that preoperative whole-liver chemolipiodolization reduces postoperative recurrence and prolongs survival in patients undergoing resection of hepatocellular carcinoma.

However, they subsequently performed a randomized controlled trial to evaluate the influence of preoperative TACE on survival after the resection of HCC, following which they concluded that preoperative selective TACE and whole-liver chemolipiodolization plus TACE do not reduce the incidence of postoperative recurrence or prolong survival in patients with resectable HCC<sup>[19]</sup>.

While intra-arterial chemotherapy is not highly appreciated in the West, HAI resulting in high local drug concentrations, is expected to improve the prognosis and prevent disease recurrence, because lesions are often localized to the liver even in advanced stages of HCC. However, various therapeutic regimens have been tried, without reaching a consensus regarding the administration method or dose level.

We previously reported that platinum agents, such as cisplatin, which are widely used for the treatment of a variety of malignancies, may be effective for HCC treatment.

In Japan, a fine powder formulation of cisplatin (cisplatin powder) (DDPH, IA call; Nippon Kayaku, Tokyo, Japan) was developed in 2004 and approved for the treatment of HCC *via* a transarterial approach, without lipiodol or embolic material. Cisplatin powder is readily soluble and more suitable for the preparation of high-concentration (about three times) aqueous solutions (1.4 mg/mL) than conventional cisplatin formulations (0.5 mg/mL). Therefore, a single session of TAI therapy with cisplatin powder has the benefit of increasing drug concentration locally in the HCC, and is expected to have a high therapeutic efficacy.

We evaluated the effectiveness of additional chemotherapy with the platinum-containing drugs carboplatin (CBDCA) and DDPH in preventing intrahepatic distant tumor recurrence<sup>[20]</sup>.

Seventy-eight patients with a diagnosis of primary stage I / II HCC who underwent TACE and RFA after

whole liver arterial infusion of CBDCA (25 patients) or DDPH (53 patients) for local control and recurrence prevention were followed up on a long-term basis. The clinical background factors, intrahepatic distant tumor recurrence rate, and intrahepatic distant tumor recurrence factors were compared between the CBDCA and DDPH groups. While no significant differences in background clinical characteristics were observed between the two groups, the intrahepatic distant tumor recurrence rate was significantly lower in the DDPH group<sup>[20]</sup>. In multivariate analysis using Cox's proportional hazard model, whole liver arterial infusion of DDPH was identified as an independent factor for the prevention of recurrence, *i.e.*, whole liver arterial infusion of DDPH significantly prevented intrahepatic distant tumor recurrence. Significant prevention of recurrence by a single infusion of DDPH compared with CBDCA suggests the utility of DDPH-based treatment strategies in patients with intrahepatic metastasis.

However, no evidence of its contribution to patient survival has been found, and TAI is not mentioned in any Western guidelines<sup>[21]</sup>. Nevertheless, it has been shown that some patients with TACE-refractory HCC were responsive to repeated TAI, with survival being prolonged in these responsive patients. According to the 18<sup>th</sup> nationwide follow-up survey of primary liver cancer, 85.8% of 1862 Japanese HCC patients treated with chemotherapy underwent TAI<sup>[10]</sup>. TAI is relatively often selected as the final choice for advanced HCC, including recurrent HCC; therefore, it is important to improve the response rate to TAI.

Thus, treatment strategies with DDPH-based TAI need to be established by conducting prospective randomized control trials<sup>[22,23]</sup>.

## CONCLUSION

Currently, the efficacy of tertiary prevention of HCC with any agent, including chemotherapy, HCV therapy, or IFN, has yet to be proven, and safe and effective chemotherapy for HCC-recurrence has yet to be established.

In this article, we reviewed our strategy for improving survival and reducing the recurrence of HCV-related HCC.

When deciding on treatment strategies for recurrence of HCV-related HCC, it is very important to select appropriate treatment according to the degree of disease progression, and to determine the patient's functional hepatic reserve. The type of recurrence and previous treatments also should be taken into consideration. It is also imperative to establish preventive strategies against precarcinogenesis associated with multicentric carcinogenesis and residual intrahepatic metastasis as early as possible, thereby improving prognosis.

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ISSN 1007-9327



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