Prevention of Recurrence After Resection of Hepatocellular Carcinoma: A Daunting Challenge

Hepatocellular carcinoma (HCC) is a common cancer worldwide. It is frequently associated with hepatitis B or C viral infection and underlying cirrhosis. Advances in ablation therapies and liver transplantation have improved the chance of curative treatment for early HCC associated with severe cirrhosis. However, surgical resection is still the mainstay of curative treatment, especially for patients who present with large tumors associated with early cirrhosis. Recent improvement in surgical techniques and perioperative care has significantly reduced operative mortality and, to some extent, has improved the long-term survival of HCC patients after resection.[1] Nonetheless, long-term prognosis after surgical resection of HCC remains unsatisfactory, compared with other common human cancers, because of a high recurrence rate and lack of effective adjuvant therapy. Most series in the literature reported a 5-year recurrence rate >70%, which is the main cause of long-term death, rather than the underlying cirrhosis.[2]

Over the past three decades, numerous studies have attempted to identify an effective strategy to prevent the recurrence of HCC. Adjuvant systemic chemotherapy is a common strategy to reduce tumor recurrence after resection of many solid organ cancers, but it has not been shown to be beneficial in HCC. The reasons for failure of systemic chemotherapy in HCC include chemoresistance of HCC cells[3] and poor tolerance of cytotoxic drugs in cirrhotic patients. Randomized, controlled trials on locoregional chemotherapy or chemoembolization as adjuvant or neoadjuvant therapy also failed to show a significant effect on the reduction of recurrence after resection of HCC.[4] Several approaches of adjuvant therapy, including transarterial radioactive iodine, adoptive immunotherapy, and use of retinoid after resection of HCC, have been reported to reduce recurrence rates in small-sample randomized trials conducted in the 1990s; however, their potential benefits have not been validated by subsequent trials.[5-7] A recent large-scale phase II/III randomized trial involving 401 patients on the use of retinoid after resection of HCC failed to demonstrate a significant effect on recurrence-free survival.[8] Evidence from meta-analyses of several recent randomized trials on interferon (IFN) showed that it may reduce recurrence after resection of hepatitis virus-related HCC.[9,10] However, the data were pooled from trials that were each with a small sample size; hence, the overall evidence is still weak. Furthermore, IFN is associated with significant toxicity and high discontinuation rates, as demonstrated in one trial conducted in my institution.[11]

Prevention of recurrence after resection of HCC is a difficult challenge, compared with other cancers, because of its tumor biology. First, the intrinsic chemoresistance of HCC cells makes it less sensitive to the usual chemotherapy strategy. Second, unlike other cancers, in which recurrence occurs primarily because of metastasis, there are two different mechanisms of recurrence in HCC. Apart from metastatic recurrence, there is a high risk of *de novo* carcinogenesis in patients with underlying cirrhosis or hepatitis viral infection. Most of the postresection recurrences occur in the liver remnant, making it impossible to differentiate the origin of recurrence clinically.[2] As the molecular mechanisms of early carcinogenesis and cancer metastasis are different, it is difficult to find an agent that can inhibit both intrahepatic metastasis and *de novo* carcinogenesis. My previous study has suggested that early recurrence within 1 year after resection is likely to be related to intrahepatic metastasis, whereas late recurrence is likely to be derived from *de novo* carcinogenesis.[12] In any trial on adjuvant therapy to reduce recurrence after resection of HCC, it is important to consider whether the agent aims to reduce metastatic recurrence or *de novo* recurrence in the trial design.

In the August issue of HEPATOLOGY, Yoshida et al.[13] reported a phase II/III randomized, placebo-controlled trial using yet another approach to inhibit recurrence after resection of HCC. In the trial, 548 patients were randomized to receive 90 mg/day of vitamin K2, 45 mg/day of vitamin K2, or placebo. The trial showed no difference in disease-free survival in the placebo group, compared with the combined treatment group,

Abbreviations: HCC, hepatocellular carcinoma; IFN, interferon.

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nor any dose-dependent increase in disease-free survival between the two vitamin K2 treatment groups. The hypothesis of this trial was based on preclinical studies that suggest vitamin K2 or its analogs could inhibit the growth of HCC via suppression of cyclin D1,[14,15] and a previous randomized trial that suggested vitamin K2 might prevent the development of HCC in female patients with underlying cirrhosis.[16] However, it has to be noted that the study in female cirrhosis patients was not initially designed to test the hypothesis that vitamin K2 could prevent the development of HCC, but rather it was an extension of the follow-up of a study to investigate the effect of vitamin K2 on bone loss in female cirrhotic patients. The sample size was only 40 patients in total in that study, and it was possible that the reduction in HCC incidence in the group treated by vitamin K2 was just a chance event. Two subsequent small-scale randomized trials with 45 patients and 60 patients, respectively, failed to demonstrate a significant effect of vitamin K2 on the recurrence of HCC after resection or ablation.[17,18] Hence, the negative result demonstrated by this larger scale phase II/III trial of Yoshida et al. is not surprising. However, it remains questionable whether the trial is convincing enough to reject any potential benefit of vitamin K2 in HCC, as suggested in preclinical studies. The trial had a large sample size, but it was flawed by two problems in its design. First, it included patients with intrahepatic recurrence treated by reresection, in addition to treatment-naïve patients. There may be a higher risk of metastatic recurrence in patients who have already developed recurrence after previous treatment, compared with patients with newly diagnosed HCC. If the role of vitamin K2 is mainly inhibition of *de novo* hepatocarcinogenesis in cirrhosis, as suggested by the previous study on female cirrhotic patients,[16] inclusion of patients with a high risk of metastatic recurrence made it more difficult to demonstrate the benefit of vitamin K2 on *de novo* recurrence. Second, the study was terminated prematurely approximately 1.5 years after the start of the study. The short median follow-up of patients also made it difficult to detect any benefit of vitamin K2 on *de novo* recurrence, which tends to occur at least 1-2 years after resection. Nonetheless, it is unlikely that there will a further large-scale randomized trial on the effect of vitamin K2 on recurrence of HCC after resection, given the negative result of this study.

The management of HCC has entered a new era of molecular targeted therapy after sorafenib has been demonstrated to improve the survival of advanced HCC patients in the SHARP trial.[19] A phase III placebo-controlled, randomized trial to evaluate sorafenib as adjuvant therapy after resection or ablation of HCC has completed recruitment with a sample size of 1,100 patients (STORM trial). The result of the trial will be available in the near future. An inhibitor of heparanase, which mediates the metastasis of HCC cells, has shown promising results in a phase II randomized trial and will be tested in a phase III trial to fully evaluate its effect on the recurrence after resection of HCC.[20] An effective agent for adjuvant therapy may be on the horizon, but it is unreasonable to expect that a single new agent could dramatically reduce the exceedingly high recurrence rate after resection of HCC. It is pertinent that further studies are conducted to evaluate the molecular mechanisms of metastatic and *de novo* recurrences of HCC to develop new molecular agents to inhibit recurrence. It is equally important that any new agents should be tested in properly designed trials with a solid hypothesis, adequate sample size, appropriate end-points, and long enough follow-up so that their efficacy can be truly evaluated.

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