Review

Adjuvant Therapy after Curative Resection for Hepatocellular Carcinoma Associated with Hepatitis Virus

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Key Words

Hepatocellular carcinoma • Hepatitis C virus • Hepatitis B virus • Interferon • Nucleos(t)ide analogues • Liver resection

Abstract

The outcome after curative resection for hepatocellular carcinoma (HCC) is still unsatisfactory because of the high rate of recurrence of HCC, including intrahepatic metastasis originating from the primary carcinoma and multicentric carcinogenesis after surgery. The rate of recurrence, particularly of multicentric carcinogenesis after surgery, is affected by persistent active hepatitis and hepatic fibrosis caused by chronic hepatitis B or C. In patients with hepatitis B virus (HBV)-related HCC, a high viral load is a strong risk factor for HCC recurrence. Nucleos(t)ide analogues improve the outcome after curative resection for HBV-related HCC. Interferon therapy improves the outcome after curative resection for hepatitis C virus (HCV)-related HCC by decreasing recurrence and preserving or improving liver function when treatment is successful. Low-dose intermittent interferon therapy has also been reported to be effective in suppressing HCC recurrence. New antiviral agents including protease or polymerase inhibitors are expected to be effective because these agents can eradicate HCV in most patients who receive such treatment.

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Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are etiological factors for hepatocellular carcinoma (HCC). Persistent active hepatitis and hepatic fibrosis play important roles in the development of HCC. The prognosis of HCC associated with hepatitis virus

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infection is still unsatisfactory because of the high rate of HCC recurrence after surgery [1–4] and progressive liver dysfunction that causes hepatic failure. Liver transplantation is the most radical treatment not only for HCC, but also for the underlying liver diseases such as chronic hepatitis B or C [5, 6]. However, the shortage of donors is one of the major problems associated with liver transplantation.

HCC recurrence includes metastasis from the primary carcinoma and multicentric carcinogenesis after treatment (multicentric recurrence). Multicentric carcinogenesis is closely related to persistent active hepatitis and hepatic fibrosis [2, 7, 8]. Thus, strategies for both HCC and chronic hepatitis caused by hepatitis viruses are required for the treatment of HCC associated with hepatitis virus infection. In this report, antiviral therapy after curative resection of HCC associated with HBV or HCV is reviewed.

Results of Liver Resection for HCC

Generally, risk factors for the recurrence of HCC after liver resection for HCC include tumor factors, such as tumor size, tumor number, tumor differentiation, and vascular invasion, and liver function factors, such as liver cirrhosis. Of these factors, tumor factors are considered to be related to intrahepatic and/or extrahepatic metastases, whereas liver function factors are considered to be related to multicentric carcinogenesis after surgery. Figure 1 shows tumor-free survival rates according to viral status after resection for HCC in patients at the Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Hospital [1]. The tumor-free survival rates in all groups decreased rapidly within 3 years after surgery. Although HCC recurred more than 3 years after surgery in a few patients who underwent liver resection for HBV-related HCC or HCC not related to either HBV or HCV infection, the tumor-free survival rate continued to gradually decrease in patients who underwent liver resection for HCV-related HCC. Such HCC recurrence within 3 years after surgery is mainly due to intrahepatic metastasis from the primary HCC, whereas recurrent tumors detected more than 3 years after surgery are mainly the result of multicentric recurrence. In resected specimens, early HCCs and dysplastic nodules, which are premalignant lesions, are often found on macroscopic and microscopic examination [7–9]. Risk factors for such hepatic nodules associated with multicentric carcinogenesis are related to persistent active hepatitis and hepatic fibrosis caused by hepatitis virus infection, particularly HCV infection [7, 8]. These findings indicate that treatment for both HCC and infection with hepatitis viruses such as HBV and HCV is important for the management of patients with HCC and hepatitis virus infection.

HBV-Related HCC

Since we first reported that a high serum concentration of HBV DNA before surgery is a strong risk factor for HCC recurrence after curative resection for HBV-related HCC [4, 10], several studies have found similar results [11–17]. We also demonstrated that the lack of an acute exacerbation of hepatitis and a sustained low serum concentration of HBV DNA after surgery were significantly associated with a low risk for HCC recurrence [16]. It has been reported that sustained viremia increased the risk for HCC recurrence after surgery [17]. These findings indicate that viral status strongly affects the outcome after treatment for HBV-related HCC and that antiviral therapy is important even after curative resection. Recently, several studies have demonstrated that antiviral therapy with nucleos(t)ide analogues (NAs) including lamivudine, adefovir dipivoxil, and entecavir is useful for

Fig. 1. Tumor-free survival rates according to viral status after curative resection for HCC [1]. C = 415 patients with anti-HCV antibody; B = 86 patients with hepatitis B surface antigen; BC = 14 patients with both anti-HCV antibody and hepatitis B surface antigen; nonB-nonC = 102 patients with neither anti-HCV antibody nor hepatitis B surface antigen.

Fig. 2. Tumor-free and cumulative survival rates after curative resection for HBV-related HCC [22]. Circles indicate 46 patients who received nucleos(t)ide analogues for a high viral load of HBV DNA. Triangles indicate 13 patients who did not receive nucleos(t)ide analogues for high viral loads.

preventing progression to cirrhosis and the development of HCC in patients with chronic hepatitis B. Since we reported that lamivudine may potentially prevent HCC recurrence after curative resection of HBV-related HCC [18], several reports have shown the effects of NAs after treatment of HCC [13, 19–21]. Recently, we have evaluated the effects of NAs, primarily of entecavir, on long-term outcomes after curative resection for HCC in patients with a high serum concentration of HBV DNA ($\geq 4 \log_{10}$ copies/ml) and without portal vein thrombus of the main portal vein as such portal vein thrombus is a strong risk factor for HCC recurrence and may obscure the effects of antiviral therapy [22]. In that study, the tumor-free survival rate after surgery was significantly higher in patients treated with antiviral therapy (antiviral therapeutic group) than in untreated patients (control group; fig. 2). However, antiviral therapy was not an independent risk factor [22]. Some studies have demonstrated the suppressive effects of NAs on HCC recurrence [13, 21], whereas other studies did not have indicated that antiviral therapy provided favorable effects [19, 20]. The differences between studies may be related to the prevalence of advanced HCC in the subjects and differences in the kinds of NAs administered. Although it is well known that NAs

suppress HBV replication and active hepatitis and reverse hepatic fibrosis, the mechanism underlying this suppressive effect of NAs on HCC recurrence is still unclear. In the antiviral therapeutic group, a second resection for recurrent tumor(s) was performed in half of the patients with tumors. In contrast, in the control group, transcatheter arterial chemoembolization was performed in most patients with HCC recurrence because of poor remnant liver function or multiple recurrent tumors. The results demonstrated that the cumulative survival rate was significantly higher in the antiviral therapeutic group than in the control group (fig. 2) [22]. Similar results have been reported in other studies [19, 20]. Thus, antiviral therapy with NAs maintained liver function after surgery, thereby increasing the chances of curative treatment for HCC recurrence. A large-scale investigation is required to clarify the effects of antiviral therapy with NAs. However, a well-designed prospective study may be difficult to conduct because antiviral therapy with NAs has been established as a treatment for chronic hepatitis B, particularly for patients with a high serum concentration of HBV DNA and active hepatitis.

HCV-Related HCC

Since Nishiguchi et al. [23] first reported that interferon (IFN) therapy suppresses the development of HCC in patients with chronic hepatitis C, many investigators have confirmed such preventive effects of IFN therapy. In addition, several studies, including randomized controlled trials regarding the effects of IFN therapy on the outcome of HCC treatment have been conducted [24–31]. We performed a randomized controlled trial on the effects of long-term IFN therapy on the outcome of liver resection for HCV-related HCC, which demonstrated that postoperative IFN therapy decreased HCC recurrence after surgery [25]. In that trial, although the difference in the tumor-free survival rate between the IFN group and the control group was small during the early postoperative stage, the incidence of HCC recurrence was low during the late postoperative stage (more than 3 years after surgery) in the IFN group alone. Other studies have also shown that recurrence during the late postoperative stage is suppressed by IFN therapy [26, 28, 29]. The suppressive effects of IFN therapy on HCC recurrence appeared to be stronger in patients who showed a sustained viral response (SVR). Thus, IFN therapy suppresses multicentric recurrence by inducing remission of active hepatitis and by improving hepatic fibrosis in patients infected with HCV [25, 26]. Furthermore, Ikeda et al. [24] have reported that IFN- β prevents recurrence of HCC during the early postoperative stage, suggesting that it acts as an anticancer agent. The anticancer effects of IFN may be another reason for the suppression of HCC recurrence after treatment.

Our study demonstrates that IFN therapy improves the overall survival rate after resection for HCC (fig. 2) [32]. Other studies have also found an improvement in overall survival after treatment of HCC with IFN therapy [26, 28]. Many previous studies have shown that IFN therapy eradicates HCV and controls active hepatitis, resulting in an improved liver function. In our randomized controlled trial, laboratory test results showed that liver function was improved in the IFN group but did not change or even worsened in the control group. At detection of recurrence, the serum concentration of total bilirubin was significantly lower in the IFN group. Moreover, 1 patient in the control group could not undergo treatment for recurrent tumors because of decompensation, whereas radical treatment including a second hepatic resection could be performed in the IFN group. IFN may increase survival in patients administered IFN therapy not only by preventing HCC recurrence but also by improving liver function and increasing the likelihood of patients being able to undergo radical treatment for HCC recurrence [32]. Several recent meta-

Fig. 3. Tumor-free and cumulative survival rates after curative resection for HCV-related HCC classified according to the Milan criteria (solitary tumor, not larger than 5 cm or no more than 3 tumors, none larger than 3 cm). Closed circles indicate 60 patients who showed SVR or BR. Open circles indicate 227 patients who were classified as nonresponders or who did not receive IFN therapy.

analyses have indicated that IFN therapy suppresses HCC recurrence and improves the outcome after treatment for HCV-related HCC [33].

Recently, the number of patients undergoing liver resection for HCC detected after IFN therapy has increased with the number of patients undergoing IFN therapy [34, 35]. We evaluated the tumor-free and cumulative survival rates for patients who underwent IFN therapy before and/or after curative resection of HCV-related HCC [36]. The tumor-free and cumulative survival rates of patients who showed a SVR or biochemical response (BR) were significantly higher than those of patients who were classified as nonresponders or who did not undergo IFN therapy (NR/non-IFN group; fig. 3). The proportion of patients who died of HCC was significantly lower in the SVR/BR group than in the NR/non-IFN group. In addition, neither SVR nor BR patients died of decompensation. Thus, in patients who undergo liver resection for HCV-related HCC, long-term survival can be expected if IFN therapy is effective.

IFN therapy itself is not indicated for older patients or those with concomitant disease. In addition, IFN therapy is not indicated for patients with advanced HCC including distant metastases or for patients with decompensated liver disease. In patients who underwent liver resection for HCC and successful IFN therapy (SVR or BR), the presence of multiple tumors was independently associated with HCC recurrence after surgery [37]. Thus, patients with a single HCC are good candidates for adjuvant IFN therapy.

The combined use of pegylated IFN and ribavirin has been shown to significantly increase SVR rates and is now recognized as a standard treatment. In addition, telaprevir combination therapy has been developed, and the percentage of patients showing a SVR has been reported to increase. However, the indications for telaprevir combination therapy are limited because the therapy is indicated for relatively young patients (<65 years old) without thrombocytopenia or anemia (low hemoglobin concentration). Previous studies have indicated that HCC and/or cirrhosis are less likely to develop in patients showing BR, even when HCV RNA is still detectable. Low-dose intermittent IFN therapy has also been reported to be effective for the suppression of HCC recurrence [30, 31]. Improvements in IFN therapy will increase the indications for adjuvant IFN therapy. New antiviral agents, including protease

inhibitors, polymerase inhibitors, and NS5A inhibitors, which will be available in the near future, are expected to be effective because these agents can eradicate HCV in a high percentage of patients who are treated with them.

Conflict of Interest

None of the authors have any conflicts of interest or financial ties to disclose.

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