Effects of Antiviral Therapy on the Recurrence of Hepatocellular Carcinoma After Curative Resection or Liver Transplantation

Yan Du 1, Tong Su 1, Yibo Ding 1, Guangwen Cao 1

1 Department of Epidemiology, Shanghai Key Laboratory of Medical Biodefense, Second Military Medical University, Shanghai, China

ABSTRACT

Context: Hepatocellular carcinoma (HCC) is a fatal disease. Chronic hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection is the major cause of HCC. High viral replication rate and related hepatic/systematic inflammation are the major risk factors in HCC recurrence after heptectomy or liver transplantation.

Evidence Acquisition: Some of the carcinogenesis-related HBV mutations are also associated with poor prognosis for HCC patients. Antiviral therapy is an option for improving HCC prognosis after surgery. In case of HBV-associated HCC, treatment with interferon and nucleos(t)ide analogues (NAs), especially interferon, is effective in improving the prognosis. However, long-term use of NAs increases the possibility of developing drug-resistant viral mutations such as the HBV rtA181T/sW172 mutation, which increases the risk of HCC recurrence.

Results: In cases of HCV-associated HCC, standard interferon with or without ribavirin therapy is effective in improving the prognosis of HCV-associated HCC; however, some HCV mutations, such as the amino acid substitution M91L, are associated with treatment failure and a poor prognosis. Therapeutic efficacy needs to be confirmed using large-scale, randomized, placebo-controlled clinical trials.

Conclusions: Surveillance of viral mutations during antiviral treatment and a better understanding of the associations of HCC recurrence with viral load, inflammation-associated signaling, and environmental factors can aid the development of more effective strategies for the prevention of postoperative HCC recurrence in clinical practice.

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Implication for health policy/practice/research/medical education:
The recurrence rate of hepatocellular carcinoma (HCC) after curative treatment is high and the survival is poor. This review focuses on effects of antiviral therapy on HCC recurrence. It should be important in determining suitable antiviral therapy regimens for the prevention of postoperative HCC recurrence in clinical practice.

Please cite this paper as:

1. Context

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third leading cause of cancer death worldwide (1). Chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) accounts for about 75–80% of HCC cases worldwide (2). In Asia and Africa, where HCC is endemic, chronic HBV infection is the predominant risk factor, while in the western countries, HCV infection is one of the major risk factors. HCC is a fatal disease. Currently, orthotopic liver transplantation (OLT) and surgical resection are the only curative treatments. OLT has excellent outcomes in patients meeting the Milan criteria (single nodule of ≤ 5 cm or 2 or 3 nodules of ≤ 3 cm), with a 5-year survival rate of 70%. Nevertheless, because of the strict selection criteria and high costs associated with the therapy, it can be offered to only a small
fraction of the affected patients (3). Therefore, surgical resection is the main curative treatment for noncirrhosis patients and cirrhosis patients with well-preserved liver function. However, it is reported that up to 70% of the patients show relapse within 5 years after curative resection (4). The high rate of recurrence is a major obstacle to improving prognosis. Early recurrence (within 2 years) is mainly related to metastasis and dissemination of primary HCC, whereas late recurrence (after ≥ 2 years) mostly results from de novo tumors arising because of the “field effect” in the diseased liver and is closely associated with high viral loads and hepatic inflammatory activity (5, 6). Therefore, antiviral and anti-inflammatory therapies before and after curative treatment may be crucial in preventing HCC recurrence and in improving survival. Current approved medications for chronic hepatitis B (CHB) treatment are interferon-α (IFNa) and nucleos(t)ide analogues (NAs), including lamivudine (LAM), entecavir (ETV), tenofovir disoproxil fumarate (TDF), adefovir dipivoxil (ADV), and telbivudine (TBV) (7). Conventional treatment with IFNa and the pegylated, long-acting formulation (PEG-IFNa) in combination with the guanosine analog ribavirin (RBV), are considered a standard modality for chronic hepatitis C treatment (8). There are no anti-inflammatory drugs available for the prevention of HCC recurrence after surgery, but antiviral treatment and antioxidants can decrease liver inflammation (9). In this review article, we have re-evaluated the reported effects of antiviral treatments on the occurrence of HCC after surgical treatment, and we have pointed out existing problems in current studies.

2. Evidence Acquisition

2.1. Why do HCC Patients Need Postoperative Antiviral Treatment and What are the Characteristics of These Patients?

High viral loads in the serum or liver and hepatitis B e antigen (HBeAg) seropositivity indicate a high viral replication rate. The presence of HBeAg either before or after curative treatment for HCC is significantly associated with early recurrence and poor survival (10-12). Serum hepatitis B core-related antigen (HBcAg), consisting of HBeAg, hepatitis B core antigen, and a 22-kDa precore protein coded with HBV precore/core gene, could be a surrogate marker for the intrahepatic covalently closed circular DNA (cccDNA) pool. A high serum level of HBcAg is an independent factor in HCC recurrence (13). The severity of hepatic inflammation, which is well correlated with viral serostatus, may also be a factor that affects intrahepatic recurrence, which is more likely to originate fromynchronous carcinogenesis (14). High levels of HBV DNA in peritumoral liver tissues of HCC patients independently predicted poor disease free survival (DFS) and overall survival (OS) after surgical resection (15). Sustained low hepatitis B viral load (<10^4 copies/mL) is significantly associated with improved long-term recurrence-free survival and OS (16). In addition, HBV viral load is one of the main prognostic factors for local recurrence after complete radiofrequency ablation (RFA) of small HBV-related HCC (12). Thus far, there is not much information on the association between HCV RNA concentration and HCC recurrence after surgery. The available data has shown that HCV concentration is an independent prognostic factor for OS and recurrence (17, 18). These data indicate that high rates of viral replication are positively associated with a high risk of HCC recurrence after surgery. Chronic inflammation supported by chronic HBV or HCV infection orchestrates a tumor-friendly microenvironment that is essential for carcinogenesis and metastasis. Chronic inflammation and high viral replication rate are important predictors of adverse outcome after HCC curative treatments. Chronic inflammation plays a crucial role in cancer initiation and promotion. Abnormal inflammation, including aberrant production of pro-inflammatory mediators and increased expression of oncogenes, matrix metalloproteinases, and pro-inflammatory transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), signal transducers and activators of transcription 3 (STAT3), activating protein-1 (AP-1), and hypoxia-induced factor-1α (HIF-1α) can activate genes mediating tumor cell proliferation, survival, invasion, and angiogenesis (19). High viral replication rates are closely related to hepatic inflammation. Many studies have provided evidence that inflammation-related host factors can predict HCC recurrence and survival after surgical resection or liver transplantation (20-22). All these data support the finding that persistent viral infection-associated inflammation plays an active role in the recurrence of HCC. Inflammation contributes to the formation of HBV mutations and the mutants can in turn facilitate HCC occurrence and progression. One of the common mechanisms of HBV mutagenesis to escape immune clearance is the reduction of CD8+ T cell epitopes. Some of the HBV mutations selected by a compromised immune system during HBV hepatocarcinogenesis are significantly associated with an increased risk of HCC (23-25). C1653T, T753V, A762T/G764A, T1674C/G, C1766T/T1768A, T53C, preS2 start codon mutation, preS1 deletion, C2964A, A2962G, C3116T, C7A, and their combinations are HBV mutations that are significantly associated with an increased risk of HCC (23-25). PreS deletion is the most common mutation in the preS region. The preS mutations may be generated during the progression of CHB, particularly in IFN-treated patients (28). The preS deletion also affects viral replication by decreasing the expression of surface proteins, which leads to intracellular accumulation of HBV envelope proteins and viral particles, formation of ground-glass hepatocytes, endoplasmic reticulum stress, and oxidative DNA damage (29). All these changes eventually result in hepatocarcinogenesis. In peritumoral tissues, a preS deletion at nt.1074-141 and
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preS2 mutations are independently associated with poor DFS and OS after surgery (23, 30). A1762T/G1764A in liver tissue can independently predict postoperative survival (15). HCV is hypervariable in a region coding for envelope proteins and escapes immune surveillance. It has been reported that 2 amino acid substitutions in the core region of HCV-1b, Q70R and M91L, are significantly associated with resistance to the standard IFNa plus RBV therapy and an increased risk of HCC (31). Moreover, M91L is significantly associated with recurrence and poor survival in HCC patients after surgery (32). Currently, there are no data showing that the viruses with HCC- or HCC prognosis-associated mutations are still sensitive to IFN and/or NA treatments. We, therefore, suggest that HCC patients who need postoperative antiviral treatments are those who (1) have a high HBV DNA level (> 10⁶ copies/ml) at the time of surgery (2); are seropositive for HBeAg or have a high serum level of HBcrAg (3); are infected with HBV with the HCC-or HCC prognosis-associated mutations (4); have recurrent HCV after OLT/hepatectomy or HCV with HCC prognosis-associated mutations (5); have high Ishak hepatic inflammation score (> 6) or abnormal alanine aminotransferase (ALT); and (6) have over-expression of inflammation-related molecules in HCC specimens or peritumoral liver tissues. Furthermore, since HCC curative resection may reactivate HBV replication (33), HCC patients with a high level of HBV reactivation within 3 months after surgery should also be considered for antiviral treatment.

2.2. Antiviral Treatment Improves HCC Prognosis

2.2.1 Effects of IFN on HBV- or HCV-Related HCC Survival and Recurrence

A meta-analysis conducted by Breitenstein et al. (34) pooled data from 7 randomized clinical trials (RCTs) (35-41) between January 1998 and October 2007 and concluded that IFNα had a significant beneficial effect on both survival and tumor recurrence. Two additional meta-analyses published in 2010 (42, 43), including RCTs and non-randomized controlled trials (NRCTs), reported similar results (44-51). Other recent studies have also supported the role of IFN treatment in preventing early recurrence and improving survival after curative treatment of HCC (52-54). However, these studies do not separate HBV-related HCC from HCV-related HCC. Since HBV and HCV have distinctive characteristics and therefore different regimens (i.e., IFN/NA for HBV-related HCC vs. IFN/RBV for HCV-related HCC) after curative surgery, we summarized the results of HBV-related HCC RCTs and NRCTs in Table 1. For HCV patients, IFNα and PEG-IFNα can achieve sustained virologic response (SVR), seronegative for HCV RNA throughout the 6-month post-treatment follow-up period. The patients who achieve SVR following treatment with IFN and RBV usually have a good prognosis; however, in those who do not respond to initial antiviral therapy, maintaining IFN therapy may not decrease HCC recurrence. These results are summarized in Table 2. HCC recurrence rates and related deaths were significantly lower in patients who received post-OLT IFN therapy for recurrent HCV (58). Since high viral load is frequently associated with late recurrence of HCC after surgery, antiviral treatment should be solely effective for the prevention of late recurrence. However, it can also efficiently prevent early recurrence of HCC after surgery (52-54). IFN is effective in preventing both early and late recurrence of HCC, possibly due to its effects on angiogenesis, Wnt/β-catenin pathways, and immune modulation. Vascular invasion (microscopic vascular invasion or macroscopic venous invasion) is associated with early HCC recurrence (6). IFNα inhibits metastasis and early recurrence of human HCC after curative resection, which is possibly mediated by anti-angiogenesis through down-regulation of expression of vascular endothelial growth factor (VEGF) (55-57). The expression of HBx in hepatocytes activates Wnt/β-catenin signaling, and Wnt pathway activation induced by β-catenin mutations is associated with a poor prognosis (22, 58, 59). PEG-IFN targets Wnt signaling by inducing nuclear export of β-catenin, and thus affects the recurrence of HCC (60). It is believed that the principal mechanisms of IFN in prevention of HCC recurrence in patients with viral hepatitis are the suppression of HBV and HCV replication, inhibition of inflammatory signaling, and tumoricidal effect (55, 57). IFN treatment has adverse effects, including flu-like symptoms, fatigue, neutropenia, thrombocytopenia, depression, bone marrow suppression, and unmasking or exacerbation of autoimmune illnesses. These are generally tolerable but may require dose modification and premature withdrawal from the treatment. In addition, antibodies to recombinant IFN, which might be generated during long-term treatment, may limit its biological effects.

2.2.2. Effects of NAs on HCC Survival and Recurrence

HBV-positive patients require both sufficient antiviral therapy with NAs and hepatitis B immune globulins (HBIG) after successful liver transplantation to effectively prevent recurrence (61). The introduction of HBIG treatment greatly reduces HBV recurrence after HBV-related OLT. Even thought there is no current consensus on the optimal HBIG dosage and duration, it is widely agreed that HBIG plasma titers should be maintained at a level of at least 100 IU/L during long-term therapy (62). The aims of NA treatment are to inhibit HBV DNA replication, normalize ALT levels, and maintain liver function. NAs target HBV DNA polymerase. Short-term treatment with NAs (< 6 months) can prevent post OLT HBV recurrence (63). Since HBcrAg is a predictor of post-treatment recurrence of HCC, suppression of serum HBcrAg and cccDNA by NAs may be important to prevent HCC recurrence (13). LAM is the first NA to treat CHB. It can inhibit viral replication,
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The HCC recurrence rate is a significant concern in patients with HCC. Several studies have compared the prognosis of HCC patients with and without NA treatments. Although most of the studies had small sample sizes and relatively short follow-up times, in general the NA treatments exhibited a potential beneficial effect in preventing HCC recurrence and improving survival after curative treatments. Long-term usage of NAs is required to effectively inhibit HBV and maintain a low HBV load; however, this strategy leads to a major challenge in HCC management-drug resistance.

2.2.3. Drug-resistant Viral Mutations Limit NA Therapeutic Effect and May Also Promote Hepatocarcinogenesis

Long-term use of NAs may generate drug-resistant viral mutations. The most frequently used antiviral therapy for HBV-related HCC is interferon (IFN). However, this strategy leads to a major challenge in HCC management-drug resistance.

Table 1. Studies of Effects of IFN on HBV-Related HCC Survival and Recurrence After Surgical Resection

<table>
<thead>
<tr>
<th>Patients</th>
<th>Therapy</th>
<th>Survival (OS, DFS, RFS)</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin, et al. (2004) (38)</td>
<td>30 patients after non-surgical treatment (transarterial chemoembolization or percutaneous acetic acid injection) of HCV- or HBV-related HCC nodules</td>
<td>IFN-α intramuscular injection. Treatment group A: 3 MIU × 3/ week × 24 months. Treatment group B: 3 MIU × 10/month × 6 months, then 5 MIU × 10/month × 6 months</td>
<td>Not analyzed</td>
</tr>
<tr>
<td>Sun, et al. (2006) (39)</td>
<td>236 patients after curative resection of HBV-related HCC</td>
<td>IFN-α intramuscular injection, 3 MIU × 2/ week × 2 weeks, then 5 MIU × 3/week × 18 months</td>
<td>Treated vs. control: Median OS, 63.8±38.8 months (P = 0.0003); Median DFS, 31.2[17.7 months, P = 0.42</td>
</tr>
<tr>
<td>Lo, et al. (2007) (41)</td>
<td>80 patients after curative resection of predominantly HBV-related HCC</td>
<td>IFN-α2b subcutaneous injection, 10 MIU× 3/ week × 16 weeks</td>
<td>Adjusted RR of death for IFN treatment was 0.42 (95%CI: 0.17-1.05; P = 0.063)</td>
</tr>
<tr>
<td>Someya, et al. (2006) (48)</td>
<td>80 patients with HBV-positive cirrhosis and HCC underwent curative treatment (surgical resection or sufficient ablation) for HCC</td>
<td>Intermittent IFN-α injections, 2-3/week × 6 months or longer.</td>
<td>Not analyzed</td>
</tr>
<tr>
<td>Qu, et al. (2010) (52)</td>
<td>568 HBV-related HCC patients underwent curative section. A median observation period of 53.3 months</td>
<td>IFN-α2b intramuscular injection, 3 MIU × 2/week × 2 weeks, and then 5 MIU × 3/week × 18 months.</td>
<td>Postoperative IFN-α therapy was an independent factor for OS. No significant difference in DFS rates</td>
</tr>
<tr>
<td>Chan, et al. (2011) (53)</td>
<td>136 HBV-related HCC patients underwent hepatectomy</td>
<td>Antiviral therapy after hepatectomy</td>
<td>Antiviral treatment conferred a significant survival benefit in stages I and II tumors or HCC without major venous invasion</td>
</tr>
</tbody>
</table>

Abbreviations: AST, Aspartate aminotransferase; DFS, Disease free survival; HBV, Hepatitis B virus; HCC, Hepatocellular carcinoma; IFN, Interferon; MIU, Million international units; NRCT, Non-randomized controlled trial; OS, Overall survival; RCT, Randomized clinical trial; RFS, Recurrence free survival.
Table 2. Effects of IFN on HCV-Related HCC Survival and Recurrence After Surgical Resection

<table>
<thead>
<tr>
<th>Patients</th>
<th>Therapy</th>
<th>Survival (OS, DFS, RFS)</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ikeda, et al. (2000) (35)</td>
<td>20 patients with HCV infection had received curative resection.</td>
<td>IFN-β injection, 6 MIU x 2/week x 36 months.</td>
<td>Not analyzed</td>
</tr>
<tr>
<td>Kubo, et al. (2002) (36)</td>
<td>30 males with HCV infection and curative surgical resection of a single HCC tumor.</td>
<td>IFN-α intramuscular injection, 6 MIU x 7/week x 2 weeks, then 6 MIU x 3/week x 14 weeks, then 6 MIU x 2/week x 88 weeks.</td>
<td>The cumulative survival rate was higher in the IFN group than in the control group (P = 0.041).</td>
</tr>
<tr>
<td>Shiratori, et al. (2003) (37)</td>
<td>74 patients with compensated cirrhosis, three or fewer nodules of HCC, and low HCV RNA loads after complete ablation of the lesions.</td>
<td>IFN-α intramuscular injection, 6 MIU x 3/week x 48 weeks</td>
<td>The survival rate was higher in the IFN group than in the control group</td>
</tr>
<tr>
<td>Mazzaferro, et al. (2006) (40)</td>
<td>150 patients after curative resection of HCV-related (n = 80) or HCV and HBV-related (n = 70) HCC.</td>
<td>IFN-α subcutaneous injection, 3 MIU x 3/week x 48 weeks</td>
<td>Treated vs. control: 45 months of median follow-up; RFS: 24.3% vs. 5.8%, P = 0.49</td>
</tr>
</tbody>
</table>

| NRCT | | |
| --- | --- | --- | --- |
| Suou, et al. (2001) (44) | 40 patients after curative treatment of small HCC-HCC (solitary, diameter ≤ 3 cm), ≤ 70 years. | IFN α or IFN-α2b intramuscular injection, 6 MIU x 7/week x 2 weeks, then 6 MIU x 3/week x 22 weeks. | The cumulative survival rate was significantly longer in the IFN group compared with the control group (P < 0.01). | IFN α therapy after the curative treatment of small HCC with HCV can inhibit intrahepatic recurrence and improve the prognosis of HCV-related HCC. |
| Hung, et al. (2005) (45) | 40 patients with 3 or fewer nodules of HCV-related HCC who received percutaneous tumor ablation and/or transcatheter arterial embolization. | IFN-α2b subcutaneous injection, 3.5 MIU x 2/week x 24-48 weeks, with the combination of oral ribavirin 1000-1200 mg/day for 24-48 weeks | Survival in sustained responders was better than in non-responders and control patients (P = 0.069, 0.055%, respectively) | No significant difference in the incidence of local recurrence in sustained responders; the 2nd recurrence-free interval in the sustained responders was significantly longer than non-responders and control group |
| Sakaguchi, et al. (2005) (46) | 57 patients with HCV-related HCC underwent radical RFA therapy. | IFN-α2b intramuscular injection, 3 MIU x 2/week for as long as possible | There was no difference in the cumulative survival rates between the IFN group and the control group (P = 0.25) | The median tumor-free period was longer in the IFN group than the control. The cumulative recurrence rate in the IFN group was lower than the control during the first 3 years; however, the recurrence rate in the IFN group increased over 3 years. |
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post-transplantation recurrence of HBV infection is LAM, but this drug is associated with a high resistance rate due to tyrosine-methionine-aspartate-aspartate (YMDD) mutants (72). The YMDD mutants may arise under immunosuppression, and emerge after 9-10 months of LAM therapy. The most frequently encountered LAM-resistant mutation at the catalytic YMDD motif is rtM204V/I (73-75, 78-80). The frequency of the mutation increases over the duration of LAM therapy year by year, up to almost 70% after 5 years (65). In terms of the current standard therapy, resistance to ETV is rare in treatment-naive patients. However, in the presence of rtM204I/V mutations, ETV resistance arose with the coexistence of rtI69F, rtL180M, rtM204I/V, and rtT286A (77, 78). As for other NAs, the rtA181T mutation is associated with ADV resistance (76, 78). The major TBV resistant mutant is rtS123T (79). Another mutant, rtI280T, may arise during prolonged LAM therapy, conferring cross resistance to TBV. Importantly, since the HBV S and polymerase genes overlap with each other, a great proportion of patients with the rtA181T mutation also carry the SW172 nonsense mutation at the catalytic YMDD motif is rtM204V/I (73-75, 78-80). The frequency of the mutation increases over the duration of LAM therapy year by year, up to almost 70% after 5 years (65). In terms of the current standard therapy, resistance to ETV is rare in treatment-naive patients. However, in the presence of rtM204I/V mutations, ETV resistance arose with the coexistence of rtI69F, rtL180M, rtM204I/V, and rtT286A (77, 78). As for other NAs, the rtA181T mutation is associated with ADV resistance (76, 78). The major TBV resistant mutant is rtS123T (79). Another mutant, rtI280T, may arise during prolonged LAM therapy, conferring cross resistance to ADV. Importantly, since the HBV S and polymerase genes overlap with each other, a great proportion of patients with the rtA181T mutation also carry the SW172 nonsense mutation.

**Figure 1. Major Events in HBV Hepatocarcinogenesis and HBV-Related HCC Prognosis**

HBV, Hepatitis B Immune Globulin; HBV, Hepatitis B virus; HCC, Hepatocellular Carcinoma; IFN, Interferon; NA, Nucleos (t)ide Analogue

**Figure 2. Major Events in HCV Hepatocarcinogenesis and HCV-Related HCC Prognosis**

HCC, Hepatocellular Carcinoma; HCV, hepatitis C Virus; SVR, Sustained Virologic Response
mutation, resulting in truncation of the preS/S reading frames, which significantly increases the risk of HCC during subsequent courses of NA therapy (80). Drug-resistant viral mutations generated during the long course of NA treatment are becoming one of the major risk factors of poorer HCC prognosis. The important events in HBV- or HCV-induced hepatocarcinogenesis and prognosis and the antiviral treatments for the prevention of HCC recurrence after surgical treatment are summarized in Figure 1 and Figure 2, respectively.

3. Results
3.1. Regimen of Antiviral Therapy Suitable for the Prevention of HCC Recurrence
So far, there is no consensus on the standard regimen, such as drug combination, dosage, and optimal time of initiation of therapy, to achieve the best prognosis for HCC after curative treatment. The current practice is largely experience-based, and most results, especially for NAs, are from NRCTs. For IFN, previous studies have indicated that there was no difference between intermittent and continuous treatment strategies. The usual dosage is 3-6 million international units (MIU), with some with a

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**Table 3. Effects of NA Therapy on HCC Survival and Recurrence After Curative Treatment**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Therapy</th>
<th>Survival (OS, DFS)</th>
<th>Recurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piao, et al. (2005) (66)</td>
<td>70 HCC patients completed HCC therapy (local ablation, transarterial chemoembolization, or surgery)</td>
<td>LAM: 100 mg/day orally for more than 24 months</td>
<td>There was no significant difference in the survivals between the two groups, but LAM treatment was associated with low cumulative rate of death due to liver failure ($P = 0.043$)</td>
<td>No difference was found between the treatment group and the control group (14/30 and 26/40)</td>
</tr>
<tr>
<td>Kuzuya, et al. (2007) (67)</td>
<td>49 HCC patients who underwent hepatic resection or RFA for initial HCC treatment.</td>
<td>LAM: 100 mg/day</td>
<td>The cumulative survivals of patients in the treatment group tended to be higher than those in the control ($P = 0.063$)</td>
<td>Cumulative recurrence rates of HCC did not significantly differ between the two groups ($P = 0.622$)</td>
</tr>
<tr>
<td>Kubo, et al. (2007) (68)</td>
<td>24 patients who had high serum concentrations of HBV DNA</td>
<td>LAM: 100 mg/day</td>
<td>Tumor-free survival rate was significantly higher in the treatment than the control group ($P = 0.0096$)</td>
<td>Not analyzed</td>
</tr>
<tr>
<td>Yoshida, et al. (2008) (69)</td>
<td>104 HCC patients underwent RFA treatment.</td>
<td>LAM: 100 mg/day</td>
<td>Overall survival did not differ between the two groups</td>
<td>Recurrence-free survival did not differ between the two groups</td>
</tr>
<tr>
<td>Li, et al. (2010) (70)</td>
<td>79 HCC patients underwent curative resection, a median follow-up of 12 months.</td>
<td>LAM with or without adefovir dipivoxil</td>
<td>OS was improved for those patients with postoperative antiviral therapy</td>
<td>No significant difference in recurrence rate between the treatment group and the control group (76.7% and 91.7%)</td>
</tr>
<tr>
<td>Zimmerman, et al. (2007) (71)</td>
<td>101 patients underwent OLT for end-stage liver disease secondary to HBV with concomitant HCC</td>
<td>LAM: 150 mg/day. HBIG: before 1998, 10,000U, iv, then 10,000U/d × 7 days, then 10,000 U/month. After 1998, 10,000U, iv, then 2000 U/d × 6 days, then 1560 U im</td>
<td>Patients treated with combination prophylaxis had a significantly lower mortality than those without</td>
<td>AFP &gt; 500 ng/mL, presence of vascular invasion, HBV recurrence, and combination prophylaxis were independent predictors of HCC RFS</td>
</tr>
</tbody>
</table>

Abbreviations: DFS, Disease free survival; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; IFN, Interferon; MIU, Million international units; NRCT, Non-randomized controlled trial; OS, Overall survival; RCT, Randomized clinical trial; RFA, Radio frequency ablation; RFS, Recurrence free survival; SVR, Sustained virologic response.
larger dosage of 10 MIU, subcutaneously or intramuscu-
larly. It is usually administrated 2-3 times per week, and
needs to last for more than 6 months. It is also a common
practice to add RBV to the IFN treatment regimen for
HCV-related HCC. IFN has a short half-life in the circula-
tion and needs frequent administration, thus can pro-
duce severe side effects. As a result, PEG-IFN has recently
been prescribed more often, with a dosage ranging from
90 to 180 μg per week. As for NAs, LAM is an often-used
agent, with a common dosage of 100 mg/day, sometimes
in combination with another NA, such as ADV, to reduce
the possibility of developing drug-resistance. Results
from NRCTs show that NAs are effective in improving
survival. However, it is difficult to make any recommenda-
tion based on these data to guide clinical practice. No
definite conclusions could be drawn without credible
evidence from RCTs. International collaborations are
needed to conduct large multi-centered RCTs in different
populations in order to evaluate the most effective com-
bination and administration of these therapeutic agents.

4. Conclusions

4.1. Summary and Suggestions

HBV and HCV related HCC cause a huge public health
burden, especially in HBV endemic areas. Only a small
proportion of HCC patients are eligible for curative treat-
ment, namely surgical resection or OLT. Further, survival
after the curative treatment is not optimal. High viral rep-
lication rates, viral mutations, and infection-associated
inflammation are major factors associated with poor out-
comes after surgery. Antiviral treatment is therefore an
optimal option to prevent HCC recurrence and improve
survival. IFN and NAs are currently the major antiviral
agents in use. Use of antiviral agents not only inhibits
virus replication and re-activation, but also decreases he-
patic inflammation and can facilitate further treatment.
IFN and NAs, especially IFN, have been proven to be effect-
ive in improving HCC prognosis. However, large multi-
center RCTs are necessary to determine the most effective
regimen of these antivirals in improving the HCC prog-
nosis after surgery. The complex interactions among viral
factors, host immunity and environmental determinants
may influence HCC recurrence and survival. However, the
underlying mechanisms of this multi-way network have
not yet been fully elucidated. A better understanding of
the relationships among these factors can aid in develop-
ing advanced treatment strategies and improving the life
quality of HCC patients. Future research should focus on
the roles of viral factors, inflammation-related signaling
molecules, and possible environmental factors on HCC
occurrence and the effect of antiviral treatments on HCC
- or HCC prognosis-associated viral mutants. A systematic
scientific approach should be adopted to direct further

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References

2. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epide-
miology and molecular carcinogenesis. Gastroenterology.
2007;132(4):2555-76.
F, et al. Liver transplantation for the treatment of small hep-
4. Hlvet JM, Schwartz M, Mazzaferrro V. Resection and liver trans-
plantation for hepatocellular carcinoma. Semin Liver Dis.
5. Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Mi-
yagawa S, et al. Risk factors contributing to early and late phase
intrahepatic recurrence of hepatocellular carcinoma after hepato-
for early and late recurrence in hepatitis B-related hepatocellu-
7. Kim SR, Yang J, Kudo M, Hino O. Recent advances in the man-
8. Hoofnagle JH, Seeff LB. Peginterferon and ribavirin for chronic
9. Emerit I. Cytogenetic methods for detection of oxidative stress and
evaluation of antioxidant therapy in hepatitis C infection. Hepat
serum hepatitis B e antigen is associated with higher risk of early
recurrence and poorer survival in patients after curative re-
section of hepatitis B-related hepatocellular carcinoma. J Hepatol.
11. Hung IF, Poon RT, Lai CL, Fung J, Fan ST, Yuen MF. Recurrence of hepatitis B-related hepatocellular carcinoma is associ-
ated with high viral load at the time of resection. Am J Gastroenterol.
2008;103(7):1663-7.
Acid and HBV Viral Load are Main Prognostic Factors of Local Rec-
currence after Complete Radiofrequency Ablation of Hepatitis
2011.
13. Hosaka T, Suzuki F, Kobayashi M, Hirakawa M, Kawamura Y, Yas-
suji H, et al. HBCrAg is a predictor of post-treatment recurrence
of hepatocellular carcinoma during antiviral therapy. Liver Int.
2010;30(10):1460-70.
al. Viral serorestatus and coexisting inflammatory activity affect
metachronous carcinogenesis after hepatectomy for hepatoce-
13.
15. Yeh CT, So M, Ng J, Yang HW, Chang ML, Lai MW, et al. Hepatitis B
virus-DNA level and basal core promoter A1762T/G1764A mutation
in liver tissue independently predict postoperative survival
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