Feasibility of combining adjuvant transarterial chemoembolization with nucleos(t)ide analog therapy for patients with HBV-associated hepatocellular carcinoma after hepatectomy (Review)

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Abstract. Hepatocellular carcinoma (HCC) is the third leading cause of cancer-associated mortalities, and its prevalence is expected to increase in future decades. Hepatitis B virus (HBV) infection is the leading cause of HCC. Although hepatectomy is the preferred curative treatment for HCC, tumor recurrence is common, which is the most frequent cause of mortality in patients with HCC. HCC recurrence may originate from the primary tumor or be associated with remnant liver tissue, and include high viral load and hepatic inflammatory activity. Adjuvant transarterial chemoembolization and postoperative nucleos(t)ide analogs therapy are the two corresponding therapies. Following systematic searching of the PubMed database, the indications for adjuvant transarterial chemoembolization and nucleos(t)ide analog therapies for HBV-related HCC after hepatectomy were acquired. Additionally, the feasibility of combining these two therapies were also reviewed.

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Postoperative antiviral therapy with NAs is another therapy commonly used following hepatectomy in patients with HBV-associated HCC (17,18). The goal of postoperative antiviral therapy in HBV-associated HCC is to reduce the viral load of HBV, protect liver function, decrease tumor recurrence, increase overall survival, and improve quality of life. The only two randomized trials (19,20) that we identified in literature searches, as well as large cohort studies (18,19,21) examining NA therapy, found that it significantly reduced late HCC recurrence and improved long-term overall survival in patients with HBV-associated HCC (17,18). The goal of postoperative antiviral therapy is to destroy small intrahepatic metastases that may not have been detected during surgery, as well as to eliminate tumor cells that may have been released during surgical manipulation of the liver (11). Adjuvant TACE appears to benefit only patients with HCC at high risk of early recurrence, including patients with multiple nodules, large tumors, vascular invasion, poor tumor differentiation, incomplete or absent tumor capsule, or a resection margin <1 cm. The idea that only high-risk patients benefit from adjuvant TACE is supported by retrospective studies (12,13) and a meta-analysis based on randomized trials involving 659 patients with HCC at a high risk of recurrence, revealed that adjuvant TACE decreased 1- and 3-year mortality rates (14). One retrospective study (15) involving 1,924 patients with HCC following curative hepatectomy found that adjuvant TACE improved overall survival in patients with tumors >5 cm, who also had other risk factors, including 2-3 nodules or microvascular invasion. However, adjuvant TACE actually reduced the overall survival of patients with a single tumor <5 cm without microvascular invasion. This lack of clinical benefit was confirmed in a more recent retrospective study (16) involving 229 patients with HCC lacking factors associated with elevated risk of recurrence or reduced overall survival. Adjuvant TACE did not improve the overall survival or reduce recurrence.

### Table I. Previous studies evaluating postoperative antiviral therapy and survival, stratified by tumor stage.

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample size (T/C)</th>
<th>Liver function (T), A/B</th>
<th>Drug used</th>
<th>Disease-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al, 2011</td>
<td>42/94</td>
<td>42/0</td>
<td>Lamivudine (100 mg/d) or entecavir (0.5 mg/d)</td>
<td>P=0.04 or 0.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td>P=0.02 or 0.004&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ke et al, 2013</td>
<td>141/337</td>
<td>141/0</td>
<td>Lamivudine (100 mg/d)</td>
<td>-</td>
<td>BCLC A/B stage: P=0.035</td>
</tr>
<tr>
<td>Zhang et al, 2014</td>
<td>40/47</td>
<td>33/6</td>
<td>Entecavir (0.5 mg/d)</td>
<td>Tumor size ≤3: P=0.006</td>
<td>Tumor size ≥3: P=0.209</td>
</tr>
</tbody>
</table>

<sup>a</sup> American joint committee on cancer stage I and II. <sup>b</sup> Patients without major vascular invasion. <sup>c</sup> American joint committee on cancer stage III. <sup>d</sup> Patients with major vascular invasion. BCLC, barcelona clinical liver cancer; C, control group; T, antiviral group. A/B, no. of patients with Child-Pugh A versus Child-Pugh B liver function.
hepatectomy. Indeed, this indication is supported by subgroup analyses in retrospective studies (22-24), which showed that postoperative NA therapy can significantly improve disease-free and overall survival in patients in relatively early stages of HCC. However, no significant clinical benefit was observed for those in relatively late stages of HCC (Table I).

5. Feasibility of adjuvant TACE combined with NA therapy

These considerations highlight the fact that the indications for adjuvant TACE differ from those for postoperative NA therapy in certain respects. This is important to take into consideration when treating patients with HBV-associated HCC following hepatectomy, particularly since the two therapies are the ones most frequently administered to such patients in HBV-endemic areas (25,26). This raises the question of whether the two therapies can be combined for an improved prognosis. Systematic searches of PubMed, EMBASE, the Cochrane Library revealed two small retrospective studies (27,28) investigating the efficacy of adjuvant TACE combined with antiviral therapy for HBV-associated HCC following hepatectomy. The first retrospective study (27) involved 60 patients, of whom 41 received both therapies and 19 received only TACE. The two groups exhibited similar 1, 2 and 3 year recurrence rates. The other study (28) included 176 patients with Child-Pugh A liver function, of whom 58 received combination therapy and 118 received TACE alone. The two groups exhibited similar disease-free survival (P=0.322), however, the combination group revealed a marginally improved overall survival (P=0.048). However, when analyses were performed with 51 pairs of propensity score-matched patients, the combination group exhibited significantly higher overall survival (P=0.033) and marginally higher disease-free survival (P=0.048). The authors concluded that the combination of adjuvant TACE and NA therapy may prevent HCC recurrence and improve the overall survival following curative hepatectomy (28).

The optimal indications for combined adjuvant TACE and NA therapy remain to be elucidated (29). The two retrospective studies (27,28) mentioned above included patients with advanced-stage HCC, and no subgroup analyses based on tumor stage were performed (27,28). Based on the indications for adjuvant TACE or postoperative NA monotherapy on their own, patients who have HBV-associated, relatively early-stage HCC and who are at high risk of recurrence may be the most suitable candidates for the two therapies combined. Adjuvant TACE is not, however, recommended for patients who have early-stage HBV-associated HCC and who lack risk factors of recurrence (15,16). Combination therapy may also be appropriate for patients with HBV-associated HCC in advanced stages. Although postoperative NA therapy in such patients may not significantly prolong their survival (22-24), it can decrease the rate of HBV reactivation and improve liver function (30,31). Two previous studies suggested that the combination of TACE and NA therapy in such patients can lead to significantly higher overall survival compared with TACE alone (32,33).

Physicians and patients must weigh the pros and cons of treatment options, including associated costs, for managing HBV-associated HCC following hepatectomy. Long-term treatment with NAs will be expensive. Additionally, drug resistance and side effects must also be determined. The most extensive evidence must also be taking into consideration, since future studies may change the picture presented here.

6. Future perspective

Several international guidelines already recommend antiviral therapy for patients with chronic HBV, however, no standardized international guidelines exist regarding postoperative antiviral therapy for patients with HBV-associated HCC following hepatectomy at present. In general, the clinical practice of antiviral therapy in HBV-associated HCC is based on the management of chronic hepatitis B. The primary goal of antiviral therapy with NAs is to continuously suppress virus replication in order to prevent progression of fibrosis and cirrhosis, and thereby reduce the incidence of liver failure and HCC recurrence. Postoperative antiviral therapy with NAs not only improves liver function, but also reduces the incidence of HBV reactivation and long-term tumor recurrence. The net result is an increase in long-term overall survival. While it is possible that patients at any stage of HBV-associated HCC can benefit from postoperative NA therapy, the precise indications and contradictions of this treatment, as well as the optimal drugs and doses, remain to be clarified. Future studies must elucidate how postoperative NA therapy prevents tumor recurrence and improves overall survival.

No international guidelines definitively recommend adjuvant TACE for patients with HCC following hepatectomy, however, evidence is mounting to suggest a clinical benefit to patients at high risk of recurrence. The present review concluded that, on the basis of existing evidence, the most suitable candidates for adjuvant TACE combined with antiviral NA therapy are patients who exhibit HBV-associated HCC and are at a high risk of recurrence.

References