Editorial

Adjuvant therapy after radical surgery for hepatocellular carcinoma: still an unmet need

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Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality. Because HCC typically occurs in patients with advanced liver disease, therapeutic decisions depend on the degree of underlying liver dysfunction and tumor burden. Curative treatment options, which result in 5-year survival rates of 60–80% (surgical resection) and 40–70% (local ablative therapies), are restricted to patients with early-stage HCC (1,2). However, surgical resection and local ablative therapies are limited by high tumor recurrence rates of 50% at 3 years and 70% at 5 years (1-6). Thus, monitoring treatment response is imperative for the clinical management of HCC patients (7), highlighting the need for adjuvant therapies.

Prevention of recurrence via adjuvant treatment after curative treatments such as resection or ablation is an important unmet medical need in patients with HCC. Adjuvant therapy in HCC represents a considerable challenge, particularly because of the specific biological nature of HCC (frequent intrahepatic metastatic recurrence) and underlying liver disease (high risk of secondary carcinogenesis).

Clinical trials of adjuvant therapy after curative treatments

Several clinical trials have been conducted to date to identify methods for preventing recurrence after curative treatment. The STORM trial is a global trial that is also the largest one performed to date; it was a multicenter, phase III, double-blind, placebo-controlled study that assessed the efficacy and safety of sorafenib versus placebo as adjuvant therapy in HCC patients with no residual lesions after curative resection (n=900) or ablation (n=214) (8). The patients were randomly assigned to two arms, one receiving 400 mg sorafenib twice daily (n=556) and a placebo arm (n=558).

However, both the primary endpoint of recurrence-free survival and the secondary endpoints time to recurrence and overall survival (OS) were not met. The median recurrence-free survival was 33.4 months for sorafenib, compared with 33.8 months for placebo (HR =0.94; 95% CI, 0.780–1.134). The median time to recurrence was 38.6 months for sorafenib, compared with 35.8 months for placebo (HR =0.891; 95% CI, 0.735–1.081). OS analysis showed approximately 75% survival in both arms with no significant difference between the two treatments. This trial clearly showed that an antiangiogenic targeted agent, sorafenib, is not effective to prevent postoperative recurrence despite the presence of microvascular invasion (MVI) in the resected HCC. This indicates that multi-kinase inhibitors are not effective for the treatment of micrometastatic lesions with an immature angiogenic status associated with MVI.

Trials of vitamin analogues are being conducted in Japan. The growth of human HCC cells can be inhibited by acyclic retinoid (vitamin A and its derivatives) or vitamin K2. However, studies of adjuvant treatment using acyclic retinoid or vitamin K2 failed to show their efficacy for the prevention of recurrence after curative therapy (9,10).

Therefore, there is currently no standard adjuvant treatment

proven to prevent recurrence after curative therapies.

Transcatheter arterial chemoembolization (TACE)

In an issue of *Hepatobiliary Surgery and Nutrition*, Wang *et al.* investigated the efficacy of postoperative adjuvant TACE in patients with two or three HCC lesions smaller than 3 cm (11). Additionally, MVI was detected to determine the efficacy of postoperative adjuvant TACE. A retrospective, single center clinical study was designed that included patients treated by curative hepatic resection, defined as no residual tumor and a negative resection margin based on histological examination. All patients received postoperative adjuvant TACE at 1–3 months after the surgical resection according to the physician's recommendation. The study enrolled 271 patients: 123 patients were assigned to the postoperative adjuvant TACE group, and the remaining 148 patients composed the non-TACE group. There were 44 (35.8%) MVI-positive patients in the adjuvant TACE group and 84 (56.8%) MVI-positive patients in the non-TACE group. The median follow-up time was 63.3 months (range, 3.87–98.97 months).

Among MVI-positive patients, disease-free survival (DFS) was significantly better in patients treated with adjuvant TACE (median DFS, 22.2 *vs.* 7.8 months; P=0.038). OS was significantly longer in patients treated with adjuvant TACE than in those without TACE (P=0.005). Among patients without MVI, DFS was similar between those with or without adjuvant TACE (median DFS, 37.1 *vs.* 25.9 months; P=0.47), and OS showed similar results (P=0.523).

The results of this study indicate that TACE may be effective for preventing postoperative recurrence only in patients with MVI, which was confirmed in the postoperative pathological study. However, the effect of postoperative TACE cannot be predicted without a detailed postoperative pathological study. The identification of a biomarker for predicting MVI before surgery would be desirable to determine the routine clinical use of TACE in this patient subgroup.

The results of this study could have a considerable effect on the prevention of recurrence in MVI-positive HCC patients receiving adjuvant TACE treatment after confirmation using postoperative pathological specimens. However, the study had some limitations. As indicated by the authors, the study was performed retrospectively in patients from a single medical center, and selection bias was inevitable. Further prospective studies of adjuvant TACE therapy including a larger number of HCC patients with MVI are warranted.

Future perspectives

A recent breakthrough in oncology is the advent of immune checkpoint inhibitors, namely, monoclonal antibodies against PD-1 that promote the anticancer immune response. Immune checkpoint inhibitors are currently approved for the treatment of a wide range of malignancies, and have shown durable responses in the metastatic setting far exceeding the expectations of conventional chemotherapy. Although the reported adverse events differ from all known side-effects generated by cytotoxic therapies (chemotherapy, radiotherapy), their severity is generally mild. Therefore, many clinical trials of immune checkpoint inhibitors (PD-1/PD-L1 antibody) and combination therapy with targeted agents (lenvatinib, bevacizumab) or other checkpoint inhibitors such as CTLA-4 are ongoing in HCC (12-14). Among them, the CheckMate 9DX trial, a phase III trial comparing nivolumab and placebo in adjuvant setting after curative therapy, is currently ongoing (14). The trial is based on the notion that resection and ablation release neoantigens and increase the recognition by dendritic cells, thereby improving the immune response and the attack on residual cancer cells after curative therapy. The results of this trial are eagerly awaited.

Conclusions

There is currently no standard of care for adjuvant therapy in HCC after curative treatments because evidence is limited in HCC patients after potentially curative treatment. Although a retrospective study by Wang *et al.* (11) showed benefit in suppressing recurrence after resection in patients with MVI, further randomized prospective studies are needed to confirm this scenario is really effective. Finally, the results of a global phase III trial of nivolumab after curative therapy are eagerly awaited.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

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