Editorial

Evolution of systemic therapy for advanced-stage hepatocellular carcinoma

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Since the introduction of sorafenib in 2007 (1), a tyrosine kinase inhibitor (TKI), there have been notable advancements in systemic therapy for advanced-stage hepatocellular carcinoma (HCC). Although the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines regarding the management of HCC was published in 2018 (2), recent progress, including the advent of several immune checkpoint inhibitors (ICIs), necessitated the revision of this guideline. Therefore, the EASL published a position paper to address the additional improvements on systemic therapy for HCC (3). Here, we aimed to summarize this position paper and comment on some updated points.

First- and second-line treatment options

Along with sorafenib, lenvatinib and combination of atezolizumab and bevacizumab (atezo-bev) are recommended as first-line therapies in treatment-naïve patients with unresectable HCC. Lenvatinib provided non-inferior overall survival (OS) compared to sorafenib (4). The IMbrave 150 study proved that patients who received atezo-bev had superior OS [hazard ratio (HR) =0.58; 95% confidence interval (CI): 0.42–0.79; P<0.001] as well as progression-free survival (PFS) (HR =0.59; 95% CI: 0.47–0.76; P<0.001) than those treated with sorafenib (5). Significant improvement in OS was maintained with a prolonged follow-up of this trial (6).

For those who experienced disease progression after sorafenib, regorafenib and cabozantinib were proven to prolong OS compared to placebo (7-9). Ramucirumab, an anti-angiogenic antibody, can be used as a second-line treatment, although its benefit is only restricted to patients with serum alpha-fetoprotein (AFP) ≥400 ng/mL (10). Pembrolizumab and combination of nivolumab and ipilimumab were also approved for second-line therapies (11-13).

It is notable that OS of patients with HCC who received systemic treatment has improved gradually over the past 15 years. The median OS of patients treated with sorafenib has been prolonged from 10.7 months in the SHARP trial to 12.3 months in the REFLECT and finally to 13.4 months in the IMbrave 150 studies (1,4,5). Furthermore, overall response rate (ORR) increased from less than 10% with TKIs to approximately 30% with combinational treatment. Several factors including the utility of subsequent treatment, better care for liver cirrhosis, and timely initiation of systemic therapy are assumed to have contributed to this improvement. However, the authors emphasized that the evidence of efficacy provided by several trials should not be generalized indiscriminately to patients in early-stage HCC or to those with poor liver function, since most of the study populations consisted of Barcelona Clinic Liver Cancer (BCLC) stage C HCCs and patients with Eastern Cooperative Oncology Group performance status of 0 or 1 and Child-Pugh class A liver function.

Considerations before the initiation of systemic therapy

Once a patient with HCC is identified as a suitable candidate for systemic therapy, atezo-bev should be considered first. To receive atezo-bev, patients should not

require full-dose anticoagulants and those with chronic hepatitis B should take antivirals to maintain a viral DNA less than 500 IU/mL. In addition, autoimmune disease is one of the major concerns regarding the use of ICIs. Cardiac or central nervous system involvement of autoimmune disease is absolute contraindication. ICIs are not contraindicated, however, for autoimmune diseases that do not cause organ malfunction. For example, patients with hypothyroidism, type I diabetes, limited psoriasis, vitiligo, or mild asthma can receive atezo-bev unless the evidence of declining organ function is identified. If immunosuppression is required in those with Graves' disease or systemic lupus erythematous, TKI can be a better choice. Since the safety of ICIs among autoimmune disorder patients was evaluated within small retrospective studies, caution is needed until more data is available, especially in HCC patients with autoimmune hepatitis or primary biliary cholangitis.

The use of antiangiogenics, such as bevacizumab and TKIs, is restricted by cardiovascular events and a history of bleeding. Cardiovascular events which contraindicate antiangiogenics include cerebral vascular accidents, ischemic heart disease, moderate to severe congestive heart failure, and critical arrhythmias. Any recent major bleeding event, especially hemoptysis or gastrointestinal bleeding, contraindicates atezo-bev and TKIs. Atezo-bev is also inhibited in patients with untreated esophageal varix at high risk of bleeding. Although bevacizumab does not worsen portal hypertension, it can cause life-threatening variceal bleeding by interfering with clot and wound formation. Therefore, evaluation of esophageal and gastric varices, at least within the last 6 months, is required to start atezo-bev. If endoscopic ligation is performed to control high-risk varices, treatment with atezo-bev or TKI should be delayed for approximately 1 month to ensure safety.

Evaluating the efficacy of systemic treatment

When evaluating the response to a systemic agent, three factors should be must be taken into account. First, it is notable that not all progression events have the same impact on the prognosis of HCC patients. For example, progression pattern following sorafenib therapy is associated with prognosis; new vessel invasion or extrahepatic metastases are associated with the poorest outcome. Therefore, limited progression inside the liver may not be sufficient to warrant switching to alternative treatments. Second, due to the action mechanism of ICIs, pseudoprogression may occur after treatment initiation and it can be misclassified as progressive disease. Although pseudoprogression occurs in less than 10% of patients, definite progression to change regimen should be confirmed at least after 4 weeks of treatment. Third, clinicians should not discontinue the ongoing treatment based on an increased level of AFP alone in the absence of radiological evidence of disease progression. Responses to atezo-bev or TKIs are known to be associated with AFP levels, but clinicians should not change treatment regimen prematurely. To preserve the advantages of sequential treatment, it is important to take into account radiological response as well as liver function, overall condition, and trend of progression.

Further recent updates

After the remarkable success of atezo-bev in advanced-stage HCC, treatment and research paradigm shifted toward including immunotherapies. Even after the release of this position paper, several revisions are still in progress. Especially, efficacy of durvalumab plus tremelimumab (durva-treme) was proven in the HIMALAYA trial, the first successful combination of PD-L1 and CTLA-4 antagonists (14). Patients were randomized into durva-treme, durvalumab, or sorafenib group. The durva-treme group demonstrated a 22% lower risk of death compared to the sorafenib group. Durvalumab alone was also confirmed to be non-inferior to sorafenib. There was no significant difference in terms of PFS between the groups. The ORR of the durva-treme group and durvalumab alone group was estimated 20.1% and 17.0%, respectively. The adverse events of grade 3 or higher were confirmed in 25.8% in the durva-treme group. However, adverse events such as hypertension, proteinuria, and hand-foot skin reaction, which were frequently observed in patients who received anti-PD-1/PD-L1 antibody plus anti-VEGF/TKI combination therapy, occurred rarely.

Based on the results of HIMALAYA trial, a recent BCLC guideline published in 2022 recommends atezo-bev and durva-treme as first-line therapies in patients with BCLC stage C HCC (15). For those not suitable for these regimens, sorafenib, lenvatinib, or durvalumab can be considered as an alternative option. Reflecting the outcomes of recent trials, expected survival in patients with advanced-stage HCC was specified as longer than 2 years, which is far extended compared to that in the 2018 BCLC guideline (>1 year). Although regorafenib, cabozantinib, or ramucirumab can be used after sorafenib, optimal treatment options were not established after the failure of initial atezo-

bev, durva-treme, or lenvatinib therapy.

Systemic treatment for advanced-stage HCC has been evolved dramatically for the last 15 years, and the advent of various TKIs and ICIs is expected to accelerate further progress. Therefore, clinicians should keep up with the updated guidelines for HCC management. In addition, further research is warranted to establish a subsequent treatment strategy after atezo-bev, durva-treme, or lenvatinib failure.

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