Systemic therapy: recent updates on targeted & immune therapy

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Lecture : Hepatocellular carcinoma (HCC) develops in the condition of uncontrolled growth of hepatic cells caused by the genetic alterations in complex signaling cascades. Therefore, we can expect the effect of targeted agents attacking important targets in carcinogenic pathways along with minimizing general adverse effects. However, we have failed to find the dominant signal pathways in hepatocarcinogenesis, yet.
Sorafenib is a multikinase inhibitor especially inhibiting serine/threonine kinases Raf-1/B-Raf, tyrosine kinases VEGFR-2/-3 and PDGFR-β, which suppresses cancer progression and angiogenesis. Sorafenib is the first systemic therapy prolonged survival significantly in HCC patients. After that sorafenib not only established a proof of concept for the use of multi-kinase inhibitors strategy for the treatment of HCC, but also is the reference standard for systemic therapy for HCC patients.
Nevertheless, subsequent clinical trials using targeted agents have failed in succession for about 10 years. The agents which failed to prove their activity in HCC were sunitinib, linifanib, brivanib, nintedanib in the first-line treatment and axitinib, ramucirumab, brivanib, erlotinib, everolimus, tivantinib, ADI-PEG20 in the second-line treatment after sorafenib failure.
Recently, lenvatinib, another angiogenesis inhibitor, showed non-inferior overall survival in the 1st-line treatment compared with sorafenib in the REFLECT trial. Lenvatinib also showed rather superior response rate, progression free survival, time to progression and preferable toxicity profiles.
For the patients who failed sorafenib treatment, regorafenib and cabozantinib, mainly angiogenesis inhibitors overcame placebo control in RESORCE and CELESTIAL trials.
In addition, nivolumab showed meaningful results for HCC in phase II checkmate 040 trial.
We have now 2 options in the 1st-line and 3 options after sorafenib failure in HCC, with angiogenesis inhibitor or immune checkpoint inhibitor.
However, the current effects of systemic treatments for HCC are far from satisfaction as ever.
By looking at the trials currently conducted for HCC, we are discussing ways to improve the prognosis of HCC patients.