Editorial

Precision oncology and molecular therapies for hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is one of the most lethal malignant tumors worldwide. It is classified by a continuously increasing morbidity, low resectable rate, high relapse rate after radical surgery, limited response to medication, and high mortality (1). To date, more than 850,000 new cases are diagnosed each year, and the annual incidence of HCC is expected to exceed 1 million cases soon. In the United States, the 5-year overall survival (OS) rate of HCC patients is less than 12%, making it the second leading cause of cancer-related death (2). The majority (90%) of HCC cases can be attributed to the infection of hepatitis B virus or hepatitis C virus, excessive drinking, and chronic metabolic disease associated with diabetes and obesity. Although surgery is still the mainstay treatment, modern treatments such as neoadjuvant chemotherapy and auxiliary strategies have led to momentous improvements in survival.

In most parts of the world, treatment allocation of HCC is based on the modified Barcelona Clinic Liver Cancer (BCLC) staging system endorsed by the European and American Liver Research Association. With assessments of tumor burden, liver function, and general health, each HCC patient can be provided with the best treatment. In developed countries, surveillance programs result in 40–50% of patients being diagnosed with early-stage HCC, a stage where potentially curative treatments are available. Patients with intermediate-stage HCC can be treated with local therapy, whereas patients with progressive disease also can be treated with systemic therapy. Overall, about 50% of patients are treated with systemic therapy in the course of disease development (1). However, most patients in developing countries or regions are diagnosed at advanced stages, with limited alternative treatment options available; in such a circumstance, poor treatment outcomes are inevitable.

Intervention strategies of HCC, including HCC screening, surveillance, and chemoprevention interventions, are essential for the success of individualized, risk-based, and tailored treatment regimens. Current precision medicine approaches require molecular information of specimens obtained from liver tissue biopsies, however, the patient reluctance to perform diagnostic biopsies and the heterogeneity of HCC hinder the effectiveness of preventive interventions. Therefore, less invasive techniques of specimen collection may have broader applicability. Precision medicine breaks the concept of "one size fits all" in the treatment of HCC and no longer diagnoses and treats patients based solely on tumor histology, but does so based on specific molecular tumor markers. The 2019 Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma in China stressed that liquid biopsy is one of the most important tools for diagnosis in early stage, and that more importance must be attached to it (3). Some fresh serological biochemical markers are mentioned in the guidelines: circulating tumor cells (CTCs), cell-free circulating microRNA (CFC miRNA), and circulating tumor DNA (ctDNA) are the most frequently mentioned. According to a recent report, a model was successfully established that could diagnose early-stage HCC very accurately using 7 plasma miRNA expression

levels, with a sensitivity of 86.1% and specificity of 76.8%). The sensitivity of this model is approximately 30% higher than that of conventional markers (4). At present, HCC detection kits based on circulating miRNAs have been clinically applied in China. In addition, the development of high-throughput sequencing technology, "massively parallel sequencing" [MPS; or next-generation sequencing (NGS)], enables the vast majority of transcript expressions (including those with minimal expression) to be quantified precisely and analyzed in detail, and allows us to better understand the molecular heterogeneity of HCC (5). Molecular information obtained from MPS may provide key breakthroughs in the future treatment of HCC patients.

High-throughput sequencing technology uses genomics and proteomics, to analyze, identify, and apply biomarkers in large samples or specific types of HCC patients, so as to accurately find therapeutic targets and formulate more accurate diagnosis and treatment plans. Based on the clinical features and high heterogeneity of HCC, for all kinds of primary and secondary liver cancers, the long-term survival and cure of patients are the best treatment outcomes. Surgical treatment is usually assisted by transcatheter arterial chemoembolization (TACE), an interventional procedure needing image-guided in which chemoembolization is used to block the hepatic artery supplying of HCC (6,7). In addition, liver parenchyma-sparing surgery can be performed by minimally invasive and open surgical techniques. Moreover, preserving the largest non-neoplastic liver parenchyma is its core principle of hepatectomy but without tissue-enhancing interventions, such as portal vein embolization (PVE), portal vein ligation (PVL) and thyroid stimulating hormone (TSH) (8,9). The main disadvantage of PVL and PVE approaches is that both require a wait of several weeks for post-occlusion, although they have been shown to be well tolerated and to effectively trigger regeneration of the contralateral hepatic lobe. The reason is possibly because the intra-abdominal adhesions are extremely grievous. In addition, mounting experimental and clinical evidence has indicated that the probability of progression of metastatic tumors was increased after portal vein occlusion. The finding that liver growth was not sufficient following portal vein occlusion prompted the emergence of other approaches and these strategies can promote liver growth and reduce the interval between stage and stage. For example, a strategy proposed in 2012 included 25 patients with various primary and secondary liver tumors, the treatment strategy involved *in situ* splitting of the liver parenchyma and PVL. In these cases, this technique enabled faster liver hypertrophy, and the time was shortened to an average of 9 days, while the median contralateral residual liver volume increased by 74% (10). This procedure belongs to the TSH family and is called associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). Currently, it is mainly used for colorectal liver metastases and HCC. Various technical improvements have implemented for ALPPS to improve its safety, including PVE-ALPPS, partial ALPPS-laparoscopic ALPPS, tourniquet ALPPS, and mini-ALPPS (11-13). These improvements are characterized by less invasiveness and higher safety. For advanced patients, the superiority of liver resection to non-surgical treatment has been demonstrated in the Asia-Pacific region.

For patients with unresectable HCC, especially those with extrahepatic metastases, the recent emergence of targeted therapies and immunotherapies based on comprehensive molecular analysis of the tumor's genome, transcriptome, and epigenomic analysis has brought hope. High-throughput sequencing technologies have focused on a few genes—such as *TERT*, *TP53*, *CTNNB1*, *ARID1A*, *ADRI2*, *NFE2L2*, and *KEAP1*—with the aim of developing anti-cancer treatments through targeted therapy. In addition, several major aberrant pathways in HCC including telomere maintenance, TP53/cell cycle, WNT/β-catenin, chromatin remodeling, the PI3K/RAS/mTOR pathway, oxidative stress pathway (KEAP1-NRF2 pathway), and angiogenesis have also received extensive attention (14). The treatment efficacy for advanced HCC with cellular immunotherapy after different intervention strategies has been demonstrated in the past few years, and the combination of immunotherapy, including tumor-infiltrating lymphocytes therapy, T cell receptor therapy, chimeric antigen receptor T cell (CAR-T) therapy, and natural killer (NK) cell therapy, with conventional treatment, has also been certified that it can improve patient prognosis. In addition, immunotherapy also can increase OS and lower the recurrence after surgical removal and local tumor ablation.

Despite great progress in early screening and diagnose approaches, therapeutic procedures and molecular therapies, HCC remains an intractable cancer. The successful intervention strategy for HCC, including screening and preventive interventions, requires an individualized, precisely custom-made, and risk-controlled mode. Few HCC patients (<10%) are cured. Most patients

will eventually develop advanced HCC, at this point, only systemic therapies can efficiently slow down the progress of this cancer. However, with the use of potent multikinase inhibitors, the median OS of patients has been improved but still relatively short. Recently, immune checkpoint inhibitors such as programmed cell death-1 (PD-1), programmed cell death-ligand 1 (PD-L1), or cytotoxic T lymphocyte-associated protein-4 (CTLA-4) are applied in clinical practice for HCC. Likewise, the combination of molecularly targeted therapy and immunotherapy is emerging as a tool to enhance the immune system's response to HCC-derived neoantigens. In day-to-day clinical practice, the transition from "grading and staging" to "treatment hierarchy" is critical to systematically direct the choice of HCC treatment to the most effective options on an individual basis. In the future, liver microenvironment-relevant studies and a deep overlook of liver heterogeneity are needed to improve the therapeutic effect of HCC.

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References

1. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
2. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. J Clin Gastroenterol 2013;47 Suppl:S2-6.
3. Zhou J, Sun H, Wang Z, et al. Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition). Liver Cancer 2020;9:682-720.
4. Zhou J, Huang A, Yang XR. Liquid Biopsy and its Potential for Management of Hepatocellular Carcinoma. J Gastrointest Cancer 2016;47:157-67.
5. Martin SP, Wang XW. The evolving landscape of precision medicine in primary liver cancer. Hepat Oncol 2019;6:HEP12.
6. Wang H, Yu H, Qian YW, et al. Postoperative adjuvant transcatheter arterial chemoembolization improves the prognosis of patients with huge hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2021;20:232-9.
7. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301-14.
8. Viganò L, Torzilli G, Troisi R, et al. Minor Hepatectomies: Focusing a Blurred Picture: Analysis of the Outcome of 4471 Open Resections in Patients Without Cirrhosis. Ann Surg 2019;270:842-51.
9. Maupoey Ibáñez J, Montalvá Orón EM, Boscà Robledo A, et al. From conventional two-stage hepatectomy to ALPPS: Fifteen years of experience in a hepatobiliary surgery unit. Hepatobiliary Pancreat Dis Int 2021;20:542-50.
10. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 2012;255:405-14.
11. Linecker M, Kambakamba P, Reiner CS, et al. How much liver needs to be transected in ALPPS? A translational study investigating the concept of less invasiveness. Surgery 2017;161:453-64.
12. Petrowsky H, Györi G, de Oliveira M, et al. Is partial-

ALPPS safer than ALPPS? A single-center experience. Ann Surg 2015;261:e90-2.
13. de Santibañes E, Alvarez FA, Ardiles V, et al. Inverting the ALPPS paradigm by minimizing first stage impact: the Mini-ALPPS technique. Langenbecks Arch Surg 2016;401:557-63.
14. He B, Lu C, Zheng G, et al. Combination therapeutics in complex diseases. J Cell Mol Med 2016;20:2231-40.

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