Viewpoint

Splenectomy may facilitate systemic therapy for advanced hepatocellular carcinoma with hypersplenism

Er-Lei Zhang, Zun-Yi Zhang, Zhi-Yong Huang^

Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Correspondence to: Dr. Zhi-Yong Huang, MD. Professor of Surgery, Hepatic Surgical Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jie Fang Avenue, Wuhan 430030, China. Email: huangzy@tjh.tjmu.edu.cn.

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Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths globally and is widely considered to be a serious threat to human health. In clinical settings, more than 70% of HCCs are unresectable at initial diagnosis and are therefore treated with palliative rather than curative treatment, which severely reduces the overall survival of HCC patients (1). In China, most HCCs develop as a result of chronic liver disease (mainly hepatitis B virus infection) and are often accompanied by clinical portal hypertension (PH). PH induces splenomegaly and hypersplenism (defined as pathologic spleen). Severe PH and hypersplenism may preclude HCC patients from curative resection, and local treatments in the early stage due to pancytopenia, which are also equally important negative factors for the systemic therapy of advanced HCCs (2). For HCC patients diagnosed in the advanced stages, including extrahepatic spread, vascular invasion, and tumor-related symptoms, systemic therapy is recommended if available. In recent years, new options for systemic therapy have been continually developed for the treatment of advanced HCCs, such as small-molecule tyrosine kinase inhibitors and immune checkpoint inhibitors. Although recent advancements in systemic therapy have dramatically improved the long-term outcomes of advanced HCC patients, the severe adverse effects of systemic therapy with these agents should be carefully considered by clinicians.

Systemic therapy-related hematologic toxicities are rare but clinically serious and potentially life-threatening adverse events. Previous studies have indicated that the proportion of advanced HCC patients undergoing systemic therapy who had high-grade (grades 3–5) leukopenia and thrombocytopenia were up to 4.2% and 12%, respectively (3). Moreover, local treatments such as transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) often receive a combined treatment modality with systemic therapy for advanced HCC. It is worth noting that local treatments based on chemotherapy will also restrict bone marrow function, and thus, the combination drug therapy will aggravate myelosuppression. In fact, patients with advanced HCC may have two kinds of liver disease: malignant tumor and liver-cirrhosis-associated hypersplenism. Meanwhile, clinicians are faced with pancytopenia due to hypersplenism and systemic therapy-related hematologic toxicities in these settings. Therefore, in the current era of systemic therapy combinationed with local treatments, dealing with pancytopenia due to hypersplenism and myelosuppression is crucial for the treatment of advanced HCC patients with hypersplenism, especially for those with a history of esophagogastric variceal bleeding.

Splenectomy can improve hypersplenism and liver dysfunction, and decrease the tendency of esophagogastric variceal bleeding. Accordingly, we speculate that splenectomy may be a promising method for advanced HCC patients with severe hypersplenism. Firstly, treatment-related drugs for advanced HCC can restrict bone marrow function, which prevents advanced HCC patients with hypersplenism from receiving a sufficient dose of drugs to be effective, or may even induce drug withdrawal. Therefore, these patients may have an even

^ ORCID: 0000-0002-2239-0674.

poorer prognosis than those who receive a more sufficient dose of drugs. Based on this, splenectomy may be a permanent method to overcome the problems of leukopenia and thrombocytopenia, which could avoid treatment interruptions or dose reduction for advanced HCC patients. In 2008, Hirooka *et al.* (4) indicated that splenectomy was an efficient method for advanced HCC patients with hypersplenism treated with chemotherapy. The objective response rate of the splenectomy group was significantly better than that of the non-splenectomy group (68.1% *vs.* 16.6%, P<0.001).

Secondly, splenectomy can help to improve liver fibrosis, restoring immune function and reducing portal venous pressure, which will significantly prolong the survival of advanced HCC patients with cirrhotic hypersplenism (5,6). It has been reported that splenectomy can inhibit the progression of HCC and prolong the overall survival of orthotopic and metastatic mice by reducing the proportion of myeloid-derived suppressor cells (MDSCs) in the peripheral blood and liver tumors, which was identified as a predictive marker for the cancer immunotherapy response (7). This suggested that synchronous splenectomy could be considered an adjuvant therapy to treat HCC. Thirdly, as splenectomy improves liver function, treatment discontinuation due to the systemic therapy-induced deterioration of liver function may also be avoided (8). In addition, for advanced HCC patients with severe hypersplenism and esophagogastric varices, splenectomy and devascularization will prevent upper gastrointestinal bleeding, which could improve the quality of life of these patients. However, whether splenectomy could enhance the efficacy of systemic therapy needs to be further studied in the future.

With the development of surgical techniques and equipments, especially in laparoscopic surgery, splenectomy has been performed with increasing ease and safety in hepatic surgery centers. The application of splenectomy in advanced HCC patients with hypersplenism, especially for those with poor liver function and esophagogastric varices, may be a promising method in clinical practice.

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Footnote

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