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【 EDITORIAL 】

Targeting Angiogenesis for Advanced Hepatocellular Carcinoma

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Hepatocellular carcinomas (HCCs) are highly vascularized tumors with a predominant arterial blood flow. Therefore, transarterial chemoembolization (TACE) has played a central role in treating unresectable HCC (uHCC). In 2008, sorafenib, a protein kinase inhibitor targeting vascular endothelial growth factor (VEGF) receptor, platelet-derived growth factor receptor, c-Kit and RAF was approved as the first molecular-targeted agent (MTA) for uHCC (1). Sorafenib was associated with a high incidence of adverse events (AEs) such as diarrhea and hand-foot skin reaction; therefore, an effective and tolerable novel first-line agent and a second-line agent after sorafenib failure were long-awaited (2). In 2018, lenvatinib was finally approved as a novel first-line (3), and regorafenib and anti-VEGF receptor-2 monoclonal antibody (mAb) ramucirumab were approved as second-line MTAs in 2017 and 2019 (4, 5). Lenvatinib has become a commonly used first-line MTA due to its high response rate and relatively manageable AE profile (6). Regorafenib and ramucirumab were proven effective in clinical trials when comparing them with a placebo after sorafenib failure; however, there is no evidence of their efficacy after lenvatinib failure. Kasuya et al. recently published the outcomes of seven patients with uHCC treated with ramucirumab after lenvatinib failure in Internal Medicine (7). They reported that the disease control rate was 28.6%, and there was no deterioration in the liver function after six weeks. Although the number of cases is not large enough and further studies with a longer follow-up period are needed, it is significant to show that ramucirumab may be effective even after lenvatinib failure.

As evidenced by the development of MTAs, targeting angiogenesis is an essential factor of HCC treatment. Meanwhile, the development of immunotherapy with immune checkpoint inhibitors (ICIs) including anti-programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) mAbs has led to a breakthrough in the therapeutic approach for cancer (8). Recently, the synergistic effects of anti-angiogenesis and ICIs have been elucidated. VEGF-A, which is mainly produced by tumor cells and tumor-associated macrophages, directly increases the recruitment of regulatory T cells (Tregs) and the release of immunosuppressive cytokines (9). VEGF-A also induces expression of Fas ligand by the tumor endothelium, which is associated with low T cell infiltration and the predominance of Tregs (10). Therefore, anti-VEGF therapy increases intratumoral infiltration and the survival of cytotoxic T cells by normalizing vascularization and modulating the immune microenvironment, thus creating a synergistic effect with ICIs. Furthermore, recent studies have revealed that thymocyte selection-associated high mobility group box protein called TOX plays a pivotal role in the development and maintenance of exhausted T cells (11, 12). TOX reduces PD-1 degradation and promotes PD-1 translocation to the cell surface, thus maintaining high PD-1 expression at the cell surface of T cells (13). Kim et al. recently reported that VEGF-A drives TOX-dependent T cell exhaustion; therefore, the combined blockade of PD-1/PD-L1 and VEGF pathways could effectively restore the antitumor function of T cells (14).

Several clinical trials of anti-PD-1/PD-L1 and anti-VEGF combination therapy have been conducted, and the result of phase 3 IMbrave 150 study evaluating anti-PD-L1 mAb atezolizumab in combination with anti-VEGF mAb bevacizumab for patients with uHCC was recently reported (15). Atezolizumab combined with bevacizumab significantly improved both the overall and progression-free survival, compared to sorafenib. While the combination of antiangiogenics and ICIs is expected to be the primary treatment for uHCC in the near future, it is essential to address multidisciplinary treatment, including surgery and TACE, and identify biomarkers to predict the treatment response.

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