Editorial

Focus on immune-related adverse events (irAEs) in immunotherapy of hepatobiliary malignancies

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There has been a chronic lack of effective treatment for hepatobiliary malignancies, and overall survival of comprehensive therapy, including targeted chemotherapy, is still low (1,2). A series of immune checkpoint blockade drugs have offered new choices for patients with advanced hepatobiliary malignancies. Although the efficacy of a PD-1/PD-L1 blockade is not satisfactory, comprehensive therapy combining traditional chemotherapy, targeted therapy, local treatment, and radiotherapy often have satisfactory results (3). The drugs including nivolumab, pembrolizumab, have been approved successively for hepatocellular carcinoma (4,5), satisfactory objective response rate (ORR), and disease control rate (DCR) were obtained with tyrosine kinase inhibitor (TKI) drugs (6). Therefore, immunotherapy is becoming a key part of the treatment for advanced hepatobiliary tumors.

Immune checkpoint inhibitors block the PD-1 and PD-L1 pathway, which activates the function of the local T cells while increasing the effects of killing tumors. However, at the same time, non-tissue specific binding may result in abnormal activation of T cells in normal tissues with immune-related side effects. Now immune-related adverse effects known to affect all body systems, include endocrine systems (such as hypophysitis, hypothyroidism, pancreatitis, etc.), colitis, and rash, while rarely include autoimmune pneumonitis, myocarditis, etc. Some severe patients can lead to death, such as the death rate of myocarditis is about 50% (7-9). Due to the lack of experience previously, doctors are often unable to find immune-related side effects early, and many patients may delay diagnosis and treatment.

Now, immune-related adverse events (irAEs) are mainly applied to the irAE classification system for evaluation. Grade 1–2 of adverse reactions need symptomatic management and low dose hormonotherapy, while grades 3 and 4 need to stop using PD-1/PD-L1 blockade if it necessarily requires steroid pulse therapy. However, among a few patients with myocarditis and autoimmune pneumonitis, the use of TNF-α and IL-6 monoclonal antibodies have been successfully controlled in a few case reports. At the same time, a large number of patients participate in the combination treatments at present, which puts forward higher requirements for doctors to distinguish the adverse effects of the treatment of PD-1 and targeted agents. As the adverse effects related to immunotherapy involve multiple disciplines, it is more important to emphasize the multidisciplinary collaboration treatment, including oncology, endocrinology, immunology, respiratory medicine, cardiology, and emergency department (8).

Although immune-related side effects may bring a series of problems during immunotherapy, the occurrence of side effects is also associated with good therapeutic responses in some patients. Recently, several studies have shown that irAEs are associated with better therapeutic effects when PD-1 antibody is used in patients with melanoma and non-small cell lung cancer (NSCLC) and is particularly the presence of thyroid, and other endocrine-related irAE tends to predict the better therapeutic efficacy of immunotherapy. Autoantibodies may play an important role in the emergence of irAEs and clinical benefits. The study suggests that preexisting autoantibodies may be associated with the development of irAEs and clinical benefits. The presence of autoantibodies is a marker of therapeutic efficacy during

treatment, particularly anti-thyroid antibodies (10,11).

In the future, several questions need to be clarified about the adverse effects of immunotherapy: (I) currently, few studies research on the characteristics of local immune status changes in organs involved irAEs. The relationship of changes between the local immune environment in normal tissues and the immune microenvironment in tumors remains unclear. (II) There are still no effective means to predict the time and severity of adverse reactions in immunotherapy. Early biomarker screening is of great significance in predicting the occurrence of grade 3–4 irAE and intervention at an early stage. (III) Now organs have certain specificity, which affected by adverse events of different PD-1/PD-L1 agents in the treatment of different tumor species, and the mechanism is not completely clear. So, understanding the time and space distribution of side effects of different drugs has guiding significance for drug selection and adjustment. (IV) Due to the unique mechanism of immunotherapy, about 10% of patients may appear pseudoprogression, however, to determine whether progress needs to wait for re-evaluation. Currently, there is no effective tool to distinguish the differences between hyperprogression for the first time. The appearance of irAE and the dynamic changes of the autoantibodies could be potential monitoring indicators.

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