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EDITORIAL

Immunotherapy: the blockbuster in cancer treatment

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Cancer immunotherapies, especially immune checkpoint inhibitors (ICIs), have changed the landscape of treatment in various types of cancer ever since 2013, when cancer immunotherapy was rated as the breakthrough of the year by Science journal. Immune checkpoint proteins, such as PD-1, could facilitate tumor immune evasion by suppressing T-cell function via binding to PD-L1, which is often expressed on tumor cell surface. ICIs could release the immune break and remotivate T-cells to attack tumor cells. Due to the unique mechanism of action, ICIs have been shown to be effective in many malignancies, both solid tumors and hematologic cancers, such as melanoma, non-small cell lung cancer, gastric cancer, head and neck squamous cell cancer, Hodgkin lymphoma, extranodal NK/T-cell lymphoma, and so on. Moreover, there has been an avalanche of clinical trials underway in the whole pipeline of cancer treatment.

Despite the enormous excitement cancer immunotherapies have brought to us, there are a lot of unknowns and great unmet needs in clinical practice. In relapsed or refractory Hodgkin lymphoma, ICIs could attain an overall response rate (ORR) of about 80%, but the complete response rate (CRR) being less than 30%. In extranodal NK/T-cell lymphoma, sintilimab (one PD-1 blockade agent) monotherapy achieved an ORR of 68%, while the CRR was only 7%. Thus, it is critical to explore the underlying mechanisms that hinder T cells completely eliminating tumor cells. Recent researches demonstrated that epigenetic modifications in the tumor microenvironment could render exhaustion of T cells, such as methylation and deacetylation, which promotes the combination of anti-PD-1 antibodies and hypomethylating agents (HMAs) or histone deacetylase inhibitors (HDACs) in clinical trials. Combined low-dose decitabine (one type of HMAs) and PD-1 inhibitor could deepen the response to a CRR of more than 60% in Hodgkin lymphoma, and a CRR of 62.5% was achieved in relapsed/refractory extranodal NK/T-cell lymphoma when chidamide (one type of HDACs) adding to sintilimab. Furthermore, more reliable biomarkers predicting the response of ICIs should be defined to facilitate precision medicine in cancer immunotherapies. Conflicting results exist regarding the predicting role of PD-L1 expression intensity in diverse clinical trials and malignancies. A recent study has found PD-L1 mutation (structural rearrangements) to be highly related to treatment response of ICIs in NK/T-cell lymphoma, in which all four patients' tumors that harbored PD-L1 mutation responded to pembrolizumab, while none of the 10 patients that were regarded as non-responders had this mutation. Unexpectedly, PD-L1 positivity was useless in predicting response of ICIs in that study, which seems contrary to previous studies done in solid tumors. Thus, there is still a long way to go before we can successfully step into the era of precision medicine.

Each coin has two sides. Disinhibition of T-cell function can lead to a variety of immune related adverse events (irAEs) while effectively killing tumor cells, although the detailed mechanisms underlying irAEs are largely unknown. IrAEs can mimic autoimmune diseases by releasing autoantibodies, or trigger cytokine releasing syndrome (CRS) by production of bulking cytokines in the process of T-cell function. Though many documented irAEs are mild to moderate, increasing fatal cases have been reported due to widespread use of cancer immunotherapies, especially in the elderly due to more comorbidities. Thus, it is of urgent need to establish a scale, which should help physicians evaluating the risk of severe irAEs in all kinds of patients. After balancing the potential risks and benefits, cancer immunotherapies could eventually shift the paradigm of cancer treatment.

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