Cancer Immunotherapy Side Effects on the Nervous System

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Abstract

In many areas of clinical oncology and haematology, immunotherapy has become a potent therapeutic strategy. The era of immune checkpoint inhibitors has begun with the approval of ipilimumab, a monoclonal antibody that targets the immune cell receptor CTLA-4. PD-1 pathway-targeting antibodies have increased the class of immune checkpoint drugs that have received clinical approval. Novel antibodies that target different immunological checkpoints are also being tested in clinic. Bispecific antibodies and adoptive T cell transfer using immune cells modified to express chimeric antigen receptors have both recently received approvals for use in specific purposes. Bispecific antibodies link T cells directly to tumour cells. More and more frequently, neurological side effects linked to the use of these innovative immunotherapeutic approaches are being identified.

Keywords: Immune checkpoint inhibitor • PD-1 • CTLA-4 • Neurotoxicity • CNS • Nerve • CAR T cell •Blinatumomab • CD19

Introduction

Immunotherapy in cancer

Inhibitors of immune checkpoints: A class of monoclonal antibodies known as Immune Checkpoint Inhibitors (ICI) aims to restore and enhance the anti-tumor function of cytotoxic T cells. They work by obstructing inhibitory signals, which lower T cell activation. This can be done by attaching to the appropriate ligand, which is present on antigen-presenting or tumour cells, or by inhibiting immune cell receptors expressed on T cells. Numerous clinical trials on a variety of cancer types have proven the therapeutic effectiveness of this idea. Despite the fact that medications targeting the Programmed Cell Death-1 (PD-1) pathway currently predominate the market, the first ICI to receive clinical approval was ipilimumab, which binds to CTLA-4 and obviates the molecule's inhibitory effect. A growing number of medications specifically target the immune cell receptor PD-1 or its main ligand PD-L1. Both tumour cells and antigen-presenting cells have the ability to express the latter. T cell activity is reduced when one of PD-1's ligands engages it. Drugs that target PD-1 or PD-L1 are administered in an effort to activate anergic but potentially cancer-targeting T cells. Inhibitors of PD-1/PD-L1 have demonstrated their therapeutic efficacy against various cancers. As a result, clinical oncology has begun using PD-1/PD-L1 inhibitors more frequently lately. Novel medications that target immune checkpoint molecules including TIGIT, GITR, or LAG3 are also being tested in clinical settings.

Issues related to the use of immune checkpoint inhibitors: Various side effects linked to the administration of ICI were detected as early as during clinical development. The precise pathophysiological mechanisms causing overshooting T cell activation are still poorly known, despite the fact that it seems evident that the majority, if not all, side effects may be related to it. Furthermore, it is yet unknown if the timing, length, and severity of the immune response vary depending on the organ. The adverse reactions to adverse reactions to ICI, also known as "Immune-Related Adverse Events" (irAE), are thought to be an inflammatory response that is fueled by a variety of causes. The T cell response against antigens that are also expressed in healthy tissue is one of them. It's possible that this circumstance, in which T cells are recognising antigens shared by tumour cells and healthy tissue, somewhat resembles classic paraneoplastic diseases. Checkpoint inhibition may also result in higher concentrations of preexisting autoantibodies, which can then recognise and attack antigens produced on healthy tissue. Pro-inflammatory cytokine levels that are elevated may be key contributors to the emergence of immune-related toxicities and act as biomarkers. Finally, inflammation may also be caused by complement system activation.

Myasthenic disorders

The anatomical link connecting the muscle and the peripheral nerve is known as the neuro-muscular junction. Autoantibodies interacting with acetylcholine receptors on the presynaptic membrane cause classical myasthenia gravis. Myasthenic syndromes in individuals receiving ICI are being described in an increasing number of studies. Diplopia and bilateral ptosis are frequent features of the clinical presentation, which is similar to ocular myasthenia. The symptoms of generalised myasthenia include weakness in additional muscle groups, dysphagia, and dyspnea. In extreme cases, patients with this condition even need intensive care. Most individuals who get treatment with checkpoint inhibitors have new-onset myasthenia, but it has also been noted that pre-existing conditions can worsen. Myasthenic symptoms were more frequently noticed after PD-1 blockage, but cases related with anti-CTLA-4 therapy were also recorded, and the majority of patients developed clinical symptoms 6 to 8 weeks after starting immunotherapy. However, only about 60% of patients exhibited cholinergic receptor antibodies. Interleukin (IL)-17 may contribute to the emergence of myasthenic syndromes following ICI therapy, according to preliminary evidence. It's important to note that myositis and myocarditis can accompany myasthenic disorders. An acetylcholinesterase inhibitor, such as pyridostigmine, may be beneficial for patients with myasthenic syndromes. Similar to classical myasthenia gravis, extra steroid therapy may be advantageous but carries the chance of a brief clinical decline at the start of treatment. If these methods are ineffective, rising treatment options include IVIG or plasmapheresis.

Conclusion

Drugs that function outside of the CTLA-4 or PD1/PD-L1 axis are in the final stages of clinical research and could soon be used on a regular basis. As a result, it is reasonable to expect that there will be an increase in the number of people suffering from neurological problems. Similar to this, therapies that are presently only available to a small number of patients, such TRBA constructs or CAR T cells, will spread to more locations and perhaps be approved for use in more cancer indications. Therefore, early and precise diagnosis is essential to begin suitable therapeutic measures and prevent enduring clinical impairments. Patient education prior to treatment beginning, close clinical monitoring, and knowledge of neurological irAE are also important. To define treatment escalation in light of this, more data, particularly from prospective studies, is needed.