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# The Impact of Immunotherapy Drugs on the Human Nervous System

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**Abstract:**

Immunotherapy is rapidly becoming one of the most promising directions in the modern approach to cancer treatment. CAR-T cell therapy, immune checkpoint inhibitors, monoclonal antibodies, and gene therapies have shown great potential in enhancing the quality of life of patients, through the activation of the body's immune system against cancerous cells. In addition to cancer, immunotherapy is being tested in neurodegenerative and neuroinflammatory disorders such as multiple sclerosis and Alzheimer disease. However, these therapies entail certain risks especially with regard to the nervous system. There is increasing evidence that immunotherapies are associated with neurotoxic side effects such as neuroinflammation, encephalitis, cognitive decline and peripheral neuropathy which can greatly affect patient's quality of life. This review focuses on the description of these immunotherapies' mechanisms and clinical use as well as their impact on the CNS and PNS adverse effects. Measures that can help avoid these risks include precision medicine, better gene delivery vectors, and selective treatment approaches, which are very helpful in maximizing the safety and efficacy of immunotherapy. One of the critical issues of further development of these novel therapeutic interventions is the optimization of desired therapeutic outcomes and possible neurological adverse effects.

**Keywords:** Immunotherapy drug; nervous system; Alzheimer disease.

## 1. Introduction

In recent years, immunotherapy has made considerable progress in the field of cancer treatment, providing a new treatment paradigm for a variety of complex diseases, especially oncology. By enhancing or altering the response of the immune system, immunotherapies such as CAR-T cell therapy and immune checkpoint inhibitors (ICIs) have demonstrated long-lasting effects and low toxicity in targeting immune receptors on the surface of T lymphocytes and eliminating tumor cells [1]. In addition to oncol-

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ogy, the application of immunotherapy strategies has also begun to expand to the treatment of neurodegenerative diseases (such as multiple sclerosis and Alzheimer‘s disease (AD)) and psychiatric disorders (such as depression), demonstrating that these therapies have great medical potential in combating neuroinflammation-induced neurodegeneration [2]. However, despite the promising therapeutic prospects of immunotherapy, their subsequent effects on the nervous system are worrying, as emerging evidence suggests that these powerful treatments may have lasting effects on the central and peripheral nervous systems [3]. The causes of some common neurodegenerative diseases are still not fully understood. In addition, the course and severity of the disease vary greatly among patients, which greatly affects the outcome of effective treatment.

This section aims to discuss the various immunotherapy modalities currently in use, focusing on their principles, clinical applications, and known effects on the nervous system. Specifically, it will examine four immunotherapies in particular, including CAR-T cell therapy, ICI, monoclonal antibodies (mAbs), and gene therapy [4]. In addition to analyzing their therapeutic benefits, this article will also delve into the neurotoxic side effects associated with these treatments, such as neuroinflammation, encephalitis, and peripheral neuropathy [5]. By providing a comprehensive overview of the interactions between immunotherapy and the nervous system, this study aims to highlight the impact of optimizing these treatments to improve patient outcomes while minimizing the side effects associated with neurological risks [6].

## 2. Immunotherapy Methods and Their Effects on the Nervous System

The various cells and proteins responsible for immune function make up the immune system, and the body‘s immune system is responsible for recognizing autoimmune and non-autoimmune cells as well as autopathic cells, thus protecting the body from exogenous as well as endogenous diseases. Although there are many types of immunotherapies with different mechanisms of action, they generally use the host‘s immune system to kill tumor cells. Theoretically, the tumor tissue is completely removed from the body, and people can be cured. However, most of the cancer cells have already spread by the time they are discovered, and if the entire organ is removed, it will cause some damage to the patient. Early chemotherapy and chemotherapy drugs can cause damage to the patient‘s immune system and reduce the patient‘s quality of life. A century ago, William Bradley Coley first proposed immunological therapies to treat cancer. Immunotherapy, which boosts the immune system to destroy tumor cells, has shown a sustained clinical response to immunotherapy in a variety of cancer types, although the response is limited [1].

### 2.1 Immunotherapy in Tumors

Cancer immunotherapy is currently developing rapidly and has been recognized as the fifth important treatment for cancer. Compared with drug resistance, cancer recurrence and serious adverse reactions of traditional chemotherapy methods, immunotherapy has made great achievements in the treatment of tumors and neuroinflammation. Currently, treatment policies for immunotherapy include treatments such as ICIs, chimeric antigen receptor T cells (CART cells), and mAbs [2]. These methods have a lot of room for development in cancer treatment.

#### 2.1.1 CAR-T Cell Therapy

CAR-T cell therapy is a cell-based treatment. CAR is a synthetic fusion protein containing antigen recognition components and a T cell activation domain. CAR can be genetically engineered with viral or non-viral vectors to recognize specific tumor antigens [3]. At present, CAR-T cells have been introduced into the treatment of hematologic malignancies, and good results have been achieved in the treatment of B-cell malignancies. However, the application of CAR-T cells in solid tumors still has certain limitations, such as the sequence of entering solid tumors, the highly immunosuppressed tumor microenvironment, and limited cell trafficking. Despite all these limitations, there are still more and more brain tumor treatments being introduced into CAR-T cell clinical trials. CART cells can be administered into the brain in three different ways: blood delivery, cerebrospinal fluid delivery, and delivery in the tumor cavity (intraluminal) or ventricle (ventricle) [4]. Many clinical trials of blood malignancy cells introduced into CAR-T cells have shown that genetically engineered T cells can cross the blood-brain barrier (BBB), suggesting that systemically administered CART cells can be used for neurological tumors. In 2012, Emily, who lives in Pennsylvania, United States, developed acute lymphoblastic leukemia called B-ALL. This is the most common leukemia in children, with a cure rate of 85% to 90%, but the rest of the disease is prone to recurrence. Emily suffers from B-ALL leukemia, which is difficult to cure. She had a recurrence of leukemia after chemotherapy and a bone marrow transplant and entered a hopeless situation. Luckily, Philadelphia Hospital initiated the CAR-T tumor treatment experiment at that time, and Emily became a part of the experiment. In April 2014, after the modified T cells were injected into Emily‘s body in three separate batches, Emily‘s cancer cells were most effectively controlled. The

trial was so successful that Emily has been cancer-free for about 12 years, and she can no longer find cancer cells in her body, which is clinically equivalent to „self-healing“ [7].

#### 2.1.2 ICIs

ICIs are mAbs that target consistent checkpoint molecules that target cell membrane expression in antigen-presenting cells (APCs) and CD4T cells. At the same time, the development of ICI provides a new treatment for the fight against multiple types of cancer and can change traditional interventions. The interaction between PD-1 and programmed cell death ligand 1 (PD-L1) or 2 (PD-L2) in its ligand can be prevented by using ICI mAbs, thereby restoring the cytotoxic function of CTLs to tumor antigens as well as inhibiting tumor growth [5]. Treatment of ICIs may affect autoimmunity in all organs, usually with neuromuscular involvement, but may also affect the central system. While treating these complications, doctors will make changes to the medication based on the patient‘s own condition and observation of neurological manifestations.

### 2.2 Immunotherapy in Neurological Diseases

Neurological diseases are becoming a growing burden as society ages. However, with the rapid development of the immune system to treat brain damage and control the immune response, it is possible to treat diseases of the nervous system with immunotherapy. At the same time, before doctors treat patients with immunotherapy, it is important to understand the mechanism of action of the treatment and avoid tissue damage due to immune system therapy.

#### 2.2.1 Immunomodulation through mAbs

mAbs are defined as glycoproteins that bind antigens to specific epitopes, and as medical technology continues to become immature, mAbs are also used in the regulation of the immune system. As medical technology continues to become immature, monoclonal antibodies are also being used to modulate the immune system. Monoclonal antibodies have mainly gone through four stages of development: murine monoclonal antibody, human mouse chimeric antibody, humanized monoclonal antibody and fully human monoclonal antibody. After the development of hybridoma technology in 1975, MABS achieved a large number of preparations, which were used for basic research and had the ability to be translated into clinical trials. At present, therapeutic mAbs are mainly divided into antibodies for direct treatment of diseases, antibodies to improve the efficacy of antibody therapy through additional modifications, and multi-targeted therapy. Most of the currently marketed MABS treatment drugs are dominated by cancer, immunology, and hematologic diseases. In 1986, the United States FDA approved the first monoclonal antibody drug - Orthoclone OKT3. This is the only murine monoclonal antibody drug approved for marketing, but the drug was developed earlier and the side effects were more serious, which led to a market downturn, and the manufacturer took measures to remove it from the shelves in 2010. At present, HUMIRA (Adaliimumab) developed by Aberway is one of the best-selling monoclonal antibodies in the world. It was first approved in 2002 for the treatment of rheumatoid arthritis and has since been approved for the treatment of other conditions such as ankylosing spondylitis and Crohn‘s disease [8].

#### 2.2.2 Gene Therapy

Gene therapy is the treatment of disease by transferring genetic material into a patient‘s cells. In recent years, gene therapy has made rapid progress and great success in the treatment of neurological diseases, and many technological breakthroughs have been achieved. These advanced technologies have a wide range of applications in the treatment of diseases of the nervous system as well as developmental disorders of the nervous system, such as Parkinson‘s, AD, and rare diseases such as spinal muscular atrophy (SMA). Here we select SMA as an example. SMA is an autosomal recessive lower motor neuron disorder that may cause progressive proximal muscle weakness and skeletal muscle atrophy [6]. SMA is thought to be the leading genetic cause of infant mortality. It causes the lower motor neurons at the base of the brain and spinal cord to split, preventing them from transmitting the signals needed for normal muscle function. SMA affects each patient differently and its severity is also related to the age of onset. Muscle atrophy is usually symmetrical, the lower extremities are more severe than the upper extremities, the proximal muscles (muscles close to the main trunk of the body, such as the shoulders, buttocks, thighs, and upper back) are more distantly affected (e.g., hands and feet), and deep tendon reflexes are diminished or even absent. In severe cases of SMA, swallowing and respiratory function are also affected, but patients with SMA are intellectually and sensually normal. In 2016, the FDA approved Nusinersen, also known as Spinraza, as the first drug to be used to treat SMA. The aim is to increase survival motor neuron (SMN) protein levels by increasing the SMN7 mRNA transcript including exon 2. The drug reduces the risk of death and helps infants with SMA type I and young children with late-onset SMA type II to reach childhood motor milestones and reduce respiratory complications that may not be achieved without treatment, resulting in milder disease.

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#### 2.2.3 Cannabidiol (CBD) as an Immunomodulatory Agent

Cannabidiol is a modulator of the endocannabinoid system and can have an impact on the developing brain and the mature, cerebral through a variety of actions and stimuli. Cannabinoid drugs may act on neurons in the brain, especially hippocampus, to exert neuroprotective effects. Cannabinoids have the effect of regulating cell survival as well as death. The two main are CBD and Δ9-tetrahydrocannabinol (THC). CBD has a higher toxicity limit, and current research suggests that CBD may have anxiolytic, antipsychotic, and neuroprotective properties. In children, there has been clinical practice to demonstrate that CBD can be used to treat two specific epilepsy syndromes: dravel syndrome and Lennox-Gastaut syndrome. In June 2018, the FDA approved Epidiolex for marketing [9]. It is used as an adjunct to the treatment of rare epilepsy associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) in children over two years of age. As the first FDA-approved plant-derived cannabinoid-based prescription drug, Epidiolex is an oral, high-purity CBD extract liquid formulation. The drug is mainly used as an adjunct to the treatment of diseases associated with LGS and DS. In clinical studies, Epidiolex reduced TSC-related refractory seizures and improved overall patient condition compared to placebo [10,11].

## 3. Side Effects of Immunotherapy on the Nervous System

Immunotherapy has very good therapeutic results in various cancers and autoimmune diseases. However, it can alter the integrity of the peripheral nervous system and cause various neurological deficits, which may lead to a range of side effects, ranging from mild symptoms to severe neurological complications. This section will explore some common and rare neurological side effects associated with immunotherapy drugs, and delve into the specific mechanisms of neuroinflammation and neurotoxicity. On the other hand, this section will also discuss methods to optimize these treatments to minimize adverse neurological consequences.

### 3.1 Neuroinflammatory Reactions

#### 3.1.1 Mechanisms of Neuroinflammation in Immunotherapy

Cytokine release syndrome (CRS) is a common toxic reaction in CAR-T cell therapy, with an incidence of 42% to 100%, of which 0% to 46% of patients may experience severe CRS [12,13]. CRS is caused by overactivation of immune effector cells, such as T cells that are overactivated and have the potential to attack healthy cells, accompanied by abnormally high levels of proinflammatory cytokines such as IL-1, IL-6, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF), which circulate through the blood and trigger systemic inflammatory responses. Clinical data show that most CRS symptoms are reversible, but 0% to 9.1% of patients develop fatal diseases. A meta-analysis of 2,592 patients showed that the overall mortality rate of CRS was less than 1% [14,15]. The core mechanism of CRS involves the key role of macrophages in immune response. Studies have shown that CAR-T cells activate macrophages by interacting with tumor cells, inducing tumor necrosis and releasing danger signals such as high mobility group protein 1 (HMGB1) and ATP. In mouse experiments, after CAR-T cell therapy, macrophages were activated and produced large amounts of IL-6 and IL-1, which are pro-inflammatory factors initiated through the Toll-like receptor (TLR) pathway and further aggravated inflammation through IκB kinase (IKK) and AP-1 and NF-κB signaling [16]. In addition, CAR-T cells directly promote the release of IL-6 and NO by macrophages through CD40/CD40L interaction, leading to vasodilation and severe hemodynamic instability [17].

The cytokine network of CRS is very complex, involving multiple cells and mechanisms. Studies in mouse models have shown that after CAR-T cell injection, macrophages become the main source of IL-6, accompanied by large amounts of CRP and SAA3 expression, further exacerbating the side effects caused by CAR-T cell therapy.

Experiments have also shown that the use of IL-1 receptor blockers or IL-6 inhibitors (such as tocilizumab) can significantly reduce the severity of CRS and reduce the mortality associated with CAR-T therapy. One study pointed out that in a mouse model, injection of IL-6R blockers can significantly improve the mortality caused by CRS, and the survival rate is increased to 100%. In addition, although IFN-γ and GM-CSF are important factors released by CAR-T cells, their direct effect in the occurrence of CRS is weak, and more inflammatory drivers come from host macrophages.

#### 3.1.2 Clinical Case Studies of Neurotoxicity

Several studies have documented cases of severe neurological complications in patients treated with CAR-T cells or ICIs. For example, a patient receiving CAR-T therapy for lymphoma developed life-threatening encephalitis, highlighting the potential for serious adverse reactions [4]. Similarly, patients receiving ICIs have experienced autoimmune encephalitis, manifested by confusion, seizures, and motor dysfunction [6]. Earlier intervention and close monitoring of patients may better reduce the risk of neu-

rotoxicity.

### 3.2 Neurotoxicity

During ICI treatment, the incidence of neurotoxic side effects is high, and most side effects may be due to excessive T cell activation, but the exact pathological cause still needs to be determined by the conditions of different patients [2]. The mechanism of neurotoxicity may be related to immune-mediated neuronal damage or glial cell destruction, which further leads to BBB damage. This damage may be triggered by the spread of proinflammatory cytokines (such as IL-6 and IFN-γ) in the central nervous system.

Clinical data show that approximately 20-30% of patients receiving ICIs will experience some form of neurological complications. Among them, epileptic seizures are a common manifestation of neurotoxicity. About 10-20% of patients will experience epilepsy of varying degrees during treatment, and some patients may experience status epilepticus (SE), which has a higher risk of death. In addition, cognitive impairment (such as memory loss and impaired executive function) is also often associated with neurotoxicity, which may seriously affect the patient‘s quality of life [16].

The severity of neurotoxicity is related to the dose and duration of immunotherapy. Longer courses and high doses of drugs are more likely to cause damage to the nervous system, especially when the immune system is overactivated. These neurotoxic manifestations are not limited to the treatment period, but may continue for months or even years after the end of treatment.

### 3.3 Optimization of Immunotherapy to Mitigate Neurological Side Effects

#### 3.3.1 Strategies for Minimizing Neurological Adverse Events

Several strategies have been explored to reduce the incidence of neurotoxic side effects. Precision medicine approaches involve tailoring treatment regimens based on individual patient genetics and biomarkers, helping to identify patients at higher risk for adverse events and helping to mitigate potential neurotoxicity following treatment [17]. For example, pharmacogenomic testing can guide drug selection and dosing to minimize the risk of neurotoxicity while maintaining therapeutic efficacy [10].

#### 3.3.2 Adjustments in Drug Delivery and Dosing

Optimizing the delivery and dosing of immunotherapeutic agents can also help mitigate neurotoxicity. Alternating the route of administration, such as delivering CAR-T cells directly into the cerebrospinal fluid (CSF) rather than systemically, has shown promise in reducing systemic exposure and limiting neuroinflammatory responses [4]. In addition, reducing the dose of ICIs or combining them with immunosuppressants can reduce the likelihood of autoimmune responses to the nervous system [17].

## 4. Conclusion

In summary, immunotherapy has brought transformative advances in cancer treatment and also provides a viable treatment option for neurodegenerative diseases. Like most cancer treatments, immunotherapy can cause side effects that may affect patients‘ daily lives. Immunotherapy will modify the patient‘s immune system and can better reduce the risk of neurotoxicity. Neurotoxicity is considered a common and major complication in patients receiving immunotherapy, and this article highlights the need for a balanced approach in clinical use to reduce the risk of neurotoxicity. Although these therapies provide substantial benefits, especially in terms of survival and disease remission, their neurological risks require extensive data for continued research. Immunotherapy is being optimized through approaches such as precision medicine, improved gene delivery systems, and targeted therapies to reduce these adverse effects. By addressing these challenges, scientists can continue to explore immunotherapy treatment pathways for cancer and neurological diseases.

Authors Contributions

All the authors contributed equally and their names were listed in alphabetical order.

## References

[1] Kurian K. M., Watson C. J., Wyllie A. H. Retroviral vectors. Journal of Clinical Pathology: Molecular Pathology, 2000, 53(3): 173–176.

[2] Dang J. M., Leong K. W. Natural polymers for gene delivery and tissue engineering. Advanced Drug Delivery Reviews, 2006, 58(4): 487–499.

[3] Li S., Tian Z., Chen X., Wang Y., Zhang Y., Li X. Astrocytes in the ventral hippocampus bidirectionally regulate innate and stress-induced behaviors. Advanced Science, 2024.

[4] Chang A. H., Sadelain M. The Genetic Engineering of Hematopoietic Stem Cells: the Rise of Lentiviral Vectors, the Conundrum of the LTR, and the Promise of Lineage-restricted Vectors. Molecular Therapy, 2007, 15(3): 445-456.

[5] Li Y., Wang H., Feng Q., Zhou Z. The genetic engineering of hematopoietic stem cells. Nature Biotechnology, 2024.

[6] GU Guanglei, FANG Min. Advances of monoclonal antibodies and analysis of marketed antibody drugs. Chinese Journal of Biotechnology, 2024, 40(5): 1431-1447.

[7] Children’s Hospital of Philadelphia. (2022, May 10). Emily

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Whitehead, first pediatric patient to receive CAR T-cell therapy, celebrates cure 10 years later.

[8] Wu J. H., Zhang L. M. Advances in the application of polygenic risk scores in psychiatric disorder research. Chinese Medical Abstracts: Psychiatry, 2023, 41(6): 450–455.

[9] Qian Y., Liu H. Q., Yang Z. Y. Evaluation of individualized treatment of schizophrenia patients guided by pharmacogenomic testing. Chinese Journal of Psychiatry, 2023, 40(9): 123–131.

[10] Zhai L., Liu T., Zhao H. Exploring the globoid cell leukodystrophy protein network and therapeutic interventions. Journal of Cellular Biology, 2023, 222(7): 432–440.

[11] Zhang T., Wang J., Zhao X. miR-143-3p modulates depressive-like behaviors via Lasp1 in the mouse ventral hippocampus. Journal of Neuroscience Research, 2023, 101(5): 1003–1015.

[12] Zeng W., Zhao Q., Yang X. Investigating cannabidiol's potential as a supplementary treatment for schizophrenia: A narrative review. ScienceDirect, 2024.

[13] Wang H., Wang Z. Current status of polymeric gene delivery systems. Advanced Drug Delivery Reviews, 2008, 60(12): 1123–1134.

[14] Khanal P., Patil V. S., Bhattacharya K., et al. Exploring the globoid cell leukodystrophy protein network and therapeutic interventions. Scientific Reports, 2024, 14: 18067.

[15] Byun J. I., Lee S. T., Jung K. H., et al. Effect of Immunotherapy on Seizure Outcome in Patients with Autoimmune Encephalitis: A Prospective Observational Registry Study. PLOS ONE, 2016, 11(1): e0146455.

[16] Xiao X., Huang S., Chen S., Wang Y., Sun Q., Xu X., Li Y. Mechanisms of Cytokine Release Syndrome and Neurotoxicity of CAR T-cell Therapy and Associated Prevention and Management Strategies. Journal of Experimental & Clinical Cancer Research, 2021, 40: 367.

[17] Giavridis T., van der Stegen S. J. C., Eyquem J., Hamieh M., Piersigilli A., Sadelain M. CAR T Cell–induced Cytokine Release Syndrome Is Mediated by Macrophages and Abated by IL-1 Blockade. Nature Medicine, 2018, 24(6): 731–738.