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Comparative Analysis of ICIs, CAR-T Therapy, and Cancer Vaccines in Immunotherapy

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Abstract. Immunotherapy is a popular cancer treatment, which mainly focuses on regulating the body's own immune response to achieve the goal of treatment. There are many different treatments available in this field, each with its own advantages and disadvantages. But there are still problems that have not yet been resolved. This article analyzes the research of ICIs, CAR-T cell therapy, and tumor vaccines, summarizes their characteristics and compares them. This study provides a horizontal comparison of ICIs, CAR-T therapies, and cancer vaccines in terms of efficacy, safety, and adaptability in cancer treatment. ICIs demonstrate broad applicability and validated efficacy but are not universally effective. CAR-T therapies show significant efficacy in hematological malignancies but face challenges in solid tumors. Cancer vaccines offer potential but are less universally effective. Safety profiles vary, with ICIs manageable through pharmacological interventions, CAR-T therapies requiring careful management due to serious side effects, and cancer vaccines showing generally mild adverse events. However, there are still substantive problems that have not been solved, and future research can focus on clinical research directions.

Keywords: Immune checkpoint inhibitors; CAR-T cell therapy; tumor vaccines；immunotherapy and its mechanisms.

1. Introduction

The tumor immune microenvironment (TME) refers to a complex environment that exists around tissues or tumors, which contains various immune cells, cytokines, chemicals, and extracellular matrix, which together influence and regulate the immune system's ability to fight tumors or other pathological states. It determines the activity and efficiency of the immune system in a particular disease state. In the process of modern cancer treatment, immunotherapy, as a revolutionary means, is closely related to immunotherapy, and understanding and intervening in TME can help optimize the effect of immunotherapy and provide patients with more effective treatment options. Compared to traditional chemotherapy and radiotherapy, The goal of immunotherapy is to combat tumor cells by stimulating the patient's immune system, which frequently results in improved long-term survival and fewer adverse effects. Additionally, it can promote immunological memory benefits that endure a lifetime and stop tumor recurrence. Numerous immunotherapy techniques, including immune checkpoint inhibitors (ICIs), CAR-T cell therapy, and cancer vaccines, have demonstrated noteworthy therapeutic benefits in a range of cancer types in recent years.

First, we utilize a common example when discussing ICIs: anti-PD-1/PD-L1 antibody. The surface of tumor cells The immunological checkpoint protein PD-L1 interacts to the PD-1 ligand to stop T lymphocytes from launching an attack. Research has shown that a better prognosis with immunotherapy is frequently linked to tumor cells expressing a high level of PD-L1 on their surface. Anti-PD-1 medications, such pembrolizumab-containing Keytruda and nivolumab-containing Opdivo, have demonstrated noteworthy effectiveness in a range of cancer therapies. The mechanism of action of CAR-T cell therapy is to alter a patient's T cells to enable them to identify and eliminate tumor cells. Whereas, a cancer vaccine is a strategy that uses the immune system to recognize and

attack tumor cells. At present, certain achievements have also been made in the field of rigidity, such as: the research of MAGE-A3 vaccine in the treatment of malignant melanoma,

With the rapid development of immunotherapy, many clinical trials and systematic reviews have delved into the efficacy and safety of different immunotherapy methods, and the different mechanisms and application scenarios of these treatments have made researchers face the challenge of how to optimize the selection and application of these therapies in clinical practice. However, immunotherapy is not effective for all patients, and its current use in certain tumor types and patient populations remains challenging. In addition, sometimes immune escape mechanisms present in the tumor microenvironment can limit efficacy.

This article will examine and compare a variety of popular cancer immunotherapy methods to explore the differences between the different approaches. We will deeply compare and analyze the advantages and disadvantages of different immunotherapy methods, and through systematic cross-sectional comparative studies, we can reveal the best application scenarios of each treatment in specific cancer types or specific patient groups, and lay a theoretical foundation for the personalization and precision of treatment strategies. It can not only help medical professionals make more informed treatment choices in clinical practice, but also provide an important reference for the development and optimization of immunotherapy methods in the future. In addition, these studies will also contribute to the understanding of the mechanism of immunotherapy, promote the innovation and development of related technologies, and contribute to the progress of cancer treatment worldwide.

2. ICIs

An essential mechanism underlying tumor-induced immunosuppression is the upregulation of ligands that bind to T cell inhibitory receptors. These ligands, which are referred to as immunological checkpoints, function physically to prevent autoimmunity at different phases of the immune response process.

A novel class of immunotherapy medications known as immune checkpoint inhibitors (ICIs) has revolutionized the management of broad-spectrum malignancies, including renal cell carcinoma, non-small cell lung cancer (NSCLC), and metastatic melanoma [1]. The anti-PD-1/PD-L1 antibody is the main topic of this section.

The immune testing signaling pathway PD1/PD-L1 is a vital tool that tumor cells can use to fend off an immunological attack and stop T cell activation.Activating anti-tumor immunity, efficiently inhibiting tumor growth, and even curing malignancies are all made possible by inhibitors that target the PD-1/PD-L1 signaling pathway [2].

As a popular treatment method, ICIs have many years of research experience and mature technology compared with other emerging immunotherapies. The FDA has approved five PD-1/PD-L1 inhibitors and one CTLA-4 inhibitor; more medications are undergoing Phase 3 clinical trials.

However, its shortcomings are also significant. The first is that the efficacy of ICIs is susceptible to interference by other factors such as age, and older patients tend to benefit less from them. It also has a high rate of medication resistance. There are numerous intrinsic and extrinsic tumor cytokines linked to the intricate, dynamic, and interdependent process of PD-1/PD-L1 antibody resistance development. It has been demonstrated that the tumor microenvironment, loss of initial and costimulatory signals, PD-1/PD-L1 expression levels on the cell surface, and epigenetic changes are linked to PD-1/PD-L1 resistance [2].

As an important part of cancer treatment, ICIs have brought significant clinical benefits, but there are also immune-related adverse events and the resistance of some patients to treatment.

IrAEs are typically rather substantial and are distinguished by clinical signs and symptoms that have a strong resemblance to autoimmune disorders. irAEs have the potential to impact almost all systems and organs.

3. CAR-T Therapy

CAR-T immunotherapy is a technique，T cells are genetically engineered to specifically target and eliminate tumor cells. With its encouraging results in the treatment of cancers, especially lymphomas, CAR-T has been a focal point for tumor immunotherapy research in the last few years.

CAR is a single-chain variable fragment (scFvs) fused with a monoclonal antibody that can specifically recognize antigens, including variable heavy (VH) and variable light (VL) and the intracellular signaling domain of T cell receptor (TCR). And CAR-expressing T cells are not MHC restricted. At present, CAR has been developed to the fourth generation, in general, the first generation of CAR has weak anti-tumor effect, and the third and fourth generations have greater toxic and side effects, so it is relatively mild second-generation CAR that is widely used in tumor treatment.

Acute lymphoblastic leukemia (ALL) can be treated with CAR-T cell products like tisagenlecleucel (tisa-cel) and brexucabtagene autoleucel (brex-cel), which have good complete response rates. However, some patients have relapsed as a result of antigen escape or CAR-T cell failure. Diffuse large B-cell lymphoma (D/R DLBCL) that has relapsed or is refractory has been treated with CAR-T cells such as Yescarta and Axiscel. CAR-T cell therapy has achieved a relatively low complete response rate in the treatment of lymphoma disease compared to ALL, and efficacy comparisons based on CR rate have been made with tisa-cel, axi-cel, JCAR014 products, and CRS-based products

Compared with the safety profile of syndrome of immunological effector cell-associated neurotoxicity (ICANS), axi-cel has a lower safety profile but better efficacy. In addition to this, there are still multiple factors such as sample size, real-world efficacy, and differences in clinical features that have not been ruled out. CAR-T has shown promising prospects in the clinical treatment of refractory/relapsed multiple myeloma (RRMM) (MM), of which B cell maturation antigen (BCMA) is the most effective target to date. However, studies still need to increase the number of cases and extend the follow-up period to observe long-term efficacy before further validation.

CAR-T therapy may trigger toxic reactions such as cytokine release syndrome (CRS). The occurrence of CRS is associated with the release of inflammatory cytokines by macrophages. Although high-grade CRS and ICANS can be controlled through surveillance and early intervention, the prediction of severe CRS response remains a challenge. Loss or downregulation of target antigens, disease progression, and persistent inadequate expansion of CAR-T cells themselves are the main limitations to sustained remission after CAR-T cell therapy. There are still certain issues with therapy in a few clinical and preclinical investigations. In addition, the effectiveness of CAR-T cells is severely limited in the case of solid tumors, where it is more difficult to infiltrate and migrate to tumor cells expressing the target antigen. This is because it is necessary to find new tumor-specific epitopes and get past the physical and metabolic barriers caused by inhibitory TME. These factors all have an impact on the initial phenotype of T cells and the structural design of CAR-T cells.

4. Therapeutic Cancer Vaccines

There are four different types of therapeutic cancer vaccines: nucleic acid-based, peptide-based, cell-based, and viral vaccines [1]. This article focuses on the first three vaccines. A big advantage of cancer vaccines is that they can provide personalized treatment to patients. Doctors can extract tumor antigens from patients to develop specific vaccines for better results. The second advantage is that as long as tumor-associated antigens can be extracted, specific cancer vaccines can be developed, such as NSCLC, gastric cancer, breast cancer, etc. [2-4]. It can also be used for some less common cancers, such as malignant peritoneal mesothelioma [5]. However, there is a common problem with cancer vaccines: it can take a long time to develop a vaccine specifically designed for patients.

4.1. Cell-based Vaccines

Based on composition, there are two primary forms of cell-based vaccines: one that uses the patient's own tumor cells and another that uses dendritic cells (DC). Tumor cells that have been treated with

an adjuvant to stimulate CD8+T cells that are specific for tumor antigen expression are present in the first vaccination. Furthermore, it is possible to genetically modify tumor cells to add new capabilities. Using this technique, numerous cancers have been treated, such as melanoma, colorectal cancer, and non-small cell lung cancer (NSCLC). DCs are present in the second vaccination. Many antigens, including as tumor cells, peptides produced from tumors, DNA, RNA, and so forth, are present on the surface of DCs. Tumor cells and DCs can merge to enhance the impact (Figure 1).

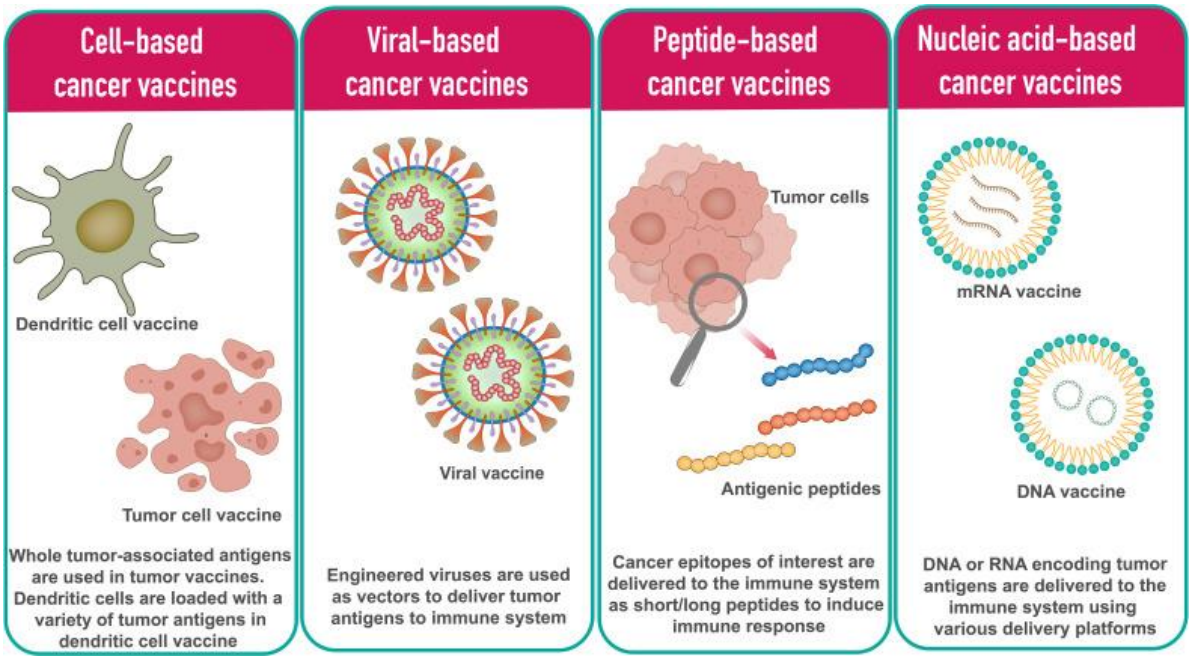

Fig. 1 Different types of cancer vaccine platforms [1].

4.2. Peptide-based Vaccine

In order to trigger an immune response, peptides that are particularly produced on tumor cells are injected into the patient as part of peptide-based vaccinations. Antigens are taken up by specialized antigen-presenting cells (APCs), which then present them on the cell surface together with human leukocyte antigen (HLA) molecules. These antigens trigger a particular immunological response from T cells that fight cancer.

4.3. Nucleic Acid Vaccine

A nucleic acid vaccine is an injection of DNA or mRNA that codes for a tumor antigen into a patient to induce an immune response. DNA enters the nucleus of APCs and is expressed. mRNA, on the other hand, enters the cytoplasm and does its job. mRNA vaccines function faster than DNA vaccines. But mRNA is easier to break down than DNA. At present, mRNA can be stabilized by modification (such as capping).

The transport of key components of nucleic acid vaccines requires vectors. The mostly used vectors are viruses (AAVs, etc.) and liposomes. In addition, some scholars are also considering bacteria, yeast and so on (Figure 2).

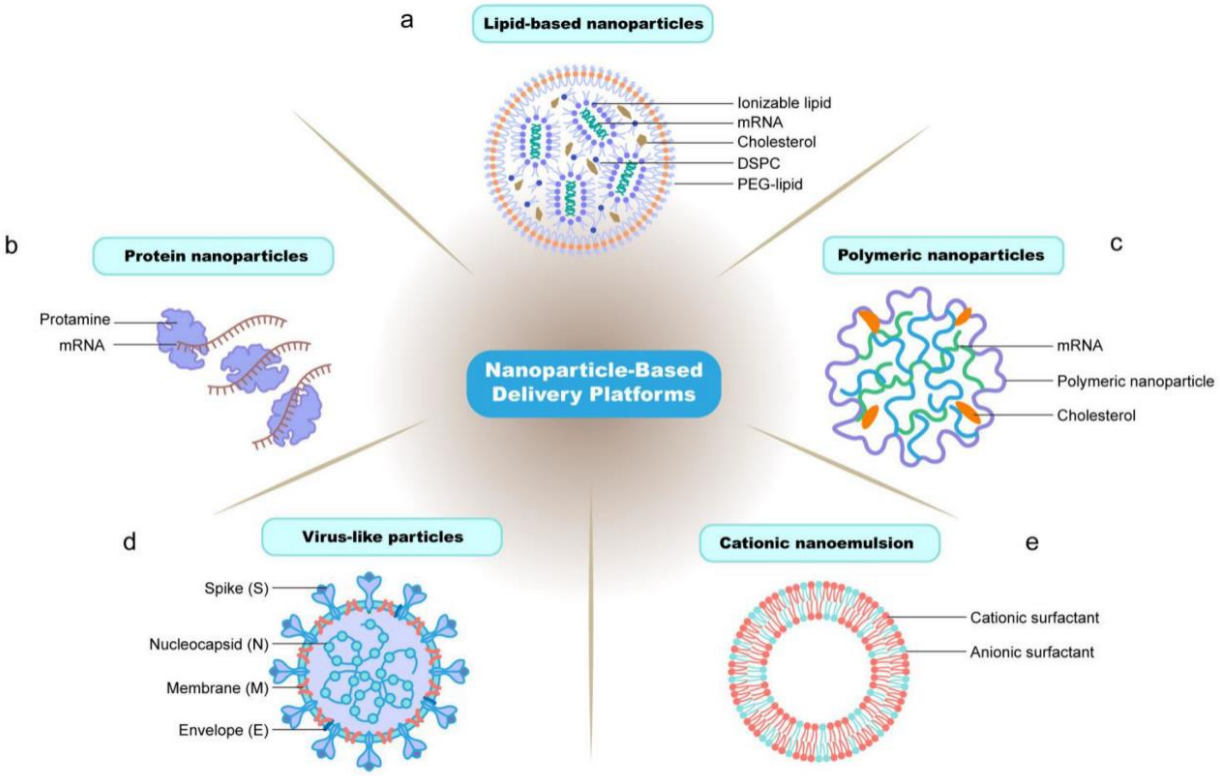

Fig. 2 The main nanoparticle-based delivery platforms for mRNA vaccines [6].

4.4. Cancer Vaccines Compared to Other Cancer Therapies

Cancer vaccines and traditional cancer therapies (such as chemotherapy, radiotherapy, etc.) have advantages in some ways. With Provenge(A DC vaccine against Prostate cancer), the first cancer vaccine approved by the U.S. Food and Drug Administration (FDA), versus Lutetium-177 (177Lu) -PSMA-617 (a radiotherapy against Prostate-specific membrane antigen (PSMA)), for instance (note the limitations of this comparison). Provenge outperforms Lutetium-177 (177Lu) - PSMA-617 in terms of efficacy. The 12-month survival rate of patients treated with Provenge was 80.4% when the median age of participants was nearly equal (the median age of patients treated with Provenge was 72 years [7] and the median age of patients treated with Lutetium-177 (177Lu) -PSMA-617 was 70 years [8].

Patients treated with lutetium-177 (177Lu) - PSMA-617 had a 12-month survival rate of 60.3% and a median survival of 15.3 months, whereas the median survival was 25.8 months. Additionally, Provenge performs better than Lutetium-177 (177Lu) - PSMA-617 in terms of safety analysis.Although a slightly higher percentage of adverse reactions occurred in patients treated with provenge (98.8% vs. 98.1%) [7], patients treated with provenge were less likely to have grade III and above adverse reactions. 52.7% of patients treated with Lutetium-177 (177Lu) -PSMA-617 experienced grade III or higher adverse reactions [8], while only 31.7% of patients treated with pravix experienced the same grade of adverse reactions [7].

4.5. Advantages and Disadvantages of Some Types of Cancer Vaccines

Due to some limitations (such as few papers from clinical trials, vaccines for different diseases, or research is regarding combination therapy), this section only discusses the advantages and disadvantages of various vaccines, and cannot objectively evaluate the priority (Table 1).

Table 1. Comparison of different types of tumor vaccines.

Tumor vaccines	Advantages	Disadvantages
Vaccines containing tumor cells	1. Rapid production 2. Highly personalizable	1. Immune escape problem 2. Immunosuppression problems 3. Technical complexity and cost
DC vaccines	1. Powerful antigen presenting ability: 2. Personalized treatment	1. Complex preparation process 2. Immunosuppression problem: TME may inhibit the effect of DC vaccine and limit its development. 3. High cost 4. Immune escape mechanisms
Peptide-based vaccines	1. Strong specificity 2. Personalization	Although studies have been going on for years, the vaccine's performance in phase III trials has been disappointing. Here are reasons: 1. Single antigen. Single antigens are not very good at inducing an immune response. 2. The presence of immunosuppressive cells (T regulatory cells, tumor-associated macrophages, tumor-associated neutrophils, etc.) in the tumor microenvironment.
Nucleic acid vaccines	1. Rapid production 2. Highly customizable 3. Activate the immune response	1. Immune escape mechanism 2. Technical challenges 3. Clinical trial phase 4. Optimization of production and delivery systems

5. Conclusion

Immunotherapies are showing great potential in the field of cancer treatment, including ICIs, CAR-T cell therapies and cancer vaccines. Horizontal comparison of these therapies can be evaluated from three aspects: efficacy, safety, and adaptability.

First, let's compare the two in terms of efficacy. ICIs are widely applicable and have a well-established track record of effectiveness in clinical settings, but not all patients will benefit from this drug class, and some patients may not respond at all. Research is still being done to determine whether CAR-T cell therapy is effective in treating solid tumors, although it has demonstrated strong efficacy in treating several hematological malignancies when compared to standard treatments. Cancer vaccines have the potential to prevent and treat specific malignancies, according to recent clinical research, although their overall efficacy and universal adaptability have not yet reached the levels of the first two. They work well in tailored treatment, but further investigation is required to confirm that their general application is feasible.

The second is a safety comparison: immunological-related adverse events, which are typically manageable with pharmaceutical therapies, are the primary side effects associated with ICIs. CAR-T cell therapy puts additional demands on the medical staff and treatment plan because it may have major side effects. Although the kind and severity of side effects can differ from person to person, cancer vaccinations generally have minimal side effects with a generally high safety profile.

Lastly, there's the appropriateness evaluation: ICIs can treat a range of cancer types, but not every patient will see a response, and individual results may differ. The primary target of CAR-T cell therapy is hematological cancers; hence, solid tumor efficacy and safety concerns must be addressed. Currently, the primary applications of cancer vaccines are in individualized medicine and cancer recurrence prevention. These three immunotherapies can be compared to better understand their respective benefits and drawbacks, as well as to help with the selection and improvement of clinical applications. Combining various treatments may have a synergistic impact that improves the effectiveness of the treatment even more. The use of ICIs in combination with other medicines and the expansion of their indications will be the subjects of ongoing research. Reducing side effects and enhancing the therapeutic efficacy of solid tumors are two potential future directions for CAR-T cell therapy. The main goals of research on cancer vaccines will be to improve universal fitness, optimize their design, and contribute more to personalized medicine.

The majority of current research focuses on certain cancer types; the mechanism of cancer and contemporary clinical issues are the main subjects of this work. Additional validation is required for individual variances, variety of treatment plans, and long-term consequences. To properly evaluate the combined efficacy and safety of these medicines, larger clinical trials and longer-term follow-up are necessary for future research. In summary, immunotherapy has demonstrated significant promise in the treatment of cancer; hence, subsequent research should focus on understanding its mechanism of action, refining treatment approaches, and encouraging the widespread use and advancement of these medicines.

Authors Contribution

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

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