Review Article

The future of cancer immunotherapy: Advances in checkpoint inhibitors and chimeric antigen receptor-T cells discussing recent progress in immunotherapy for cancer, focusing on checkpoint inhibitors and chimeric antigen receptor-T cell therapies

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How to cite this article: Devi R, Pegowal S, Rajput A, Kaur V, Kaur J, Verma M, Dhingra AK. The future of cancer immunotherapy: Advances in checkpoint inhibitors and chimeric antigen receptor-T cells discussing recent progress in immunotherapy for cancer, focusing on checkpoint inhibitors and chimeric antigen receptor-T cell therapies. Innov Pharm Planet (IP-Planet) 2024;12(4):1-72.

Source of Support: Nil.
Conflicts of Interest: None declared.

Date of Submission: 01-11-2024
Date of Revision: 15-11-2024
Date of Acceptance: 30-11-2024

ABSTRACT

Cancer remains one of the leading causes of morbidity and mortality worldwide, necessitating the development of innovative therapeutic strategies beyond traditional treatments. Recent advances in cancer immunotherapy, particularly checkpoint inhibitors and chimeric antigen receptor T (CAR-T) cell therapy, have revolutionized the landscape of oncological care. These therapies leverage the body's immune system to effectively target and eliminate malignant cells, demonstrating substantial efficacy in various malignancies, including melanoma, lung cancer, and hematologic cancers. This review comprehensively examines the mechanisms of immune response in cancer, detailing the functioning of checkpoint inhibitors and CAR-T cell therapies, along with their Food and Drug Administration-approved variants and associated clinical outcomes. Moreover, we address ongoing challenges such as immune-related adverse events and manufacturing complexities, while highlighting emerging research and future directions that promise to enhance therapeutic efficacy and broaden patient access. By providing a detailed exploration of the current landscape and future possibilities in cancer immunotherapy, this review aims to contribute to the advancement of personalized and effective treatment strategies for cancer patients globally.

Keywords: Cancer immunotherapy, chimeric antigen receptor-T cell therapy, checkpoint inhibitors, immune response, personalized treatment

Introduction

Cancer remains a leading cause of morbidity and mortality globally, prompting an urgent need for innovative therapeutic strategies beyond conventional approaches. Traditional cancer treatments, including surgery, chemotherapy, and radiation, have historically been the mainstay of oncological care; however, they often come with significant limitations, including severe side effects and the potential for incomplete tumor eradication. In recent years, cancer immunotherapy has emerged as a revolutionary approach that harnesses the body's own immune system to recognize and combat malignant cells. Among the various modalities of immunotherapy, checkpoint inhibitors and chimeric antigen receptor T (CAR-T) cell therapy have shown remarkable success in clinical trials and real-world applications, particularly in cases of melanoma, lung cancer, and hematologic malignancies. These therapies represent a paradigm shift in cancer treatment, offering

Access this article online

Website: https://innovationaljournals.com/index.php/ip | e-ISSN: 2348-7275

DOI: 10.31690/ipplanet.2024.v012i04.019

not only enhanced efficacy but also the potential for durable responses in patients who may have exhausted other therapeutic options.

This review aims to provide an in-depth examination of the current landscape of cancer immunotherapy, with a specific focus on the advances in checkpoint inhibitors and CAR-T cell therapy. We will explore the underlying mechanisms of action, the spectrum of Food and Drug Administration (FDA)-approved therapies, and the latest clinical outcomes that underscore their effectiveness. In addition, we will discuss the challenges faced in these therapeutic approaches, such as immune-related adverse events (irAEs) and the complexities of manufacturing CAR-T cells. By highlighting ongoing research and future directions in the field, this review seeks to underscore the importance of understanding these advancements, ultimately contributing to the development of more effective and personalized cancer treatment strategies for patients worldwide.

Mechanisms of Immune Response in Cancer

Immune system overview

The immune system plays a critical role in the recognition and elimination of cancer cells. It is composed of various cell types that work together to mount an effective response against tumorigenesis. Among these, T cells are paramount; they can directly kill cancer cells or help coordinate the immune response. There are several subsets of T cells, including cytotoxic T cells (CD8+ T cells), which specifically target and destroy cancer cells, and helper T cells (CD4+ T cells), which support other immune cells by producing cytokines that enhance the immune response. B cells also play a vital role by producing antibodies that can bind to tumor antigens, facilitating the opsonization and elimination of cancer cells.

Dendritic cells serve as crucial antigen-presenting cells that capture and process tumor antigens before presenting them to T cells in lymph nodes, thus initiating a targeted immune response. In addition, macrophages contribute to tumor immunity through their ability to phagocytose cancer cells and secrete pro-inflammatory cytokines. However, the dual role of macrophages in the tumor microenvironment (TME) must be acknowledged; while they can have anti-tumor effects, they can also be co-opted by tumors to promote growth and metastasis. Together, these key players of the immune system form a complex network that can recognize, attack, and eliminate cancer cells, although their effectiveness can be significantly influenced by the TME.[1]

TME

The TME plays a pivotal role in shaping the immune response to cancer. It consists of not only cancer cells but also various stromal components, including immune cells, blood vessels, fibroblasts, and extracellular matrix. The interaction between cancer cells and immune cells within the TME can lead to a complex dynamic where immune cells may either mount an effective anti-tumor response or become suppressed. Tumors can exploit this microenvironment to evade immune detection through several mechanisms. For instance, cancer cells can express immune checkpoint molecules, such as programmed death-ligand 1 (PD-L1), which engage with the programmed death 1 (PD-1) receptor on T cells to inhibit their activity, effectively dampening the immune response.[2]

Moreover, the TME can be immunosuppressive due to the presence of regulatory T cells (Tregs) and myeloid-derived suppressor cells, which can inhibit the activation and proliferation of effector T cells. In addition, tumors can release various soluble factors, such as cytokines and chemokines that further modulate the immune response in their favor. For instance, transforming growth factor-beta can promote tumor progression and immune tolerance, while vascular endothelial growth factor can contribute to the formation of an immunosuppressive vasculature. Understanding the intricate interactions within the TME and the mechanisms of immune evasion utilized by tumors is crucial for the development of effective cancer immunotherapies that can enhance anti-tumor immunity and improve patient outcomes.[3]

Checkpoint Inhibitors

Overview of checkpoint inhibitors

Checkpoint inhibitors are a class of immunotherapeutic agents designed to enhance the body's immune response against cancer. They work by targeting specific inhibitory pathways in the immune system that tumors exploit to evade detection and destruction. Key molecules involved in these pathways include PD-1, PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). PD-1 is a receptor expressed on T cells that, when bound to PD-L1 (expressed on tumor cells and antigen-presenting cells), inhibits T cell activation and function. By blocking this interaction, PD-1 inhibitors effectively rejuvenate exhausted T cells, allowing them to mount an effective immune response against tumors. Similarly, CTLA-4 functions as a negative regulator of T cell activation. Inhibiting CTLA-4 promotes T cell proliferation and enhances the immune response to cancer.[4]

The strategic blockade of these checkpoints has revolutionized cancer treatment, providing a new avenue for patients who do not respond well to traditional therapies. This mechanism of action not only facilitates the reactivation of existing T cells but also promotes the establishment of a long-term immunological memory against cancer cells, thereby potentially leading to sustained anti-tumor effects even after treatment cessation.[5]

FDA-approved checkpoint inhibitors

Numerous checkpoint inhibitors have been approved by the FDA, marking a significant advancement in oncology. Notable examples include nivolumab (a PD-1 inhibitor), pembrolizumab (another PD-1 inhibitor), and ipilimumab (a CTLA-4 inhibitor). Nivolumab is approved for various malignancies, including melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma, while pembrolizumab is indicated for similar cancer types, along with head

and neck squamous cell carcinoma and certain types of bladder cancer. Ipilimumab is primarily used in melanoma and has shown improved overall survival when combined with nivolumab. The clinical outcomes associated with these therapies have demonstrated durable responses in a subset of patients, with some experiencing long-term remission, which is particularly promising given the historically poor prognosis for advanced-stage cancers.[6]

Advances in checkpoint inhibitor therapy

Recent advances in checkpoint inhibitor therapy have focused on combination strategies and biomarker identification to enhance therapeutic efficacy. Combination therapies that integrate checkpoint inhibitors with traditional treatments such as chemotherapy or targeted therapy have shown synergistic effects, improving response rates in various cancers. For instance, combining nivolumab with chemotherapy has been particularly effective in NSCLC, leading to improved overall survival compared to chemotherapy alone. In addition, the identification of biomarkers has become increasingly important in predicting patient response to checkpoint inhibitors. PD-L1 expression levels on tumor cells and microsatellite instability status are among the most studied biomarkers, guiding treatment decisions and optimizing patient selection for these therapies.[7]

Challenges and limitations

Despite the successes of checkpoint inhibitors, several challenges and limitations persist. irAEs can occur due to heightened immune activation, leading to conditions such as colitis, dermatitis, and endocrinopathies. These side effects can be severe and require careful management to ensure patient safety. Furthermore, resistance mechanisms can limit the effectiveness of checkpoint inhibitors in some patients. Tumors may develop alterations that enable them to evade immune detection, such as upregulating alternative immune checkpoints or downregulating antigen presentation machinery. Strategies to overcome resistance, including combination therapies targeting multiple pathways or the use of novel agents that modulate the immune microenvironment, are currently under investigation and represent critical areas for future research.[8]

CAR-T Cell Therapy

Overview of CAR-T cell therapy

CAR-T cell therapy is a revolutionary form of adoptive cell transfer that harnesses the power of genetically modified T cells to target and destroy cancer cells. The process begins with the collection of a patient's T cells, which are then genetically engineered in the laboratory to express a CAR that recognizes specific tumor-associated antigens. This modification allows the T cells to identify and bind to cancer cells more effectively. Upon reintroduction into the patient, these CAR-T cells proliferate and mount a robust immune response against the tumor, leading to targeted destruction of malignant cells.

The production of CAR-T cells involves several steps: First, leukapheresis is performed to isolate T cells from the patient's blood. These T cells are then activated, typically using anti-CD3 and anti-CD28 antibodies, and transduced with a viral vector containing the CAR gene. After sufficient expansion in culture, the modified CAR-T cells are infused back into the patient. This personalized approach enables a tailored immune response, aiming for enhanced efficacy in combating hematologic malignancies and solid tumors.

FDA-approved CAR-T therapies

Several CAR-T therapies have received FDA approval, marking significant progress in the treatment of certain hematologic cancers. Notable examples include tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta). Tisagenlecleucel is approved for the treatment of acute lymphoblastic leukemia (ALL) in patients up to 25 years old and for certain types of large B-cell lymphoma. In clinical trials, tisagenlecleucel demonstrated high remission rates in pediatric and young adult patients with ALL. Axicabtagene ciloleucel, on the other hand, is indicated for adult patients with large B-cell lymphoma who have not responded to or have relapsed after at least two lines of systemic therapy. Both therapies have shown promising clinical outcomes, with many patients achieving complete remission, which underscores the potential of CAR-T cell therapy in oncology.[9]

Advances in CAR-T cell therapy

The field of CAR-T cell therapy is rapidly evolving, with several advancements that aim to enhance efficacy and broaden the applicability of this treatment. Next-generation CAR-T cells are being developed to improve targeting and persistence. For example, dual-target CARs are engineered to recognize multiple antigens, which may help overcome antigen escape by cancer cells and enhance the overall anti-tumor response. In addition, armored CARs are designed to produce cytokines that can support T cell function and survival within the TME, potentially increasing their effectiveness against resistant tumors.[10]

Another significant advancement is the development of off-the-shelf CAR-T cell products, which aim to provide a more accessible and cost-effective treatment option. These products are generated from healthy donor T cells and engineered to be universally applicable to multiple patients, reducing the time and complexity associated with personalized CAR-T cell manufacturing.[11] This approach could greatly expand the reach of CAR-T therapies to a broader patient population, particularly those with limited access to individualized treatments.

Challenges and limitations

Despite the remarkable success of CAR-T cell therapy, several challenges and limitations persist. One major concern is the occurrence of cytokine release syndrome (CRS), a potentially severe and life-threatening condition that arises from the rapid activation and proliferation of CAR-T cells, leading to excessive cytokine production. CRS can result in symptoms ranging from mild flu-like signs to severe complications, necessitating careful monitoring and management. In addition, neurotoxicity is another serious adverse effect associated with CAR-T therapy, manifesting as confusion, seizures, or other neurological symptoms in some patients.

Moreover, manufacturing CAR-T cells remains a complex and costly process, which can limit patient access to these therapies. The personalized nature of CAR-T cell production requires significant time and resources, making it challenging to meet demand, particularly in urgent clinical situations.[12] Addressing these manufacturing challenges and developing cost-effective solutions will be critical for the broader implementation and accessibility of CAR-T cell therapy in clinical practice.

Future Directions

Ongoing clinical trials and research

The landscape of cancer immunotherapy continues to evolve rapidly, with numerous ongoing clinical trials aimed at enhancing the efficacy of checkpoint inhibitors and CAR-T cell therapies. These trials explore innovative combination strategies, novel agents, and new indications. For instance, combining checkpoint inhibitors with targeted therapies or other immunotherapeutic approaches, such as vaccines or oncolytic viruses, is being extensively studied to improve response rates and overcome resistance mechanisms. In addition, trials are assessing the effectiveness of CAR-T cell therapy in solid tumors, which have historically posed challenges due to the immunosuppressive TME. The results from these studies will be pivotal in shaping future treatment paradigms and expanding the utility of these therapies to a broader range of cancer types.[13]

Novel combinations and approaches

As research advances, the potential for novel combinations and approaches in immunotherapy is becoming increasingly evident. The integration of dual-target CAR-T cells, which can recognize and engage multiple antigens, may provide a solution to tumor heterogeneity and the challenge of antigen escape. Moreover, the use of bispecific T-cell engagers, which are designed to simultaneously bind to T cells and tumor cells, represents another promising avenue for enhancing anti-tumor responses. Exploring the use of immune modulators, such as toll-like receptor agonists or immune checkpoint inhibitors that target additional pathways, may also enhance the effectiveness of existing therapies.[14]

Personalized medicine and biomarker development

The future of cancer immunotherapy will likely hinge on the advancement of personalized medicine, where treatment strategies are tailored to individual patient profiles. Ongoing research into biomarkers for predicting response to checkpoint inhibitors and CAR-T cell therapies is critical for optimizing patient selection and enhancing outcomes. Emerging biomarkers, such as tumor mutational burden and specific gene expression profiles, may provide insights into which patients are more likely to benefit from immunotherapy. In addition, understanding the TME and its immune landscape will be essential for developing effective combination strategies and improving the predictability of treatment responses.[15]

Expanding indications

Future directions in cancer immunotherapy also involve expanding the indications for existing therapies to include a broader range of malignancies and earlier stages of disease. Researchers are exploring the use of checkpoint inhibitors and CAR-T cell therapies in combination with standard treatments in adjuvant and neoadjuvant settings, which may enhance their effectiveness and improve long-term outcomes. Efforts are underway to evaluate these therapies in rare cancers and specific patient populations, potentially unlocking new avenues for treatment and providing options for patients with limited therapeutic alternatives.

Conclusion

The advancements in checkpoint inhibitors and CAR-T cell therapies represent a significant leap forward in the fight against cancer, offering new hope for patients who have previously exhausted conventional treatment options. Ongoing research continues to refine these therapies, aiming to overcome existing challenges and broaden their application across diverse cancer types.

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