Review

Evolving Cancer Immunotherapy: Advances and Hurdles

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ABSTRACT

Nowadays, cancer immunotherapy is a cutting-edge tumour treatment. Immunotherapy has been shown to offer unmatched benefits over conventional anti-tumour therapy in a number of tests and clinical investigations, which can extend overall survival and progression-free survival. In the late 1890s, well-known oncologist Dr. William B. Coley (1862–1936), who was also an expert, developed cancer immunotherapy. He was an American-born specialist who was well-known for his prior work on the topic of immunotherapy in cancer and for being an excellent analyst of diseases like cancer. During the course of treating a patient, he discovered that when a small number of specific microorganisms entered the body of a Patient who was currently suffering from a neoplasm, there was a remarkable effect on the developing tissues that could potentially result in the disappearance of the disease. This serves as a foundation for many immunotherapy treatments for cancer research today.

By weighing the benefits and drawbacks of immunotherapy and closely monitoring its future development trend, this study provides an overview of current advancements in the field and suggests a new approach to tumour treatment. Immunotherapy has completely transformed the treatment of cancer by using the body's defence mechanisms to target and eliminate cancer cells. This survey covers the deterrents, such as immune-related adverse effects, resistance tools, and expensive treatment, in addition to discussing the important advancements in immunotherapy, such include resistant checkpoint inhibitors, CAR-T cell therapy, and cancer vaccinations.

Keyword: Cancer immunotherapy, CAR-T, PD-1

Abbrevations:
T-Cell T Lymphocytes CAR-T Chimeric Antigen Receptor T Cells, PD-I T Lymphocytes, Adoptive Cellular Immunotherapy (ACI), Dendritic Cells (DC), Natural Killer Cells (NKC), Cytokine-Induced Killer Cells (CIK), Tumour-Infiltrating Lymphocytes (TIL), Lymphocyte Activated Killer Cells (LAK), Macrophage-Activated Killer Cells (MAK),PD-L1-Programmed Cell Death Ligand 1, CD3+-CLUSTER OF Differentiation, Intratumoral Heterogeneity (ITH), CTLA-4 – Cytotoxic T-Lymphocyte-Associated Antigen 4, IL-6 Interleukin 6, Antigen-Presenting Cells (Apcs), Major Histocompatibility Complex (MHC),Immune Checkpoint Inhibitors (Icis) , Microsatellite Instability (MSI) Immune-Related Adverse Events (Iraes)

INTRODUCTION

After heart disease, cancer is the second leading cause of death worldwide. In general, cancer prevalence has increased significantly in the United States alone. About 1,665,540 people suffered from cancer in 2014, and 585,720 of them passed away as a result of the disease's urgent spread among sufferers. This data indicates that cancer is a real problem that affects the well-being of various human social orders.[1]

Unfortunately, it is a tissue-level illness, which poses a significant obstacle to its specific outcome, which is determined by the feasibility of therapy. Prostate cancer has the highest incidence of any type of cancer in males, but it can also spread easily and quickly to the lung, bronchus, colon, rectum, and bladder[2,3]. Research on related anti-tumour medications is steadily progressing, and the market and use of medications are steadily growing. In women, the breast, lung and bronchus, colon and rectum, uterine corpus, and thyroid have the highest rates of cancer[4]. According to this data, breast and prostate cancer make up a significant portion of cancer in women and men, respectively[2]. Malignancies of the brain and lymph nodes, as well as malignancies that spread through the blood, are the most common types of cancer in children. A series of gradual alterations in characteristics that alter cell capacity are what cause cancer[4].

Both malignant cells and quality alterations are clearly shaped by chemical chemicals. Furthermore, smoking contains a variety of carcinogenic chemicals that can affect flight routes and result in lung cancer[5,6]. Interests, Natural chemicals having carcinogenic qualities affect particular or indirectly affected cell components, such as the cytoplasm and cell core, and cause genetic disruptions and changes in quality. The gold standard for a successful use of CIT must be the ability to produce a long-lasting reaction and to improve outcomes in patients with advanced or early-stage cancer.[1,7,8]

TUMOUR CELLULAR IMMUNOTHERAPY

Tumours can be recognised and eliminated by immune cells. Immune cells can once again contribute to tumour surveillance and clearance by activating immune cells and utilising the body's own tumour-specific immune response to defeat tumour escape. Once more, immune cells may be involved in the surveillance and removal of tumours. Although cell immunotherapy is now successful in treating hematologic tumours, its effectiveness for solid tumours is not as anticipated because of the heterogeneity of solid tumours and their external microenvironment.[2,9,10]

TYPES OF CANCER IMMUNOTHERAPY

Adoptive cellular immunotherapy (ACI)

Because of its high selectivity, ease of preservation, and lack of drug resistance, ACI—the therapy of killing tumour cells by injecting immunologic effector cells that have been altered and expanded by genes has emerged as a popular study area and significant tumour treatment

method[11]. The peripheral blood's lymphocytes or cytokines stimulate the immune cells in nonspecific ACI, which can eradicate a range of tumours. However, they are only utilised for adjuvant therapy because of their poor tumour targeting and insufficient killing capabilities. Dendritic cells (DC), natural killer cells (NKC), cytokine-induced killer cells (CIK), tumour-infiltrating lymphocytes (TIL), lymphocyte activated killer cells (LAK), macrophage-activated killer cells (MAK), and other immune effector cells are involved in nonspecific ACI.[1,12]

Immune checkpoint inhibitors:-

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The primary target for preventing T cell over-activation is the immunological checkpoint, which is found on the surface of T cells or tumour cells. Inhibitory checkpoint protein normally prevents harm from autoimmune diseases, but when it comes into contact with a tumour, it will stop T cells from getting close to the tumour, making it harder for the immune system to identify and eliminate tumour cells.[13,14]

CAR-T Cell Therapy ,

CAR-T stands for chimeric antigen receptor T-cell immunotherapy, an effective adoptive cell treatment method. It primarily uses the leukocyte reduction procedure to extract the patient's bodily T cells duress, and by genetic engineering, changed into the surface CAR-T[3,15,16]

People with safe or backslid lymphomas who received CAR-T therapies, such as axicabtagene ciloleucel (Yescarta) and tisagenlecleucel (Kymriah), have shown long-lasting decreases.

Patients with safe or backsliding lymphomas have shown long-lasting improvements with CAR-T treatments including axicabtagene ciloleucel (Yescart) and tisagenlecleucel (Kymriah). Have shown evidence of long-lasting abatements in patients with backsliding or safe lymphomas.[15]

FACTORS INFLUENCING TUMOUR IMMUNOTHERAPY

Numerous factors affect how well tumour immunotherapy works. First, it has to do with human immunity, which is intimately linked to internal macrobiotic and genetics.[4,5] Secondly, it has to do with tumour cells. Tumour neoantigen intra-tumour heterogeneity, the quantity of novel antigens acquired from clones, tumour cell mutation target, and tumour the therapeutic efficacy is greatly impacted by the load, Patients with a high number of clonal source neoantigens and little intra-tumour heterogeneity of tumour neoantigen have more treatment potential. Benefits.[6] Third, environmental factors like daily routine, food, drug use, and bacterial infections are linked to it. Third, environmental factors like daily routine, food, drug use, and bacterial infections are linked to it.[17]

IMPACT OF TUMOUR CLASSIFICATION ON TREATMENT EFFECTIVENESS

Tumours can be classified into three immune types based on their immune characteristics:

1. **Immunosuppressed (Immune Desert Type)**: This type is characterized by the absence or very low density of T cells in both the central and marginal areas of the tumour. Even though some lymphocytes might be present, their number and density are minimal. Tumour-specific killer T cells are the primary cause of immune inhibition in this type. Clinically, PD-1/PD-L1 therapies are largely ineffective for treating these tumours[20].
2. **Immune Excluded (Immune Exemption Type)**: In this type, there is a significant presence of CD3+ and CD8+ lymphocytes around the tumour's edges. However, these T cells are unable to penetrate into the tumour centre. The suppression of the immune response is mainly due to T cell exclusion from the tumour core[20].
3. **Immune Inflammatory Type**: This type is characterized by the presence of PD-L1, pro-inflammatory factors, and effector cells around the tumour. However, tumour

escape mechanisms inhibit the immune response, even though the inflammatory environment is present.[20]

For tumours in the immunosuppressive and immune-excluded categories, treatment strategies may involve targeting T cell trafficking regulators, soluble factor regulators, and approaches aimed at disrupting physical barriers to enhance immune infiltration and response.[7,21,23]

IMPACT OF THE TUMOUR MICROENVIRONMENT ON TREATMENT EFFICACY

The tumour microenvironment comprises tumour cells, peripheral immune cells, neovascularization, endothelial cells, fibroblasts, and the extracellular matrix. In clinical practice, analysing the composition, quantity, and other characteristics of immune cells within the tumour core and surrounding microenvironment helps assess tumour progression, predict its aggressiveness, and evaluate the potential efficacy of immunotherapy. Additionally, the response to immunotherapy in inflammatory tumours can be anticipated by integrating genetic and environmental factors. Inflammatory cells, mediators, and key proteins in inflammatory signalling pathways serve as potential drug targets. While treatment outcomes remain variable, these insights contribute to enhancing therapeutic efficacy and facilitating personalized treatment strategies for patients.[8,9]

Neoantigens

Intratumoral heterogeneity (ITH) of neoantigens, a limited number of clonal neoantigens, and an increase in subclonal neoantigens are key factors contributing to the reduced efficacy of anti-PD1/CTLA4 immunotherapy. A higher presence of clonal neoantigens and lower tumour heterogeneity are associated with significantly prolonged overall survival in patients. Reduced neoantigen heterogeneity, along with an increased number of clonal neoantigens, correlates with elevated expression of pro-inflammatory genes such as PD-L1, IL-6, and IFN-γ in tumours. This suggests a potential link between congenic neoantigens and the activation of effector T cells within inflammatory tumour environments, possibly driven by immune checkpoint molecules and their ligands.[10,23,24]

When the proportion of clonal neoantigens is higher and ITH is lower, patients tend to respond more effectively to immunotherapy. For those exhibiting a strong therapeutic response, peripheral blood analysis can help identify clonal neoantigens recognized by T cells.[25]

However, in some cases, patients undergoing multi-line radiotherapy may develop multiple subclonal neoantigens within tumours. This can lead to a reduction in the proportion of clonal neoantigens, ultimately diminishing the effectiveness of immunotherapy. Despite a high overall mutation burden, these patients often experience poor treatment outcomes. The underlying mechanisms behind this phenomenon are still being explored.[12,26,27]

UNDERLYING MECHANISMS OF PRIMARY IMMUNE RESISTANCE

Tumour-specific T cells exert antitumor effects by producing interferon-γ, which enables the recognition of tumour cells and their corresponding antibodies by antigen-presenting cells (APCs). This mechanism directly inhibits tumour cell proliferation, promotes apoptosis, recruits additional immune cells, enhances tumour antigen presentation, and increases the expression of antigen presentation proteins, such as major histocompatibility complex (MHC) molecules.[13,14]

However, mutations in this pathway can lead to abnormal PD-L1 expression. When cancer cells up regulate PD-L1 expression, the efficacy of PD-L1 or PD-1 blockade therapies is compromised. Additionally, tumour cells can directly express PD-L1, which binds to PD-1 on T cells, suppressing activated cytotoxic T lymphocytes (CTLs), inhibiting cytotoxic T cell activation, and ultimately weakening the immune response. This suppression can lead to T cell

exhaustion and primary resistance to immunotherapy.[15,16,17]

CANCER VACCINES

Increasing the resistant system's ability to identify and eliminate cancer cells is the aim of cancer vaccinations. Instead than anticipating contaminations as is the case with regular immunisations, cancer vaccines, such as the sipuleucel-T antibody for prostate cancer, function by designing a safe framework to attack antigens specific to the disease. Despite the limited effectiveness of restorative cancer antibodies against headstrong or backsliding lymphomas, personalised neoantigen antibodies are a promising area of current research.

ADVANCEMENTS IN IMMUNOTHERAPY

Breakthroughs in Resistant Tumours Immunotherapy has achieved significant progress in treating resistant tumours, which can be more challenging to manage than hematologic malignancies due to the complexities of the tumour microenvironment. Immune checkpoint inhibitors (ICIs) have shown remarkable efficacy in treating non-small cell lung cancer and melanoma, offering long-term survival opportunities to patients who previously faced poor prognoses. The combination of ICIs with targeted therapies or chemotherapy has further improved survival rates across various cancer types.[32,35]

Table 1

Benefits of immunotherapy	Limitations of immunotherapy
Immuno inflammatory tumours respond well to treatment, leading to a significant improvement in long-term survival rates	Immunotherapy has limitations in its target patient group and is highly selective. Its effectiveness is poor for tumors classified as 'immune suppression type' or 'immune exclusion type.
Immunotherapy offers high accuracy, specificity, and targeted action, with long-lasting effectiveness	The use of immune checkpoint inhibitors can trigger negative regulation, potentially leading to autoimmune diseases and even death. Some patients may experience various non-specific toxic side effects, and in some cases, hyper progressive disease may occur, accelerating patient mortality.

PROGRESS IN PERSONALIZED MEDICINE

With the advancement of therapies tailored to each patient's unique tumor biology, personalized immunotherapy has gained increasing popularity. Biomarkers such as microsatellite instability (MSI) and PD-L1 expression have improved the ability to accurately identify patients most likely to respond to immune checkpoint inhibitors (ICIs). Additionally, technological advancements in sequencing have facilitated the identification of tumor-specific neoantigens, contributing to the development of customized vaccines and T cell therapies.[35]

BLOCKERS

PD-1/PD-L1 Blockade

The development of checkpoint inhibitors like pembrolizumab (Keytruda) and nivolumab (Opdivo) marks a major breakthrough in cancer immunotherapy. These therapies target the PD-1/PD-L1 pathway, which malignant tumours exploit to evade immune detection. By blocking this interaction, these treatments enhance the immune system’s ability to recognize and attack cancer cells more effectively. They have demonstrated significant success in treating various cancers, including bladder cancer, non-small cell lung cancer, and melanoma.[36]

OBSTACLES IN CANCER IMMUNOTHERAPY

Immune-Related Adverse Events (irAEs)

The effectiveness of immunotherapy is challenged by immune-related adverse events (irAEs), which occur when immune cells mistakenly target healthy organs. Common side effects include

endocrinopathies, colitis, hepatitis, and pneumonia. In some cases, managing these complications requires immunosuppressive treatments, which may reduce the overall efficacy of cancer immunotherapy.[37]

RESISTANCE TO IMMUNOTHERAPY

Although ICIs and CAR-T therapies have shown significant effectiveness, many patients either fail to respond or develop resistance over time. Mechanisms of resistance include the down regulation of antigen expression, modifications to the tumour microenvironment, and the overexpression or substitution of immune checkpoints. To overcome these challenges, researchers are exploring combination therapies, such as integrating ICIs with radiation therapy or targeted treatments, to enhance therapeutic outcomes.[40,41]

COMBINATION THERAPIES

Combination therapies provide a promising approach to overcoming resistance and improving treatment outcomes by integrating immunotherapy with other modalities such as chemotherapy, radiation, or targeted therapy. For instance, pairing ICIs with anti-angiogenic agents has been shown to enhance immune cell infiltration, normalize tumour vasculature, and ultimately extend survival in various cancers.[42,45]

CONCLUSION

Immunotherapy has transformed cancer treatment, offering hope to patients with previously incurable diseases. However, to fully harness its potential, challenges such as resistance, adverse events, and high costs must be addressed. Future research and clinical trials are expected to drive the development of innovative combination therapies, personalized treatment approaches, and novel strategies to enhance both the effectiveness and accessibility of cancer immunotherapy.

Over the past decade, cancer immunotherapy has significantly reshaped patient care, demonstrating remarkable efficacy in cases where conventional treatments failed. Despite this progress, optimizing immune checkpoint inhibitor (ICI) therapies remains a challenge. Further research is needed to explore alternative checkpoint pathways that contribute to tumour evasion, as well as the immunosuppressive effects of the tumour microenvironment (TME) on ICI efficacy.

Chimeric antigen receptor T-cell (CAR-T) therapy has shown promising results in hematologic malignancies but remains less effective in solid tumours due to the highly immunosuppressive TME. Targeting immunosuppressive components of the TME, such as tumour-associated macrophages (TAMs), may enhance the efficacy of both CAR-T and ICI therapies. Clinical trials investigating the use of these agents alongside ICIs or as preconditioning for CAR-T therapy will be crucial in identifying the most effective treatment strategies.

By leveraging ICIs to target various immune escape mechanisms, new therapeutic combinations are emerging. Advances in CAR-T engineering, aimed at improving trafficking to solid tumours and reducing immunosuppression, could further enhance treatment outcomes. Additionally, cancer vaccine research has made significant strides, particularly in combination with TME-targeting strategies and neoantigen vaccines, opening exciting new avenues for future cancer immunotherapy development.

Tumour-specific T cells recognize and target tumour cells by producing IFN and corresponding antibodies, thereby recruiting additional immune cells and triggering an anti-tumour response.

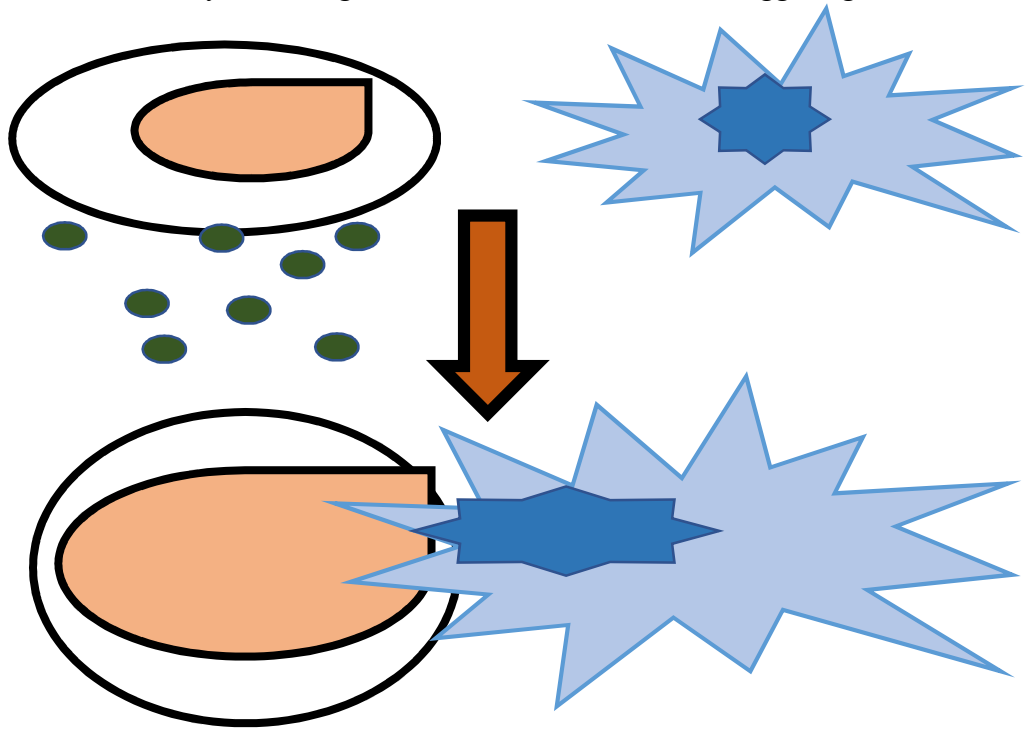

Fig 1: the immunotherapy medication resistance mechanism. Both the primary immune resistance mechanism and the secondary immunological system of cancers can facilitate the escape of anti-tumor medications. Additionally, anti-tumor therapies can be resisted by tumor cell targets self-neutralizing, antigen-presenting cell targets, and tumor exosomes suppressing immunity, which can lessen or even eliminate the effectiveness of immunotargeted medications.

Declaration of Interest:

The author declare no conflict of interest, financial or otherwise

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