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Review Article

Role of immunotherapy in cancer management

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ABSTRACT

Cancer remains one of the leading causes of mortality worldwide accounting for nearly 20 million new cases and 10 million deaths, prompting continuous research for more effective treatments. In recent years' immunotherapy has transformed the landscape of cancer treatment, with significant breakthroughs promising more targeted and durable outcomes. Unlike standard treatments, such as surgery, chemotherapy, and radiation, which directly target cancer cells, immunotherapy aims to boost or replace the immune system's natural ability to fight cancer. Since it is a new mode of therapy most of the practicing doctors are unaware of the details about it. In this context, we conducted a narrative review based on available literature. This article explores the historical background and evolution of immunotherapy, the mechanisms of various immunotherapeutic plans, recent advancements, future directions, and challenges in this field. Our paper focused on, checkpoint inhibitors, chimeric antigen receptor T (CAR-T) cell therapy, oncolytic virus therapy, and cancer vaccines. As the field continues to evolve, collaboration among researchers, clinicians, and patients is essential to drive these advancements and improve outcomes in cancer care.

Keywords: Immunotherapy, Checkpoint inhibitors, CAR-T cell therapy, Oncolytic virus therapy

INTRODUCTION

Cancer remains one of the leading causes of mortality worldwide accounting for nearly 20 million new cases and 10 million deaths in 2020, almost one-sixth of all deaths, prompting continuous research for more effective treatments.[1] The field of cancer therapy is rapidly evolving, with ongoing research promising to refine existing treatments and discover new modalities. Traditional modalities of treatment, including surgery, chemotherapy, and radiation, have limitations related to specificity and toxicity. In recent years' immunotherapy has transformed the landscape of cancer treatment, with significant breakthroughs that aim to enhance the body's natural immune response against tumours, offering the promise of more targeted and durable outcomes.[2]

With the advent of immunotherapy in cancer, there has been a major improvement in patient's quality of life (QOL) and survival. Unlike standard treatments, such as surgery, chemotherapy, and radiation, which directly target cancer cells, immunotherapy aims to boost or replace the immune system's natural ability to fight cancer. The immune system comprises white blood cells, cytokines, antibodies, and the lymphatic system which help your body to fight infections and other diseases.[3] As part of its normal function, the immune system detects and destroys abnormal cells and most likely prevents the growth of many cancers and it was seen that immune cells are sometimes found in and around tumours also. These cells are called tumour-infiltrating lymphocytes (TILs) showing the immune system's response towards the tumour.[4] People whose tumours contain TILs often do better than people whose tumours don't contain them. Even though the immune system can prevent or slow cancer growth, cancer cells have many methods to overcome them.[5,6] They have genetic changes that make them less visible to the immune system or have proteins on

their surface that turn off immune cells or even change the normal cells around the tumour.[7]

In this context, we conducted a narrative review based on available literature. This article explores the historical background and evolution of immunotherapy, mechanisms of various immunotherapeutic plans, recent advancements, and future directions in this field focused on, checkpoint inhibitors, chimeric antigen receptor T (CAR-T) cell therapy, oncolytic virus therapy, and cancer vaccines.

HISTORICAL BACKGROUND AND EVOLUTION OF IMMUNOTHERAPY AS A TREATMENT OPTION

The idea of using the immune system to fight against cancer was established over a century. Dr. William Coley (1862-1936), a surgeon known as the "Father of Immunotherapy," in the late 19th century, observed that some cancer patients experienced tumour regression after contracting infections.[6] He postulated that the immune response triggered by the infection might be responsible for this phenomenon. He began experimenting with injecting patients with bacterial toxins, which were later known as Coley's toxins, to stimulate immune responses. While results were contradictory, this early work laid the foundation for future immunotherapeutic approaches.[8]

In the following decades, researchers began to identify specific immune cells, such as lymphocytes, and their functions. It was found out that certain substances are produced by cancer cells known as tumour antigens that can arouse immune response- further driving interest in controlling the immune system for cancer treatment.[9] During the 1970s and 1980s, the idea of adoptive cell transfer emerged, where immune cells could be harvested from patients, activated, and reinfused. This approach laid the groundwork for the later development of CAR-T cell therapy.[10]

The 1990s marked a turning point in immunotherapy with the introduction of monoclonal antibodies (mAb). One of the first mAb rituximab was approved by the United States Food and Drug Administration (US FDA) in 1997 for B cell non-Hodgkin lymphoma was a milestone in this direction.[11] During the same period Interferons and Interleukins were also developed as treatment choices, further confirming the role of immune modulation in cancer therapy.[12-14] The discovery of immune checkpoint proteins in the 2000s, particularly the programmed cell death protein (PD-1), programmed cell death ligand 1 (PD-L1) and cytotoxic T lymphocyte antigen 4 (CTLA-4) pathways, alter dramatically the field of immunotherapy. Researchers found that tumours could avoid immune detection by utilizing these checkpoints. The first checkpoint inhibitor, ipilimumab, was approved in 2011 by the US FDA for melanoma, marking a remarkable landmark. This was followed by the approval of other checkpoint inhibitors, such as nivolumab (2014) and pembrolizumab (2014) giving rise to unparalleled responses in various malignancies, both were included in the World Health Organization (WHO) list of essential medicines.[15]

The development of CAR-T cell therapy represented another significant advancement in immunotherapy. Therapies like tisagenlecleucel (Kymriah) and axicabtageneciloleucel (Yescarta) were approved for certain haematological cancers by 2017. This is considered to be a personalized approach to therapy involving modified patient's T cells to attack their specific cancer cells, resulting in remarkable clinical responses and durable remissions.[15-17]

In addition, the identification of new biomarkers for patient selection and the emergence of neoantigen vaccines that target specific proteins on tumour cells and oncolytic virus therapies that kill cancer cells also continue to drive a revolution in this field (Table 1). Clinical trials are ongoing to improve these therapies and mark the challenges such as immune-related adverse events and tumour resistance.

TYPES OF IMMUNOTHERAPY

Immune checkpoint inhibitors

Immune checkpoint inhibitors represent a notable development, offering new hope for patients with various malignancies.[17] Immune checkpoints are the normal components of the immune system and are inhibitory molecules that prevent exaggerated immune response and maintain immune tolerance in normal physiological conditions. These inhibitory molecules are over-expressed in the tumour microenvironment (TME), contributing to tumour-promoting immunosuppression.[17] So, by blocking these molecules or checkpoints, these therapies can renovate T-cells, allowing them to effectively target tumours, and free the immune system allowing T-cells to proliferate, activate, and prepare an effective attack against cancer cells which leads to increased immune-mediated tumour destruction. They are considered a novel class of cancer therapies that enhance the immune system's ability to recognize and kill cancer cells. The most commonly seen immune checkpoints are CTLA4, PD1, and programmed cell death ligand 1 (PD-L1). The three major classes of checkpoint inhibitors currently used are anti-CTLA-4 antibodies (e.g. ipilimumab), anti-PD-1 (nivolumab and pembrolizumab) and anti-PD-L1 antibodies (atezolizumab and durvalumab).[18] Some cancer cells express PD-L1, which binds to PD-1 on T cells to inhibit their function. Checkpoint proteins, such as PD-L1 on tumour cells and PD-1 on T cells, help keep in hold of immune responses. The binding of PD-L1 to PD-1 keeps T cells from killing tumour cells in the body. Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumour cells. Drugs like atezolizumab and durvalumab target PD-L1 to prevent this immune evasion.[19-21] By rejuvenating the immune system's ability to fight cancer,

these therapies have changed the treatment outlook and continue to be an area of intense research and clinical interest.[22-24] They are often combined with other treatments, such as chemotherapy, targeted therapy, or other immunotherapy, to enhance efficacy and broaden the range of receptive tumours. Indications for checkpoint inhibitors are mainly melanoma, non-small cell lung cancer (NSCLC), bladder cancer, and Hodgkin lymphoma.[24]

Table 1: Immunotherapy drugs in cancer.

Types of immune therapy	Mechanism	Common indications	Examples
Immune check point inhibitors (ICI)	Blocking immune check points – anti CTLA-4, PD 1, programmed cell death ligand (PDL1)	Melanoma, non-small cell lung cancer, bladder cancer, Hodgkin lymphoma	Anti CTLA4 antibody: ipilimumab; anti PD 1: nivolumab, and pembrolizumab; anti PDL1: atezolizumab and durvalumab
T cell therapy/adoptive cell therapy (ACT), and CAR-T cell therapy	Tumor infiltrating lymphocytes (TIL) therapy, modified T cells with CARs target cancer cells	B cell precursor ALL (young patients), large B cell lymphoma	Tisagenlecleucel, axicabtageneciloleucel, brexucabtageneautoleucel (Tecartus), ciltacabtageneautoleucel (Carvykti), idecabtagenevicleucel (Abecma), lisocabtagenemaraleucel (Breyanzi), actalycabtagene autoleucel (Acaty-cel)
Cancer vaccines	Enhance immune system ability to identify and eliminate malignant cells	Early stage bladder Ca, asymptomatic castrate resistant prostate cancer	Prophylactic: hepatitis B vaccine, and human papilloma virus vaccine; therapeutic: BCG, and sipuleucel T (Provenge)
Oncolytic virus therapy	Modified viruses to selectively infect and kill cancer cells	Melanoma	Talimogenelahrparepvec (T-VEC or imlygic)

T cell transfer therapy or adoptive cell therapy

Another type of immunotherapy is T-cell transfer therapy which makes immune cells better able to attack cancer cells, which are mainly two types tumour-infiltrating lymphocytes or TIL therapy and CAR T-cell therapy. Immune cells are collected and then these cells are grown and expanded in large numbers in a laboratory setting. Finally, these amplified cells are reintroduced to the patient who has undergone a lymphocyte-depleting predatory regimen.[25]

TIL therapy uses T cells that are found in and around the tumours which are tested in the lab to find out which ones best recognize the tumour cells. Then, these selected lymphocytes are treated with substances that make them grow in large numbers quickly. The idea behind this approach is that the lymphocytes that are in or near the tumour have already shown the ability to recognize the tumour cells. But there may not be enough of them to kill the tumour or to overcome the signals that the tumour is releasing to suppress the immune system. Therapy using a large number of the lymphocytes that react best with the tumour can help to overcome these barriers.[25]

CAR- T cell therapy is similar to TIL therapy, but the T cells are modified in the lab where a specific antigen receptor known as chimeric antigen receptor (CAR) is introduced, allowing them to recognize tumour-specific antigens. CARs are designed to allow the T cells to attach to specific proteins on the surface of the cancer cells, improving their ability to attack the cancer cells. This innovative treatment has shown remarkable success, particularly in certain haematological malignancies, and represents a significant advancement in cancer treatment.[23] Two FDA-approved CAR-T cell therapies are tisagenlecleucel and axicabtageneciloleucel. Tisagenlecleucel is for the treatment of paediatric patients and young adults with refractory or relapse (R/R) B cell precursor acute lymphoblastic leukaemia (ALL), whereas axicabtageneciloleucel is for the treatment of adult patients with R/R large B cell lymphoma. Both of them are genetically modified autologous T cells expressing a CD19-specific CAR, lysing CD19-positive targets (normal and malignant B lineage cells). The differences between them are mainly in the vectors used, where the lentiviral vector for tisagenlecleucel and ϒ-retroviral vector for axicabtageneciloleucel.[26,27] Other FDA-approved CAR-T cell therapies are brexucabtageneautoleucel (Tecartus), ciltacabtageneautoleucel (Carvykti), idecabtagenevicleucel (Abecma), lisocabtagenemaraleucel (Breyanzi).[27,28] India's Central Drugs Standard Control Organization (CDSCO) approved actalycabtagene autoleucel (Actaly-cel) to treat refractory B cell lymphomas and leukaemia which was launched in October 2023.[28-30]

While CAR-T cell therapy has shown tremendous success in haematological malignancies, its application in solid tumours has been more challenging due to factors like the tumour microenvironment and antigen heterogeneity. Research is ongoing to improve its efficacy in solid tumours.

In haematological malignancies, CAR-T cell therapy represents a monumental advancement in the treatment. By transforming patients' T cells into powerful tools against cancer, CAR-T cell therapy has provided new hope for many who have exhausted other treatment options. Ongoing research and development aim to expand its applicability, improve safety, and enhance outcomes for a broader range of cancer patients.[25]

Apart from checkpoint inhibitors and CAR-T cell therapy, several other innovative strategies are being developed and tested to control the immune system's power against cancer. Here are some of the most promising novel approaches.

Cancer vaccines

Cancer vaccination, also known as cancer immunization or cancer immunotherapy, is a therapeutic strategy designed to stimulate the immune system to recognize and target cancer cells. The primary goal is to prevent tumour growth, recurrence, and metastasis by enhancing the immune system's ability to identify and eliminate malignant cells. The mechanisms involve eliciting a targeted immune response against specific tumour-associated antigens (TAAs) which are proteins expressed or overexpressed by cancer cells, serving as recognizable targets for the immune system. They trigger a multifaceted immune response, activating T cells, B cells, and other immune cells to target and destroy cancer cells. They can be categorized into two main types, which are prophylactic which is designed for high-risk populations to prevent developing cancer (e.g. hepatitis B vaccine, and human papilloma virus vaccine) and the other one is therapeutic. Therapeutic vaccines are for individuals already diagnosed with cancer, to bolster the immune system's fight against the disease. By leveraging the immune system's power, cancer vaccination offers promising strategies for both cancer prevention and treatment.[31,32] Two examples of therapeutic cancer vaccines are Bacillus Calmette–Guérin (BCG) and Sipuleucel-T (Provenge). The former is accepted for a patient with early-stage bladder cancer and the latter is proven for asymptomatic metastatic castrate-resistant prostate cancer. Sipuleucel-T works by generating an immune response, targeting the prostatic acid phosphatase antigen, which is overexpressed in the majority of prostate cancers.[33,34]

Oncolytic virus therapy

The concept of oncolytic virus therapy originated from the finding that virus-infected tumour cells are killed by the cytotoxic effects of viruses that are capable of infecting living cells and replicating within the cells by utilizing the host genetic machinery. In this method, genetically modified viruses that selectively infect and kill cancer cells are used.[35] Oncolytic virus therapy, is sometimes described as a type of cancer treatment vaccine.

The first FDA and European Union-approved oncolytic virus therapy was talimogenelaherparepvec (T-VEC, or Imlygic) in 2015 to treat melanoma which is based on herpes simplex virus type 1. T-VEC is injected directly into a tumour. Although this virus can infect both cancer and normal cells, normal cells can kill the virus while cancer cells cannot. As the virus makes more and more copies of itself, it causes cancer cells to burst and die. The dying cells release new viruses and other substances that can cause an immune response against cancer cells throughout the body.[35]

CHALLENGES AND FUTURE DIRECTIONS IN CANCER IMMUNOTHERAPY

While cancer immunotherapy has made significant advancements, several challenges remain unresolved. They are mainly on immune-related adverse events, tumour heterogeneity primary and acquired resistance, limited efficacy in solid tumours, biomarker identification, and cost and accessibility. Addressing these challenges will be crucial for maximizing the potential of immunotherapeutic strategies and improving patient outcomes.

Immune-related adverse events

The adverse events (AE) are mainly autoimmune reactions, leading to side effects that affect various organs, such as colitis, pneumonitis, and endocrinopathies. These adverse events can limit the treatment options and affect patients' quality of life, necessitating effective management strategies.[36]

Tumour heterogeneity

Inter and intra-tumour heterogeneity poses a significant challenge to immunotherapy. Tumours can exhibit substantial variability within a single patient and across different patients, leading to diverse antigen expression profiles and immune responses.[36]

This heterogeneity can compromise the efficacy of immunotherapies, highlighting the need for personalized and adaptive treatment strategies.

Primary and acquired resistance

Not all patients respond to immunotherapy, and some may develop resistance over time. Understanding the mechanisms of resistance, such as loss of antigen expression or immune evasion tactics, is critical for improving treatment strategies.

Limited efficacy in solid tumours

While immunotherapy has shown remarkable success in haematological cancers, its efficacy in solid tumours has been more variable. Factors such as the tumour

microenvironment, immune suppression, and insufficient T-cell infiltration pose significant challenges.[36,37]

Cost and accessibility

Many immunotherapies are expensive and require specialized manufacturing processes. High costs can limit patient access, particularly in low-resource settings, and present challenges for healthcare systems.

Biomarker identification

Identifying reliable biomarkers to predict patient response to immunotherapy is still a developing area. Effective biomarker identification is essential for patient selection and optimizing treatment strategies.[36,37]

CONCLUSION

Despite the remarkable progress made in cancer immunotherapy recently, several challenges must be addressed to maximize its potential. By focusing on combination therapies, personalized medicine, and innovative research, the future of immunotherapy holds promise for overcoming current limitations and expanding treatment options for patients with cancer. As the field continues to evolve, collaboration among researchers, clinicians, and patients will be essential to drive these advancements and improve outcomes in cancer care.

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