ABSTRACT: Immunotherapy is a type of cancer treatment that aims to enhance the body's immune system to detect and destroy cancer cells. It can be used alone or in combination with other treatments like chemotherapy and radiation therapy. Immunotherapy works by using substances produced by the body or created in a laboratory to stimulate the immune response against cancer. A model called the cancer immunity cycle summarises the research on each phase of a productive anti-cancer immune response. The stages involved in an effective anti-tumor immune response for tumour elimination are described by the cancer immunity cycle. The cycle starts when the immune system recognises cancer antigens. Dendritic cells (DCs), one kind of antigen-presenting cell (APC), phagocytose dying cells. These cells have the ability to seize antigens and transfer them to T lymphocytes, which can then identify and eliminate cancer cells. On the other side, cancer cells are able to evade detection by lowering T cell activation or secreting checkpoint chemicals that prevent T cell function. It is crucial to look beyond the tumour microenvironment (TME) in order to understand cancer immunology properly. It is essential to have a peripheral immune system.

KEYWORDS: Immune, surgery, oncology, vaccines, oncolytic, neoantigens, antibodies

Introduction: [1-14]
Immunotherapy is a type of cancer treatment in which substances produced by the body or in a laboratory are used to enhance the immune system and assist the body in locating and destroying cancer cells. It can be used either alone or in conjunction with chemotherapy and/or other cancer treatments to treat a wide range of cancer types. Immunotherapy works by assisting the immune system in its fight against cancer. Immune checkpoint inhibitors, cancer vaccines, and immune system modulators are all types of immunotherapy used to treat cancer. Although immunotherapy medications have been licenced to treat a variety of cancers, they are not as extensively utilised as surgery, chemotherapy, or radiation therapy. The goal of immunotherapy is to alter the ongoing immune response from tumor-promoting to tumor-rejecting, resulting in long-term cancer control. Understanding the interaction between the immune system and cancer has resulted in the creation of several immunological medicines for cancer treatment. Oncology medications come in a variety of forms and are used to treat cancer. Here are some search results examples:

Targeted therapy drugs: These medications are intended to target particular chemicals involved in cancer cell growth and dissemination. The FDA has authorised targeted therapy medications for the treatment of several cancers, including breast cancer, bladder cancer, brain cancer, lung cancer, and lymphoma.

Immunotherapy drugs: These medications function by stimulating the immune system allowing the body to detect and eliminate cancer cells. Immunotherapy medications are classified into numerous kinds, including checkpoint inhibitors cancer vaccines and combination treatment with immune checkpoint blockers.

Checkpoint inhibitor: These medications inhibit certain proteins on the surface of immune cells, allowing the immune system to recognise and destroy cancer cells. Nivolumab, atezolizumab, pembrolizumab, avelumab, durvalumab, and cemiplimab are examples of checkpoint inhibitors.

Cancer vaccines: These vaccines can lower cancer risk by eliminating cancer-causing viruses. They can cure cancer by activating the immune system to attack cancer cells in a specific section of the body. Gardasil and spleucel-T are two cancer vaccinations.

Combination therapy with immune checkpoint blockers: In order to increase the efficacy of checkpoint inhibitors, this type of therapy involves combining them with additional medications.

Immune inhibitors: Immune inhibitors are immunotherapies that prevent immune checkpoint proteins from interacting with partner proteins. Some immune system cells, such as T cells, and some cancer cells produce checkpoint proteins. They function similarly to switches that must be switched on (or off) to initiate an immune response. Cancer cells may employ these checkpoints to avoid being attacked by the immune system. Immune checkpoint inhibitors prevent checkpoint proteins from interacting with their partner proteins, which is how they function. Because of this, the T cells are able to destroy cancer cells because the "off" signal is not transmitted. Immune checkpoint inhibitors come in a variety of forms, such as CTLA-4 inhibitors, PD-L1 inhibitors, and PD-L1 inhibitors. Immune checkpoint inhibitors include atezolizumab (Tecentriq), nivolumab (Opdivo), pembrolizumab (Keytruda), and ipilimumab (Yervoy). Some persons with a range of cancer types, including as breast cancer, bladder cancer, lung cancer, and melanoma skin cancer, may be treated with immune checkpoint inhibitors.
A current perspective on the anti-cancer response: [15, 16, 17, 18, 19, 20]

The cancer immunity cycle is a model that summarises scientific information on each stage of a successful anti-cancer immune response. The cancer immunity cycle describes the phases involved in an efficient anti-tumor immune response for tumour eradication.

When tumour antigens are recognised by the immune system, the cycle begins. Antigen-presenting cells (APCs) such as dendritic cells (DCs) phagocytize dying cells. These cells can grab antigens and deliver them to T lymphocytes, which can then recognise and destroy tumour cells. Cancer cells, on the other hand, can avoid detection by decreasing T cell activation or producing checkpoint molecules that impede T cell activity. To gain a better knowledge of tumour immunology, it is necessary to go beyond the tumour microenvironment (TME). The peripheral immune system is necessary to promote successful antitumor immune responses, both naturally and therapeutically. Changes in antitumor immunity after surgery can result in new and accelerated metastatic development despite original tumour excision. Anticancer immunotherapies should aim to reactivate all stages of the cancer immunity cycle, including immunogenic cell death, antigen-presenting cell maturation, T cell priming and activation, T cell trafficking to tumours, T cell infiltration into tumours, T cell recognition of cancer cells, and T cell killing of cancer cells. Immune checkpoint inhibition, with a focus on anti-PD-L1 and anti-CTLA-4 antibodies, chimeric antigen receptor T (CAR-T) cells, bispecific T cell engagers (BiTEs), and cancer vaccines are all current immunotherapeutic treatments against cancer. An adaptive immune response to cancer in HPV-mediated cervical cancer has been characterised in seven essential phases or steps known as the cancer-immunity cycle (CIC). Cancer cell antigens are released to start the CIC, and T lymphocytes destroy cancer cells to finish it.

CHALLENGES:

Some of the major challenges associated with immuno-oncology agents in cancer treatment are listed below-

1) Lack of response in certain patients: While immuno-oncology agents have shown remarkable efficacy in some patients, a significant proportion of patients do not respond to these treatments. Several factors contribute to this lack of response, including tumor heterogeneity, immune evasion mechanisms employed by cancer cells, and a suppressive tumor microenvironment. Understanding the underlying mechanisms of resistance and identifying predictive biomarkers are active areas of research [1].

2) Development of acquired resistance: While some patients initially respond to immuno-oncology agents, resistance can develop over time. Cancer cells can evolve mechanisms to escape immune surveillance, such as upregulation of alternative immune checkpoints or alterations in antigen presentation machinery. Unraveling the mechanisms of acquired resistance and developing strategies to overcome it is a significant challenge in the field [2].

3) Toxocities and immune-related adverse events (irAEs): Immune checkpoint inhibitors can lead to immune-related adverse events affecting various organs, including the skin, gastrointestinal tract, liver, and endocrine system. These toxicities require vigilant monitoring and appropriate management to minimize patient morbidity and optimize treatment outcomes [3].

4) Cost and accessibility: Immuno-oncology agents can be expensive, limiting their accessibility for some patients. The high cost of development and manufacturing, along with the need for long-term treatment, pose challenges for widespread adoption of these therapies. Efforts are underway to improve cost-effectiveness and explore alternative treatment strategies [4].

5) Combination therapy complexities: While combination therapies hold promise for enhancing the efficacy of immuno-oncology agents, determining the optimal combinations and sequencing of treatments can be complex. Identifying synergistic combinations, understanding potential overlapping toxicities, and conducting appropriate clinical trials to establish safety and efficacy are ongoing challenges [5].

6) Resistance to immune checkpoint inhibitors: Resistance mechanisms can hinder the effectiveness of immune checkpoint inhibitors, leading to treatment failure. Tumor heterogeneity, alterations in antigen presentation and immune escape mechanisms contribute to resistance [6].

7) Lack of predictive biomarkers: Identifying reliable biomarkers that can accurately predict patient response to immuno-oncology agents remains a challenge. Current biomarkers, such as PD-L1 expression, have limitations in predicting treatment outcomes [7].

8) Limited efficacy in certain tumor types: Immuno-oncology agents have demonstrated remarkable efficacy in some tumor types, but their effectiveness in others remains limited. Developing strategies to enhance responses in tumors with low immunogenicity is a challenge [8].

9) Optimal timing and sequencing of therapies: Determining the optimal timing and sequencing of immuno-oncology agents with other treatment modalities, such as chemotherapy or targeted therapy, is challenging. Finding the right combination and order of treatments is crucial to maximize therapeutic benefits [9].

10) Development of new immune checkpoints: Identifying and targeting additional immune checkpoints beyond PD-1 and CTLA-4 is an ongoing challenge. Discovering and understanding new checkpoint molecules could lead to improved treatment options [10].


These challenges underscore the ongoing efforts to optimize immuno-oncology agents and overcome barriers to improve patient outcomes in cancer treatment. It’s important to note that the field of immuno-oncology is rapidly evolving, and ongoing research is addressing these challenges to optimize the use of immuno-oncology agents in cancer treatment.
NEW PERSPECTIVES:
New perspectives and advancements in the field of immuno-oncology agents in cancer treatment are:

1) **Combination therapies:** Combination strategies involving immuno-oncology agents with other modalities, such as targeted therapies, chemotherapy, radiation therapy, and other immunotherapies, are being explored. Researchers are exploring the use of multiple immune checkpoint inhibitors or combining immune checkpoint inhibitors with other immunotherapeutic approaches, such as adoptive cell transfer or cancer vaccines. Immuno-oncology agents are being combined with other treatment modalities, such as radiation therapy or targeted therapy, to achieve synergistic effects. These combination strategies aim to enhance the immune response and overcome resistance mechanisms and improve treatment outcomes [12-14].

2) **Personalized medicine and biomarker discovery:** Efforts are underway to identify predictive biomarkers that can guide patient selection for immuno-oncology therapies. Various biomarkers, including tumor mutational burden, gene expression signatures, and immune cell profiling, are being investigated to develop comprehensive predictive models and enable personalized treatment approaches. Advances in genomic profiling and biomarker discovery are enabling the development of personalized immunotherapies tailored to individual patients. Precision medicine approaches aim to identify specific genetic alterations or immune signatures that can guide the selection of immuno-oncology agents [15-16].

3) **Targeting novel immune checkpoints:** In addition to the well-known immune checkpoints like PD-1 and CTLA-4, researchers are exploring and targeting other immune checkpoints, such as LAG-3, TIM-3, TIGIT, and IDO-1. Targeting these checkpoints offers potential avenues to enhance the efficacy of immuno-oncology agents and overcome resistance [17].

4) **Adoptive cell therapies:** Adoptive cell therapies, including chimeric antigen receptor (CAR) T-cell therapy and tumor-infiltrating lymphocyte (TIL) therapy, are being explored as complementary approaches to immuno-oncology agents. These therapies involve engineering or expanding patient-derived immune cells to enhance their tumor-targeting capabilities [18].

5) **Nanoparticle-based immunotherapies:** Nanoparticles are being developed as delivery systems for immuno-oncology agents, allowing targeted and controlled release of these therapies. This approach aims to improve drug delivery to the tumor site, enhance immune cell activation, and minimize off-target effects [19].

6) **Microbiome modulation:** Mounting evidence suggests that the composition of the gut microbiome influences the response to immuno-oncology agents. Modulating the microbiome through approaches like fecal microbiota transplantation or targeted interventions could enhance treatment outcomes [20].

7) **Engineering immune cells for enhanced efficacy:** Advances in gene editing technologies, such as CRISPR/Cas9, are enabling the engineering of immune cells to enhance their tumor-targeting capabilities and resistance to immune suppression. This includes strategies like CAR-T cells and TCR-engineered T cells [21].

8) **Immunomodulatory antibodies beyond checkpoints:** Beyond immune checkpoint inhibitors, researchers are developing immunomodulatory antibodies that target different molecules or pathways involved in immune regulation. These novel antibodies can modulate immune responses and enhance anti-tumor activity [22].

9) **Overcoming immunosuppressive tumor microenvironment:** Researchers are exploring strategies to overcome the immunosuppressive tumor microenvironment, such as targeting immunosuppressive cells (e.g., regulatory T cells) or inhibitory molecules within the tumor microenvironment to enhance immune cell activity [23].

These new perspectives and advancements in immuno-oncology offer exciting opportunities to further improve cancer treatment outcomes and expand the scope of immunotherapeutic strategies.

DEVELOPMENT OF IMMUNO ONCOLOGY AGENTS:
The field of immuno-oncology has witnessed significant development in the discovery and development of novel agents that enhance the immune response against cancer.

Immune Checkpoint Inhibitors: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by targeting molecules that regulate immune responses, such as programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) [6 & 10].

Bispecific Antibodies: Bispecific antibodies are designed to simultaneously bind to cancer cells and immune cells, facilitating their interaction and enhancing anti-tumor immune responses. They can redirect T cells to recognize and eliminate tumor cells [24-25].

Oncolytic Viruses: Oncolytic viruses are designed to selectively infect and destroy cancer cells while stimulating an immune response against the tumor. These viruses can be engineered to express immunostimulatory molecules or target specific cancer antigens [26-27].

Cancer Vaccines: Cancer vaccines aim to stimulate the immune system to recognize and attack cancer cells. They can consist of tumor antigens, immune stimulators, or personalized neoantigens derived from the patient's own tumor [28-29].
**APPLICATIONS: [30-37]**

Immunoncology agents have shown significant promise in cancer treatment across various types of malignancies. Here are some key applications of immunoncology agents.

1. **Melanoma:** Immune checkpoint inhibitors, such as anti-PD-1 antibodies (nivolumab, pembrolizumab), have shown significant efficacy in metastatic melanoma.
2. **Lung Cancer:** Immune checkpoint inhibitors, particularly anti-PD-1/PD-L1 antibodies, have shown efficacy in non-small cell lung cancer (NSCLC), both as monotherapy and in combination with chemotherapy.
3. **Renal Cell Carcinoma:** Immune checkpoint inhibitors, such as nivolumab and pembrolizumab, have shown efficacy in advanced renal cell carcinoma (RCC).
4. **Bladder Cancer:** Immune checkpoint inhibitors, including atezolizumab and pembrolizumab, have shown efficacy in advanced bladder cancer.
5. **Head and Neck Cancer:** Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, have shown efficacy in recurrent or metastatic head and neck squamous cell carcinoma (HNSCC).
6. **Lymphoma:** CAR T-cell therapy, particularly axicabtagene ciloleucel and tisagenlecleucel, has shown significant efficacy in relapsed or refractory B-cell lymphomas.
7. **Colorectal Cancer:** Immune checkpoint inhibitors, such as pembrolizumab, have shown efficacy in microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) metastatic colorectal cancer.
8. **Hepatocellular Carcinoma:** Immune checkpoint inhibitors, such as nivolumab and pembrolizumab, have shown efficacy in advanced hepatocellular carcinoma (HCC).
9. **Breast Cancer:** Immune checkpoint inhibitors, such as atezolizumab, in combination with chemotherapy, have shown efficacy in advanced triple-negative breast cancer (TNBC).
10. **Prostate Cancer:** Immune checkpoint inhibitors, such as pembrolizumab, are being investigated in metastatic castration-resistant prostate cancer (mCRPC) with specific biomarkers like microsatellite instability-high (MSI-H).

**Conclusions and future perspectives:**

The development of cancer immunotherapy for ICI-resistant cancers has been a challenge. Current ICI-based combination therapy strategies have achieved some, albeit limited, success. A deep understanding of TIME biology in the IO field is necessary for generating next-generation immunoncology therapeutic strategies. ICIs, CAR-T therapy, adoptive cell therapy, and other anti-tumor immunity enhancement approaches will continue to lead the way in the clinical IO space. However, new classes of immunotherapy are emerging. These new classes aim at normalizing the “defective” TIME by targeting immunosuppressive components unique to the tumors, priming effector T cells by in situ oncolytic therapy, broadening effective T cell repertoire with multi-valent neoantigen-based vaccines, modulating metabolic programming for sustained T cell function and promoting effective immune-mediated cell death. All together, these emerging strategies point towards a promising new wave of cancer immunotherapies that may allow us to surmount the limitations of previous ones.

**REFERENCES:**