

THE ROLE OF IMMUNE CHECKPOINT INHIBITORS IN CANCER TREATMENT

Murodova Gulasal Xurshid qizi

Samarkand State Medical University

murodovagulasal2007@gmail.com

Rasulov Jo'rabek Odil o'g'li

Termez Branch of Tashkent State Medical University

jorabekrasulov2005@gmail.com

Murodov Diyorbek Otabek o'g'li

Termez Branch of Tashkent State Medical University

murodovdiyorbek200@gmail.com

Po'latov Samandar Sherali o'g'li

Termez Branch of Tashkent State Medical University

snsjd10samandar@gmail.com

Tojiddinov Davronbek Ulug'bek o'g'li

Termez Branch of Tashkent State Medical University

davronbekoffic@gmail.com

Abstract: Immune checkpoint inhibitors have become an important approach in cancer treatment by enhancing the immune system's ability to recognize and destroy tumor cells. This review examines the mechanisms of PD-1, PD-L1, CTLA-4, and LAG-3 inhibition, their clinical applications, predictive biomarkers, immune-related adverse events, and treatment resistance. Despite promising results, treatment effectiveness depends on tumor characteristics and individual patient factors. Further research may improve patient selection and treatment outcomes.

Keywords: Cancer, immunotherapy, immune checkpoint inhibitors, PD-1, PD-L1, CTLA-4, biomarkers, treatment resistance.

1.Introduction

Cancer remains a major global public health challenge and is associated with substantial

morbidity and mortality. Traditional cancer treatment methods, including surgery, chemotherapy, and radiotherapy, have improved outcomes for many patients. Nevertheless, treatment resistance, disease recurrence, metastasis, and treatment-related toxicity remain important clinical challenges.

In recent decades, cancer immunotherapy has emerged as a significant development in oncology. Unlike conventional treatments that primarily target malignant cells directly, immunotherapy aims to strengthen or redirect the body's immune response against cancer. One of the most important advances in this field has been the development of immune checkpoint inhibitors (ICIs). These drugs block inhibitory signals that cancer cells can exploit to evade immune surveillance. By interfering with these pathways, ICIs may restore the antitumor activity of T lymphocytes and promote tumor control. Immune checkpoint inhibitors have changed the treatment landscape for several malignancies. However, their effectiveness varies among patients, and not every tumor responds to treatment. Therefore, understanding their mechanisms of action, clinical indications, predictive biomarkers, and adverse effects is essential for their appropriate use.

The aim of this review is to examine the biological basis, clinical applications, limitations, and future prospects of immune checkpoint inhibitors in cancer treatment.

2. Biological Basis of Immune Checkpoint Inhibition

The immune system can recognize and eliminate abnormal cells through a process known as immune surveillance. T lymphocytes play a central role in this process by identifying antigens presented by cells and initiating immune responses against potentially harmful targets.

However, immune activity must be carefully regulated to prevent excessive inflammation and damage to healthy tissues. Immune checkpoint pathways help maintain this balance by limiting T-cell activation and function. Cancer cells may exploit these regulatory mechanisms to avoid immune destruction. Tumors can express checkpoint ligands or create an immunosuppressive tumor microenvironment that reduces the effectiveness of antitumor immune responses.

Immune checkpoint inhibitors interfere with these inhibitory pathways. As a result, T cells may regain the ability to recognize and attack malignant cells. The principal immune checkpoint targets currently used in cancer immunotherapy include PD-1, PD-L1, and CTLA-4. LAG-3 is another important target, and its inhibition has become part of selected treatment strategies.

3. Major Types of Immune Checkpoint Inhibitors

3.1 .PD-1 Inhibitors

Programmed cell death protein 1 (PD-1) is an inhibitory receptor expressed on activated T cells and certain other immune cells. Its interaction with PD-L1 or PD-L2 can reduce T-cell activity.

Tumor cells and cells within the tumor microenvironment may express PD-L1, thereby suppressing antitumor immune responses.

PD-1 inhibitors block the interaction between PD-1 and its ligands, helping restore T-cell function.

Examples include:

Pembrolizumab

Nivolumab

Cemiplimab

These agents are used in selected malignancies according to tumor type, disease stage, treatment setting, and applicable clinical indications.

3.2. PD-L1 Inhibitors

PD-L1 inhibitors target programmed death-ligand 1 (PD-L1), preventing it from interacting with PD-1.

Examples include:

Atezolizumab

Durvalumab

Avelumab

These drugs are used in specific clinical settings, including selected cases of lung cancer, urothelial carcinoma, and other malignancies, depending on the agent and applicable treatment guidelines.

PD-L1 expression may help guide treatment decisions in certain cancers. However, its interpretation depends on the tumor type, testing method, and therapeutic indication. PD-L1 expression alone does not reliably predict response in every patient.

3.3. CTLA-4 Inhibitors

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is an inhibitory receptor that regulates T-cell activation, particularly during the early stages of the immune response. CTLA-4 competes with the costimulatory receptor CD28 for binding to CD80 and CD86 on antigen-presenting cells. By blocking this pathway, CTLA-4 inhibitors can enhance T-cell activation.

Ipilimumab is a well-established CTLA-4 inhibitor used in selected cancer treatment regimens.

CTLA-4 inhibition may be combined with PD-1 inhibition to improve treatment

outcomes in certain malignancies. However, combination therapy can also increase the risk of immune-related adverse events.

3.4. LAG-3 Inhibitors

Lymphocyte-activation gene 3 (LAG-3) is an inhibitory immune receptor that can contribute to reduced T-cell function in the tumor microenvironment. Relatlimab, a LAG-3 inhibitor, is used in combination with nivolumab in a specific treatment regimen for advanced melanoma. Targeting LAG-3 alongside PD-1 may enhance antitumor immune activity in selected patients. Nevertheless, its clinical role depends on the specific indication and approved treatment regimen.

4. Clinical Significance of Immune Checkpoint Inhibitors

Immune checkpoint inhibitors have become important treatment options for several malignancies. Their use depends on factors such as histological diagnosis, disease stage, previous treatments, molecular characteristics, and patient fitness.

4.1. Melanoma

Melanoma is one of the malignancies in which immune checkpoint inhibitors have demonstrated substantial clinical benefit.

PD-1 inhibitors and CTLA-4 inhibitors may be used as monotherapy or in combination in selected patients. Combination treatment can improve outcomes in appropriate clinical settings, although it is generally associated with a higher risk of toxicity.

4.2. Non-Small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) is another major area of application for immune checkpoint inhibitors.

Depending on the clinical setting, these drugs may be used alone or in combination with chemotherapy or other systemic treatments. Decisions may depend on PD-L1 expression, tumor molecular characteristics, disease stage, and the presence of actionable genetic alterations.

Immunotherapy is not appropriate for every patient with NSCLC, and treatment selection requires an individualized assessment.

4.3. Urothelial Carcinoma

Immune checkpoint inhibitors have an established role in selected patients with urothelial carcinoma, including certain treatment settings involving advanced disease. The choice of treatment depends on disease characteristics, previous therapy, contraindications, and current clinical recommendations.

4.4. Other Malignancies

Immune checkpoint inhibitors may also be used in selected patients with other cancers, including certain cases of renal cell carcinoma, hepatocellular carcinoma, head and neck cancer, and colorectal cancer.

In some malignancies, treatment eligibility depends on specific molecular features, such as MSI-H or dMMR status. Other indications are based on tumor type, disease stage, treatment history, and validated clinical criteria.

Therefore, immune checkpoint inhibitors should not be considered universally effective for all cancers. Their benefits are strongly influenced by tumor biology and the clinical context.

5. Biomarkers for Predicting Treatment Response

Although immune checkpoint inhibitors can produce durable responses in some patients, others experience limited benefit or no response. Biomarkers are used to help estimate the likelihood of treatment response in specific clinical settings.

5.1. PD-L1 Expression

PD-L1 expression can be assessed using immunohistochemistry. In certain cancers, PD-L1 levels help determine whether a patient may benefit from a particular immune checkpoint inhibitor.

However, PD-L1 expression is an imperfect predictive biomarker. Some patients with low or undetectable expression may respond, while others with high expression may not.

5.2. Microsatellite Instability-High and Deficient Mismatch Repair

Microsatellite instability-high (MSI-H) and deficient mismatch repair (dMMR) are molecular features associated with impaired DNA repair. These abnormalities can increase the number of mutations in tumor cells, potentially generating neoantigens that make the tumor more recognizable to the immune system. In appropriately selected patients, MSI-H or dMMR status can support the use of immune checkpoint inhibitors, including in certain tumor-agnostic treatment settings.

5.3. Tumor Mutational Burden

Tumor mutational burden (TMB) refers to the number of somatic mutations detected in a tumor, usually expressed relative to the amount of DNA analyzed. A higher TMB may be associated with an increased likelihood of response to immunotherapy in some settings. However, its predictive value varies by cancer type, assay, threshold, and clinical indication.

5.4. Other Predictive Factors

Additional factors under investigation include tumor-infiltrating lymphocytes, gene-expression signatures, circulating tumor DNA, and characteristics of the tumor microenvironment.

No single biomarker can accurately predict treatment outcomes in every patient. Integrating molecular, pathological, and clinical information may improve patient selection.

6. Immune-Related Adverse Events

Immune checkpoint inhibitors enhance immune activity, but this effect may also lead to inflammation and damage in healthy tissues. These complications are known as immune-related adverse events (irAEs).

The severity of adverse events ranges from mild symptoms to life-threatening complications.

Commonly affected organs and systems include:

Skin: rash, itching, and inflammatory skin reactions.

Gastrointestinal tract: diarrhea and colitis.

Endocrine system: thyroid dysfunction, hypophysitis, and, less commonly, adrenal insufficiency or type 1 diabetes.

Lungs: pneumonitis.

Liver: immune-mediated hepatitis.

Kidneys: interstitial nephritis.

Heart and nervous system: rare but potentially severe inflammatory complications. The onset of immune-related adverse events varies. They may occur during treatment or, in some cases, after treatment has ended. Early recognition and appropriate management are essential. Depending on the severity and affected organ, management may include treatment interruption, corticosteroids, or other immunosuppressive therapy.

Patients receiving immune checkpoint inhibitors require clinical monitoring and should promptly report new or worsening symptoms. Severe breathlessness, chest pain, significant diarrhea, jaundice, or new neurological symptoms require urgent medical assessment.

Treatment decisions should follow established clinical guidelines and be made by the treating oncology team.

7. Mechanisms of Resistance to Immunotherapy

Despite their benefits, immune checkpoint inhibitors do not produce durable responses in every patient. Resistance may be classified as primary or acquired. Primary resistance occurs when a tumor fails to respond adequately from the beginning of treatment.

Acquired resistance develops when a tumor initially responds but subsequently progresses.

Potential mechanisms include:

1. Insufficient tumor antigen recognition: Tumor cells may lack suitable antigens or lose antigens recognized by the immune system.
 2. Defective antigen presentation: Alterations in antigen-processing and presentation pathways may reduce the ability of T cells to recognize malignant cells.
 3. Immunosuppressive tumor microenvironment: Regulatory T cells, suppressive myeloid cells, and inhibitory cytokines may limit antitumor immune activity.
 4. Alternative immune checkpoint pathways: Tumors may exploit additional inhibitory pathways that are not blocked by the administered drug
 5. Tumor heterogeneity: Different tumor cell populations may respond differently to treatment, allowing resistant cells to survive and proliferate.
- A better understanding of these mechanisms may support the development of new therapeutic strategies, including rational combination treatments and more effective biomarkers.

8. Research and Clinical Perspectives in Uzbekistan

The development of cancer immunotherapy also has relevance for oncology research and clinical practice in Uzbekistan. Local research into tumor biology, immune responses, and the tumor microenvironment may contribute to a better understanding of cancer progression and potential therapeutic targets.

For example, Uzbek scientific literature has examined immunological factors associated with ovarian cancer metastasis. Such studies provide a local research context for investigating the relationship between tumor biology and immune mechanisms. However, research on tumor immunology should not automatically be interpreted as evidence of the clinical effectiveness of a particular checkpoint inhibitor. Demonstrating treatment efficacy requires appropriately designed clinical studies and reliable outcome data.

Further development of this field may benefit from:

- Strengthening molecular and immunohistochemical diagnostic capacity.
- Improving access to validated biomarker testing.
- Conducting clinical research on the effectiveness and safety of immunotherapy.
- Developing multidisciplinary collaboration among oncologists, pathologists, immunologists, and molecular biologists.

Evaluating treatment outcomes and adverse events in local patient populations.
Promoting evidence-based treatment decisions in accordance with current clinical

guidelines.

These priorities may help support the responsible integration of cancer immunotherapy into clinical practice.

9. Future Directions

Research into immune checkpoint inhibitors continues to evolve. Current areas of investigation include combination immunotherapy, personalized treatment selection, new immune checkpoint targets, and strategies to overcome resistance. Combining checkpoint inhibitors with chemotherapy, radiotherapy, targeted therapy, or other immunotherapeutic approaches may improve outcomes in selected cancers. However, combination strategies can also increase toxicity and should be evaluated according to evidence from clinical trials. Artificial intelligence and advanced molecular profiling may eventually help identify patients most likely to benefit from immunotherapy. In addition, research into tumor microenvironment characteristics may reveal new ways to overcome immune suppression.

Future progress will depend on identifying reliable biomarkers, improving the management of immune-related adverse events, and developing safer and more effective treatment combinations.

10. Conclusion

Immune checkpoint inhibitors represent a major advancement in modern cancer treatment. By targeting inhibitory immune pathways such as PD-1, PD-L1, CTLA-4, and LAG-3, these agents can enhance antitumor T-cell activity and produce meaningful clinical benefits in selected patients.

Their effectiveness varies according to tumor type, disease stage, molecular characteristics, and individual patient factors. Biomarkers such as PD-L1 expression, MSI-H, dMMR, and TMB can help guide treatment decisions in specific clinical settings, although none is universally predictive.

Immune-related adverse events and treatment resistance remain important challenges. Consequently, careful patient selection, regular monitoring, early recognition of toxicity, and adherence to evidence-based clinical guidelines are essential. Continued research into tumor immunology, predictive biomarkers, and resistance mechanisms may improve the effectiveness of immunotherapy and expand its role in personalized oncology.

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