

PEMBROLIZUMAB AS AN IMMUNE CHECKPOINT INHIBITOR IN CANCER THERAPY

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ABSTRACT

Cancer is characterized by uncontrolled proliferation of abnormal cells and the ability of malignant cells to evade immune surveillance. Immune checkpoint pathways, particularly the programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway, play an important role in tumor immune evasion. Pembrolizumab is a humanized IgG4 monoclonal antibody that binds to PD-1 and prevents its interaction with PD-L1 and PD-L2, resulting in restoration of T-cell antitumor activity. This review highlights the pathophysiology of cancer with emphasis on immune evasion and discusses the mechanism of action, pharmacokinetics, pharmacodynamics, clinical applications, dosage and administration, contraindications and precautions, and safety profile of pembrolizumab. Clinical evidence has

identified pembrolizumab as an important treatment option for several cancers, although immune-related adverse events are an important limitation. Appropriate patient selection and management of immune-related adverse events are critical to achieving optimal therapeutic outcomes. Pembrolizumab is an important step in cancer immunotherapy and continues to play a significant role in the treatment of selected malignancies.

KEYWORDS: Pembrolizumab; PD-1; PD-L1; immune checkpoint inhibitor; cancer immunotherapy; immune evasion; monoclonal antibody.

INTRODUCTION

Cancer poses a major global health challenge and is one of the leading causes of morbidity and mortality worldwide. Cancer is a heterogeneous category of diseases that are characterized by an unbridled proliferation of abnormal cells that arise due to the accumulation of genetic and epigenetic alterations in normal cells. These transformed cells acquire their malignant potential as they acquire mutations that allow them to escape regulatory mechanisms and subsequently infiltrate neighboring tissues and distant organs, thus acquiring metastatic potential.^[24,30] Conventional treatment regimens including surgery, chemotherapy, radiotherapy, and targeted therapies have been very effective at improving clinical outcome for many malignancies however treatment toxicity, resistance, recurrence, and ineffective tumor ablation present major challenges.

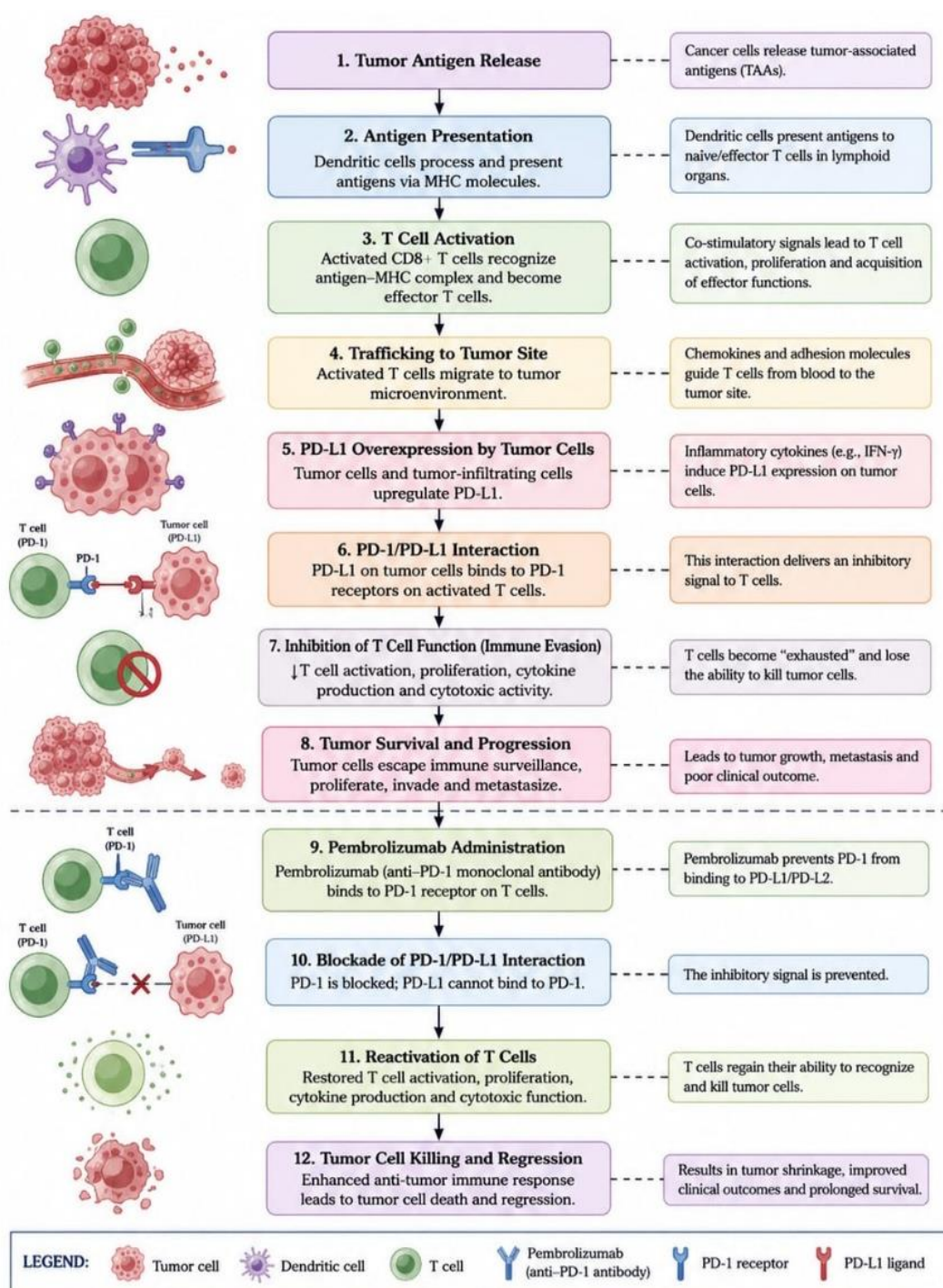
Recent advances in tumor immunology have demonstrated the immune system's ability to recognize and destroy tumor cells through immune surveillance. However, tumor cells can use immune-regulatory mechanisms, including immune checkpoints, to avoid immune attack. The programmed death-1 (PD-1) receptor is an inhibitory receptor expressed on activated T lymphocytes, and its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), are immune-checkpoint molecules that regulate T-cell activation. Upregulated expression of PD-L1 on tumor cells prevents T-cell-mediated antitumor immunity, thereby promoting tumor progression and metastasis.^[24,30]

The identification of immune-checkpoint pathways has revolutionized cancer therapy and resulted in the development of immune-checkpoint inhibitors. Pembrolizumab is a highly selective humanized IgG4 monoclonal antibody against the PD-1 receptor, preventing engagement of PD-L1 and PD-L2, thus blocking downstream PD-1 signaling and restoring antitumor immune responses. Pembrolizumab has demonstrated clinical efficacy and survival benefits in numerous malignancies, including melanoma, non-small cell lung cancer, head and neck squamous cell cancers, urothelial carcinomas, renal cell carcinomas, and other cancers, and is considered a successful therapeutic agent for the treatment of various malignancies as demonstrated by KEYNOTE trials.^[24,30]

This review focuses on the biology of immune checkpoint inhibition, the pharmacology, mechanism of action of Pembrolizumab, indications, therapeutic efficiency, safety, immunological toxicities, and recent advances in its use for the treatment of cancer.^[24,30]

PATHOPHYSIOLOGY OF CANCER: IMMUNE EVASION

The immune system plays a critical role in the detection and destruction of abnormal cells through the process of immune surveillance. Cytotoxic T lymphocytes (CD8⁺ T cells), natural killer (NK) cells, dendritic cells, and macrophages recognize tumor-associated antigens and destroy transformed cells before they are able to become clinically apparent cancers. However, tumor cells can acquire multiple mechanisms to evade immune destruction, leading to uncontrolled proliferation and progression of disease.^[24]



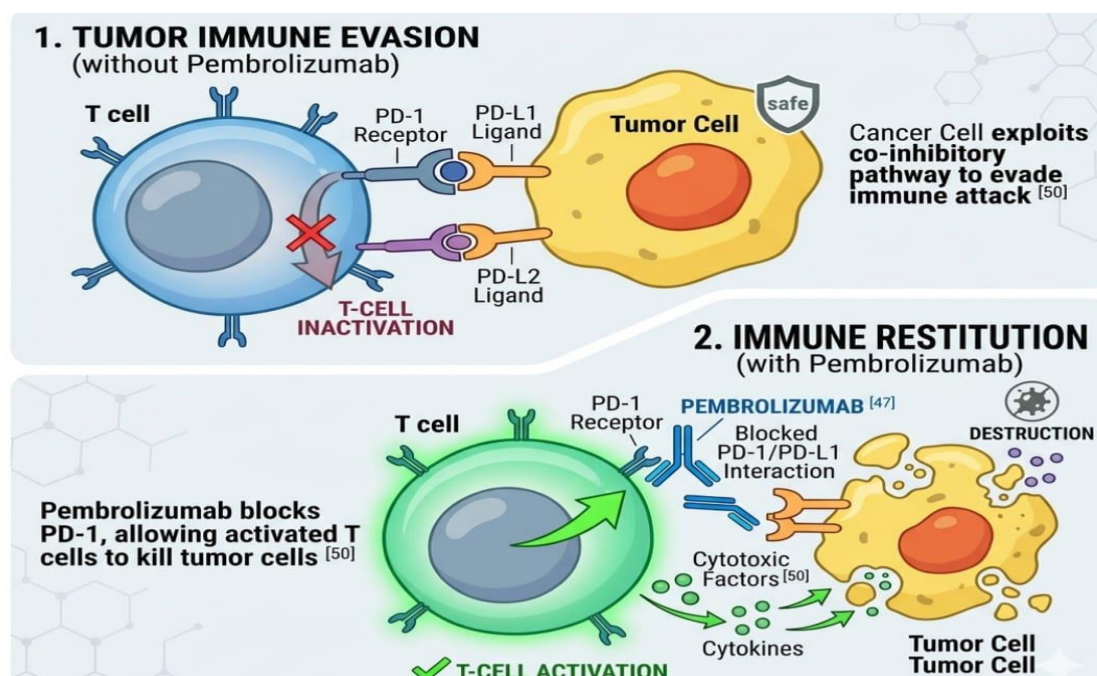
One of the key mechanisms of action of immune evasion is the activation of immune checkpoint pathways, particularly the programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1). PD-1 is an inhibitory receptor that is expressed on activated T lymphocytes. Programmed death-ligand 1 is a ligand that is expressed on the surface of antigen-presenting cells and is upregulated on tumor cells. Under normal physiological conditions, the interaction between PD-1 and PD-L1 regulates immune homeostasis.

In many cancers, the PD-L1 is overexpressed on tumor cells, which binds to the PD-1 receptors on activated T lymphocytes. This interaction inhibits T-cell activation and proliferation, decreases the production of cytokines, and reduces cytotoxic activity, resulting in T-cell exhaustion. Consequently, the tumor escapes immune surveillance and grows unchecked, and malignant cells survive, proliferate, and metastasize despite the presence of tumor-specific immune responses.

Immune escape via the PD-1/PD-L1 pathway is a common mechanism for tumor immune evasion, and its inhibition is a promising therapeutic approach. Pembrolizumab is an immune checkpoint inhibitor that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, leading to increased antitumor immune responses and tumor cell death.

MECHANISM OF ACTION: PEMBROLIZUMAB

Pembrolizumab is a monoclonal antibody^[21] that inhibits tumor growth by acting as an immune checkpoint inhibitor.^[22] It binds to the human programmed death-1 (PD-1) receptor on T cells and prevents engagement of this receptor with its ligands (PD-L1&PD-L2).^[21] In general, immune checkpoint pathways downregulate T-cell activity to limit inappropriate or excessive immune responses; however, neoplasms can exploit this system to evade immune surveillance and destruction.^[23] Inhibition of the PD-1/PD-L1 pathway results in the proliferation of tumor-specific T cells and increased production of cytokines, culminating in an enhanced antitumor immune response.^[23]



PHARMACOKINETICS OF PEMBROLIZUMAB

Pembrolizumab is a humanized IgG4κ monoclonal antibody that targets the programmed cell death-1 (PD-1) receptor on activated T lymphocytes, blocking its interaction with PD-L1 and PD-L2 ligands. The drug's linear pharmacokinetics (PK) were observed after single-dose intravenous (IV) administration within the approved dose range. The volume of distribution for pembrolizumab was limited to 6–8 L, suggesting that the drug mainly circulates within the vascular and interstitial fluids. The peak concentration of the medication was found at the end of IV infusion, with steady-state levels reached after 16 weeks of repeated doses.

The terminal elimination half-life of pembrolizumab is between 22 and 27 days, which allows for a dosing schedule of 200 mg every 3 weeks or 400 mg every 6 weeks in adults. The drug's clearance mechanism is predominantly proteolytic catabolism, resulting in the production of small peptides and amino acids, rather than hepatic CYP450 metabolism or renal excretion. Therefore, no significant drug-drug interactions were reported for pembrolizumab. Moreover, population PK analysis revealed that age, sex, race, body weight, and mild to moderate renal and liver impairments do not considerably affect the drug's PK profile.

The treatment's pharmacodynamics (PD) were characterized by continuous PD-1 receptor occupancy of peripheral T cells, which restores anti-tumor immune responses. The exposure-response analyses from the KEYNOTE-001 trial showed that pembrolizumab's approved

doses were close to maximum receptor occupancy for most tumor types, resulting in optimal therapeutic efficacy without the need for therapeutic drug monitoring during treatment.

PHARMACOLOGICAL ACTION

The active substance is a highly selective humanized immunoglobulin G4 (IgG4 κ) monoclonal antibody directed against the programmed cell death-1 (PD-1) receptor expressed on the surface of activated T cells. Binding of PD-1 to its ligands, programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2), delivers an inhibitory signal that downregulates T-cell activation, proliferation, cytokine production, and cytotoxicity, thereby playing a critical role in peripheral immune regulation and the prevention of autoimmunity. Many tumor types exploit this immune checkpoint pathway by up-regulating the expression of PD-L1 on malignant and, to a lesser extent, on adjacent stromal and immune cells, thereby potentiating immune evasion.

Pembrolizumab binds with high affinity to the PD-1 receptor, blocking its interaction with PD-L1 and PD-L2 and resulting in increased cytotoxic function of effector T cells. Inhibition of the PD-1-mediated immune checkpoint increases anti-tumor immune responses, including cytotoxic activity mediated by CD8⁺ T lymphocytes, through enhanced proliferation and recruitment of cytotoxic T lymphocytes, natural killer cells, and dendritic cells, as well as increased expression of pro-inflammatory cytokines and chemokines. The cytotoxic T-cell activity leads to the destruction of tumor cells by the secretion of perforin, granzymes, and interferon- γ .

Unlike traditional cytotoxic chemotherapy, pembrolizumab does not directly kill tumor cells. Rather, it boosts the host's immune response by restoring antitumor immune function. Restoring antitumor immune function can halt tumor progression and lead to the immune-mediated destruction of malignant cells. This leads to tumor regression and improved clinical outcomes in responsive patients.

As a result of pembrolizumab's immunostimulatory properties, immune-related adverse events including pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, and dermatologic events can occur. These are often serious and require timely immunosuppressive management to improve therapeutic efficacy and minimize toxicity.

CLINICAL APPLICATION

Pembrolizumab is an anti-PD-1 monoclonal antibody, which is indicated as a treatment for a wide range of malignancies. As a treatment, it can be administered as monotherapy, in combination with chemotherapy, or as part of a perioperative treatment regimen, depending on the indication and patient factors, including tumor type, tumor stage, biomarker status, and previous treatment. Approved by the FDA for the treatment of various cancers, including melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, classical Hodgkin lymphoma, urothelial carcinoma, gastric and gastroesophageal-junction adenocarcinoma, esophageal cancer, cervical cancer, renal cell carcinoma, endometrial carcinoma, triple-negative breast cancer, colorectal cancer with specific mismatch-repair characteristics, and several other malignancies.

DOSAGE AND ADMINISTRATION

Pembrolizumab is typically delivered as an intravenous infusion by a healthcare professional. Commonly used regimens for adults are 200 mg every 3 weeks or 400 mg every 6 weeks, depending on the particular indication and treatment setting.

Pembrolizumab is administered as an intravenous infusion, which takes approximately 30 minutes to complete.

The appropriate dosage and duration of treatment depend on the particular indication and patient population; therefore, the disease-specific prescribing information should be followed.

For children, the typical practice is to base the dose on weight, and the FDA prescribing information recommends 2 mg/kg (maximum 200 mg) every 3 weeks for the applicable indications. The duration of treatment varies according to the indication and clinical circumstances; therefore, the disease-specific prescribing information should be followed rather than using a single universal timeframe

Dose adjustment

Unlike traditional chemotherapy, pembrolizumab is generally not reduced for toxicity. The management of significant immune-mediated adverse reactions typically requires treatment interruptions, appropriate corticosteroid or other immunosuppressive therapy when indicated, and permanent discontinuation of pembrolizumab for specified severe or life-threatening toxicities.

Patient selection

For certain indications, the choice of treatment is dictated by the need for biomarker testing. Depending on the tumor type, the indicated biomarker can include PD-L1 expression, microsatellite instability (MSI-H), or defective mismatch repair mechanism (dMMR). Various methods can be used to evaluate the PD-L1 tumor proportion score (TPS) or combined PD-L1 tumor proportion score (CPS) in tumors that relate to specific tumor types and indications.

Since the drug is indicated in a number of malignancies and has several dosing schedules, it is important not to compare a dose with a malignancy that is not specifically indicated. For example, in the absence of such indication, it is inappropriate to recommend “pembrolizumab 480 mg every 3 weeks”.

Suggested table title

Table 1: Major clinical scope and recommended dose schedules of pembrolizumab.

Table 1. Major clinical applications and commonly used dosing regimens of pembrolizumab.

Cancer / Indication	Common Adult Regimen*	Infusion Time	Treatment Setting / Key Notes
Melanoma	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	30 minutes	Unresectable or metastatic melanoma; adjuvant treatment in selected patients with completely resected stage IIB, IIC, or III melanoma.
Non-small cell lung cancer (NSCLC)	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	30 minutes	Monotherapy or in combination with chemotherapy; use depends on stage, histology, molecular alterations, and PD-L1 expression.
Esophageal cancer	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	30 minutes	Locally advanced or metastatic esophageal squamous cell carcinoma or adenocarcinoma; often in combination with platinum- and fluoropyrimidine-based chemotherapy.
Cervical cancer	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	30 minutes	Persistent, recurrent, or metastatic cervical cancer; used according to approved indications and biomarker status.
Head and neck squamous cell carcinoma	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	30 minutes	Recurrent or metastatic disease; as monotherapy in PD-L1-expressing tumors or in combination with chemotherapy.
Urothelial carcinoma	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	30 minutes	Locally advanced or metastatic urothelial carcinoma in selected patients.
Gastric / Gastroesophageal junction (GEJ) adenocarcinoma	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	30 minutes	Advanced gastric or GEJ adenocarcinoma; used in combination therapy based on HER2 status and PD-L1 expression.
Renal cell carcinoma	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	30 minutes	Advanced renal cell carcinoma; usually as part of combination therapy in approved settings.
Endometrial carcinoma	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	30 minutes	Advanced or recurrent endometrial carcinoma not MSI-H or dMMR.
Triple-negative breast cancer	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	30 minutes	High-risk early-stage or metastatic triple-negative breast cancer (in combination with chemotherapy as indicated).
MSI-H/dMMR solid tumors	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	30 minutes	Tumor-agnostic indication for unresectable or metastatic solid tumors that are MSI-H or dMMR.

CONTRAINDICATION AND PRECAUTIONS OF PEMBROLIZUMAB

This drug is generally well tolerated but it has several contraindications due to its mechanism of action and specific precautions based on the patient's conditions that require a closer monitoring. The only absolute contraindication according to the drug information is a known hypersensitivity to Pembrolizumab or any of its excipients. In patients with life-threatening hypersensitivity reaction to Pembrolizumab such as anaphylaxis, the drug should not be administered again.

It is advised to use Pembrolizumab with caution in patients with existing autoimmune diseases, for instance, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis or myasthenia gravis, since immunocheckpoint inhibitor therapy may induce an exacerbated form of the disease. Caution should also be exercised when administering Pembrolizumab to solid organ transplant recipients or allogeneic hematopoietic stem cell transplant (HSCT) recipients due to the possibility of enhanced occurrence of graft rejection or graft-versus-host disease (GVHD). Close evaluation and consideration of risks and benefits prior to initiation of treatment are required in these populations.

Pembrolizumab should also be used with caution in patients with severe immune-related adverse events during previous immune checkpoint inhibitor therapy. Permanent discontinuation is recommended in patients who develop grade 4 immune-mediated toxicities or recurrent severe immune-related adverse reactions despite appropriate corticosteroid therapy.

The safety of pembrolizumab during pregnancy has not been established. As PD-1/PD-L1 signaling plays an important role in maintaining maternal-fetal immune tolerance, blockade of this pathway may increase the risk of fetal harm. Effective contraception is recommended during treatment and for at least 4 months after the final dose. Breastfeeding is also not recommended during therapy because of the potential risk to the infant.

Patients with active uncontrolled infections, including active tuberculosis, hepatitis, or HIV infection not adequately controlled, should be carefully evaluated prior to starting treatment. Therapy may be delayed until the infection is adequately managed.

Overall, patient selection, baseline clinical evaluation, and continuous monitoring are

essential to minimize serious immune-related complications and optimize the therapeutic benefits of pembrolizumab.

SAFETY AND ADVERSE EFFECTS OF PEMBROLIZUMAB

Pembrolizumab has shown a favorable safety profile compared with conventional cytotoxic chemotherapy because it selectively enhances the host immune response rather than directly damaging rapidly dividing cells. However, immune activation can manifest as immune-related adverse events (irAEs) affecting multiple organ systems. Most adverse events are mild to moderate (Grade 1-2), whereas severe (Grade 3-4) toxicities are less common but require timely recognition and management.

1. Immune Related Adverse Events

The mechanism for the development of immune related adverse events is loss of immune tolerance to self-antigens on PD-1 blockade, resulting in T cell mediated inflammatory responses in normal tissues. These events may occur during treatment or months after discontinuation of treatment.

Dermatological toxicity

- Hair loss
- Itching
- Rashes
- Skin damage

Cardiovascular toxicity

High blood pressure (20%-60%)

Endocrine toxicity

- High levels of cholesterol
- High levels of sugar in the blood
- High levels of triglycerides
- Low levels of albumin in the blood
- Loss of weight

Gastrointestinal toxicity

- Constipation
- Altered sense of taste

- Dry mouth
- Reduced appetite

Hematologic toxicity

- Low level of hemoglobin (26-69%)
- Low lymphocytes count

Hepatic toxicity

ALT/SGPT increased

Ophthalmic toxicity

Dry eyes

Renal toxicity

Protein in the urine

Respiratory toxicity

Nosebleeds

OVERALL SAFETY PROFILE

Overall, large clinical trials, including the KEYNOTE trials, demonstrate that pembrolizumab provides durable antitumor responses with a manageable toxicity profile. Compared with traditional chemotherapy, pembrolizumab monotherapy typically has a distinct toxicity profile, with less hematologic toxicity associated with chemotherapy but with an increased risk of immune mediated adverse events. With close clinical monitoring and appropriate treatment, most immune mediated toxicities are reversible and many patients can continue therapy successfully.

CONCLUSION

Pembrolizumab has made a remarkable contribution to the treatment of a considerable number of malignancies by offering a unique opportunity for the host immune system to fight tumours. The drug is a monoclonal antibody that targets the immune checkpoint protein called programmed cell death-1 (PD-1) and is exceptionally potent and innovative in that it allows the body to deal with cancer by inhibiting this PD-1 receptor. Unlike traditional cytotoxic and DNA-targeting chemotherapy, pembrolizumab is an immune checkpoint inhibitor that helps the patient's immune system to destroy cancerous cells.

The KEYNOTE trials and KEYNOTE-based trials, as well as other clinical investigations, have established the clinical benefit of pembrolizumab for the treatment of a variety of diseases, including malignant melanoma, non-small cell lung cancer, head and neck cancer, cervical cancer, esophageal cancer, bladder cancer, and other PD-L1 expressing tumours, among others. Besides the KEYNOTE trials and KEYNOTE-based trials, it has been determined that the medication has a favorable safety profile and is relatively simple to administer.

Nevertheless, as with any other treatment, pembrolizumab is associated with a significant number of adverse effects that need to be taken into consideration. Moreover, despite being a very potent and powerful medication, it is critical to choose the right patients for treatment. Thus, there is an urgent need to conduct more research on pembrolizumab in order to further elucidate its potential benefits for malignancy patients and to identify the most relevant biomarkers for selecting patients who will obtain the most significant clinical benefit from the treatment.

Finally, pembrolizumab appears to be a major innovation in cancer immunotherapy and is quickly becoming a critical component in the treatment of many cancers. This medication allows patients with various tumors to live longer and improves their quality of life, and there is every reason to believe that it will continue to do so in the future.

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