Mechanism and Clinical Application of Pembrolizumab in Treatment of Advanced Melanoma

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Abstract. Traditional treatment methods have poor prognosis for patients with advanced melanoma. However, immunotherapy can significantly improve the prognosis of patients. Among them, immune checkpoint inhibitors, as one of the commonly used clinical treatment methods, have made considerable progress in recent clinical treatments. Currently, most studies focus on the efficacy of pembrolizumab alone or in combination with other immune checkpoint inhibitors, but there is a lack of comparison of the efficacy of pembrolizumab alone with other treatment regimens. This article provides a comprehensive literature review of the PD-1 inhibitor pembrolizumab, aiming to summarize and analyze the mechanism and clinical application of pembrolizumab in the treatment of melanoma and clarify its application advantages. This study uses the literature review method to integrate data and mechanisms and reaches the following results: In terms of mechanism, CTLA-4 may cause an excessive immune response, but its precise regulation of tumor-specific T cells is relatively weak; the effect of PD-1 on the immune response mainly occurs in the effector phase of targeted immune responses, directly inhibiting the killing activity of T cells. In terms of biomarkers, PD-1 can better predict disease efficacy compared to CTLA-4. In clinical data, pembrolizumab can achieve long-term disease control, reduce the risk of treatment interruption, and has fewer side effects. Based on the analysis of the results, pembrolizumab has changed the prognosis of advanced melanoma, significantly improving the survival rate of patients and making advanced melanoma no longer an incurable disease.

Keywords: Advance melanoma ICIs Pembrolizumab Combined therapy.

1. Introduction

Melanoma is a highly aggressive skin malignancy that originates from melanocytes, and its incidence has been continuously increasing over the past few decades. Although early-stage melanoma can be cured by surgical resection, the prognosis for patients with advanced-stage disease is extremely poor. In recent years, tumor immunotherapy, which activates the patient's own immune system to kill tumor cells, has completely transformed the treatment landscape of advanced solid tumors. The interaction between programmed death receptor-1 (PD-1) and its ligand PD-L1 is one of the core mechanisms of tumor immune escape: tumor cells escape immune surveillance by highly expressing PD-L1 and binding to PD-1 on the surface of T cells, thereby inhibiting T cell activation and inducing their exhaustion. Monoclonal antibodies that block the PD-1/PD-L1 pathway can restore the anti-tumor activity of T cells, providing a new therapeutic direction. Pembrolizumab is a commonly used PD-1 immune checkpoint inhibitor in clinical practice. However, current research on pembrolizumab is more focused on studying the efficacy of a single treatment method, such as monotherapy or combination therapy, without comprehensive comparisons of different treatment strategies. This study aims to compare different clinical treatment strategies of pembrolizumab and explore the mechanism of different treatment regimens to investigate the advantages of pembrolizumab monotherapy over other treatment strategies. The research conclusions obtained can provide references for clinical practice and the formulation of treatment plans.

2. The mechanism of Pembrolizumab and its advantages

2.1. The mechanism of Pembrolizumab

Pembrolizumab, a prototypical PD-1/PD-L1 inhibitor, exerts its therapeutic effects through targeted blockade of the PD-1/PD-L1 signaling axis. The widespread expression of PD-L1 on malignant cell surfaces enables critical immunosuppressive interactions: PD-L1 engagement with PD-1 receptors on T lymphocytes suppresses key cytokine production (including IL-2, IFN-γ, and TNF-α) and disrupts CD28-mediated costimulatory signaling essential for T-cell proliferation, thereby establishing a permissive microenvironment for immune evasion.

PD-L1 overexpression in tumors arises primarily through two distinct biological mechanisms. The intrinsic oncogenic signaling is that tumor-autonomous genetic alterations, particularly constitutive activation of AKT/STAT pathways, drive PD-L1 transcriptional upregulation. For the extrinsic microenvironmental regulation, it includes IFN-γ-mediated paracrine induction of PD-L1 expression, PD-L1 secretion by infiltrating myeloid-derived suppressor cells (MDSCs) including dendritic cells and monocytes and antigen-presenting cell-mediated differentiation of regulatory T cells (Tregs) via PD-L1/PD-1 interactions, effectively dampening cytotoxic T lymphocyte (CTL) functionality.

Notably, PD-L1 demonstrates pleiotropic signaling beyond classical immune checkpoint functions. As a transmembrane protein, it initiates reverse signaling cascades within tumor cells that enhance resistance to CTL-mediated cytotoxicity, thereby conferring dual survival advantages through both immune modulation and intrinsic pro-survival mechanisms. The PD-1/PD-L1/PD-L2 axis orchestrates T cell dysfunction through three synergistic mechanisms, as is shown in the following part[1-3].

2.1.1 Attenuation of TCR signaling cascades

Phosphatase-dependent signal decay: The immunoreceptor tyrosine-based switch motif (ITSM) in PD-1's cytoplasmic domain recruits SHP-2 phosphatase, which dephosphorylates proximal TCR signaling molecules (ZAP70, Lck) and inhibits downstream PI3K/AKT/mTOR pathways, ultimately suppressing effector cytokine production (e.g., IL-2, IFN-γ). Costimulatory blockade: PD-1 competitively inhibits CD28-B7 interactions, disrupting CD28-PI3K signaling essential for T cell coactivation.

2.1.2 Metabolic reprogramming toward dysfunction

Glycolytic suppression: PD-1 signaling downregulates GLUT1 expression and inhibits hexokinase 2 (HK2)/lactate dehydrogenase A (LDHA) activity via AKT/mTORC1 axis suppression, impairing ATP generation. Mitochondrial insufficiency: Reduced PGC-1α expression induces mitochondrial fragmentation and diminishes oxidative phosphorylation capacity, exacerbating bioenergetic deficits.

2.1.3 Epigenetic enforcement of exhaustion phenotype

Exhaustion-associated transcriptional programming: PD-1 signaling upregulates BATF/TOX transcription factors and DNMT3A epigenetic modifiers, increasing chromatin accessibility at exhaustion marker loci (TIM-3, LAG-3). Apoptotic priming: Activation of the FoxO1-BIM axis coupled with BCL-2 family inhibition promotes activated T cell elimination.

As a clinically validated PD-1/PD-L1 checkpoint inhibitor, pembrolizumab demonstrates multifaceted therapeutic effects. It reverses the aforementioned PD-1-mediated immunosuppressive mechanisms and remodels Tumor microenvironment by attenuating immunosuppressive activity of Tregs and MDSCs, enhancing dendritic cell-mediated antigen cross-presentation, Promoting M1 macrophage polarization (via IFN-γ upregulation) and increasing CD8+ T cell/Treg ratio within tumor infiltrates. This dual mechanism synergistically restores systemic antitumor immunity while reprogramming the local immunosuppressive milieu.

2.2. The advantage of anti PD-1 ICIs(compared with anti CTLA-4 ICIs)

The differential clinical efficacy between PD-1 and CTLA-4 inhibitors in melanoma stems from their distinct immunomodulatory properties across following critical dimensions:

2.2.1 Temporal specificity of immune modulation

CTLA-4 inhibitors primarily intervene during the lymphoid priming phase, where they enhance polyclonal T cell activation by blocking B7 (CD80/86)-CTLA-4 interactions on antigen-presenting cells. This broad-spectrum activation frequently induces systemic immune hyperactivation, with grade 3-4 immune-related adverse events (irAEs) occurring in 25-30% of patients. In contrast, PD-1 inhibitors exert their effects predominantly within the tumor effector phase, selectively reversing PD-L1-mediated suppression of tumor-infiltrating lymphocytes (TILs) while maintaining systemic immune homeostasis (irAE incidence: 10-15%) [1] [3].

2.2.2 Spatiotemporal targeting of tumor immunity

The immunosuppressive tumor microenvironment (TME) in melanoma features dense PD-L1 expression and exhausted PD-1+CD8+ TILs. PD-1 inhibitors directly counteract these mechanisms by restoring mitochondrial oxidative phosphorylation in TILs through PGC-1α upregulation, re-establishing TCR signaling via SHP-2 phosphatase inhibition and reducing TOX-driven epigenetic silencing of effector genes

Conversely, CTLA-4 inhibitors primarily increase peripheral naïve T cell diversity but demonstrate limited penetration into PD-L1-enriched TME regions. Preclinical studies reveal CTLA-4 blockade increases intratumoral Treg infiltration by 2.3-fold ($p=0.017$), potentially counteracting therapeutic benefits.

2.2.3 Biomarker-driven precision

PD-1 inhibitors exhibit well-defined predictive biomarkers: PD-L1 positivity (≥1% by IHC) correlates with 45.6% ORR vs 16.5% in PD-L1- tumors; high tumor mutational burden (TMB >10 mutations/Mb) associates with 2.9-fold longer progression-free survival; And MSI-H/dMMR status (FDA-approved pembrolizumab indication)

CTLA-4 inhibitors lack equivalent predictive biomarkers, with response rates remaining at 10-15% regardless of PD-L1 or TMB status. This biomarker-agnostic approach contributes to their diminished therapeutic precision.

2.2.4 Exhaustion reversal vs priming amplification

PD-1 blockade uniquely reverses T cell exhaustion by reprogramming glucose metabolism through GLUT1/hexokinase 2 restoration, attenuating BIM-mediated apoptosis in antigen-experienced T cells and rescuing IFN-γ production capacity (3.8-fold increase vs baseline, $p<0.001$)

CTLA-4 inhibition predominantly expands naïve T cell pools but fails to resuscitate terminally exhausted clones, as evidenced by single-cell RNA sequencing showing persistent exhaustion signatures in 82% of CTLA-4-treated TILs.

3. The clinical efficacy of pembrolizumab as a monotherapy

3.1. Clinical data of pembrolizumab as a single agent

Biomarker analysis: The expression level of PD-L1 is positively correlated with therapeutic efficacy. The detection method involves using the 22C3 antibody to detect the expression of PD-L1 in tumor cells (TC) and immune cells (IC), with TPS (Tumor Proportion Score) as the scoring standard. TPS ≥ 50% (high expression), TPS 1-49% (low expression), and TPS ≤ 1% (negative)[4].

KEYNOTE-001 is a phase I clinical trial for PD-1 pembrolizumab, aiming to evaluate its anti-tumor activity and safety. Among all patients, the 5-year survival rate was 34% when pembrolizumab was administered at a dose of 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks. The 5-year survival rate for patients receiving initial treatment was 41%. The objective response rate (ORR) was 52%,

with the longest response duration being 66 months. The incidence of grade 3-4 adverse events was 17%. After comparison, it was found that patients with PD-L1 expression ≥ 50% had an ORR of 45.2%, with a progression-free survival and overall survival of 12.5 months, both higher than those in the low-expression and negative groups, suggesting that PD-L1 expression is an important predictor of therapeutic efficacy.

This study confirmed that pembrolizumab has sustained anti-tumor activity and tolerability in advanced melanoma. From a molecular perspective, the long-term response of pembrolizumab may be due to the induction of tumor cell lysis-related and natural killer cell-related gene expression by PD-1. In advanced melanoma, its long-term response may be maintained by significantly increasing CD8 memory cells.

3.2. Efficacy of pembrolizumab monotherapy and chemotherapy drugs

KEYNOTE-002 is a phase II randomized controlled trial, which includes patients who experienced disease progression after previous treatment with ipilimumab and those who showed progression within 25 weeks before enrollment after receiving treatment with ipilimumab and/or BRAF/MEK inhibitors. Subsequently, they received pembrolizumab treatment. The therapeutic efficacy of pembrolizumab was more pronounced in patients with advanced melanoma who failed the treatment with ipilimumab[5] (Table 1).

Table 1 Comparison of the efficacy of pembrolizumab ammunition and chemotherapy drugs[5,6]

Monotherapy comparison	Pembrolizumab	Chemotherapy drugs
6-Month Progression-Free Survival Rate	38%	16%
Average Progression-Free Period	5.4months	3.6months
Grade 3-4 Adverse Events	11%	26%

3.3. Therapeutic effects between pembrolizumab and STLA-4 inhibitors

The KEYNOTE-006 experiment compared the therapeutic efficacy of pembrolizumab and the CTLA-4 inhibitor ipilimumab in patients with unresectable or metastatic melanoma. The following data prove that pembrolizumab is significantly superior to ipilimumab in advanced melanoma. The mechanism is related to the changes in genes associated with cell lysis and natural killer cell functions due to PD-1 blockade. In patients who responded to PD-1 antibody treatment, the frequencies of CD8 effector memory T cells and tissue-resident memory T cells increased, which supports the durable responses observed in patients treated with pembrolizumab in the KEYNOTE-006 study[7,8]. (Table 2)

Table 2 Comparison of the efficacy of pembrolizumab monotherapy and CTLA-4 inhibitors

Comparison of Monotherapy with Immune Checkpoint Inhibitors	Pembrolizumab	Ipilimumab
Overall survival period	32.7months	15.9months
Duration of sustained remission	53.5months	20.96- not attained
Objective response rate	42%	17%
Grade 3-4 Adverse Events	17%	20%

3.4. Therapeutic Effects of Pembrolizumab and Combination Therapy

Based on the available data, there are significant differences in efficacy and safety between pembrolizumab monotherapy and combination therapy with CTLA-4 inhibitors. Pembrolizumab monotherapy demonstrates advantages in long-term disease control, with a 5-year overall survival

rate of 41% and an objective response rate of 52%. Additionally, it has a lower incidence of grade 3-4 adverse events (17%), making it suitable for patients prioritizing sustained disease control and better treatment tolerability. In contrast, the combination therapy shows superior short-term efficacy, with a 1-year overall survival rate of 89% and an improved objective response rate of 61%. Owever, it is associated with a significantly higher rate of grade 3-4 adverse events (45%), making it more appropriate for patients seeking rapid remission who can tolerate greater toxicity. The choice between these regimens should be guided by treatment goals (long-term control vs. rapid response) and the balance between efficacy and safety[9] (Table 3).

Table 3 A Comparison of the Therapeutic Efficacy of Pembrolizumab Monotherapy and the Combination Therapy

Comparison of combination therapy	Pembrolizumab monotherapy	Combination with CTLA-4
Efficacy (Overall survival rate, Objective response rate)	5-year Overall survival rate: 41%; Objective response rate: 52%	1-year Overall survival rate: 89%; Objective response rate: 61%
Side effect occurrence rate	Lower (3-4 grade event occurrence rate): 17%	Higher (3-4 grade event occurrence rate): 45%
Treatment goal	Long-term disease control, reduce the risk of treatment interruption, and have fewer side effects.	Pursue rapid remission, but with more side effects.

4. Conlusion

Advanced melanoma, characterized by its strong invasiveness, high metastatic potential and limited efficacy of traditional treatments, has long been confronted with the severe challenges of low survival rates and frequent drug resistance. With the breakthroughs in tumor immunotherapy, PD-1 inhibitors represented by pembrolizumab have significantly restored the anti-tumor activity of T cells by blocking the PD-1/PD-L1 immune checkpoint pathway, bringing significant survival benefits to patients. Compared with CTLA-4 and chemotherapy drugs in terms of mechanism of action, PD-1 inhibitors have obvious advantages. Clinical treatment data also show that they have good single-drug treatment effects and can maintain a high disease remission rate. Moreover, pembrolizumab has relatively few side effects and can achieve long-term disease control.

Clinical studies have confirmed that pembrolizumab monotherapy can significantly prolong overall survival and is safer than traditional chemotherapy and ipilimumab regimens. In comparisons with combination treatment regimens involving CTLA-4 inhibitors, it has demonstrated stronger efficacy and lower side effects. Pembrolizumab has now become a core choice for first-line treatment. In the future, it is necessary to further explore the mechanism of drug resistance and develop individualized treatment plans to further break through the treatment bottleneck of advanced melanoma and achieve a leap from "prolonging survival" to "potential cure".

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