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Clinical Applications and Challenges of Immune Checkpoint Inhibitors in the Treatment of Melanoma

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Abstract. Researchers have increasingly focused on enhancing antitumor immunity to fight cancer. Immune checkpoints, including proteins such as PD-1/PD-L1 and CTLA-4/B7, play pivotal roles in modulating T-cell responses and maintaining immune balance. However, cancer cells often exploit these checkpoint pathways to escape immune detection and promote malignancy. This review, with a focus on the therapeutic potential of both monotherapy and combination strategies, explores clinical and experimental progress in applying immune checkpoint blockade to melanoma treatment. Conventional approaches like surgery, chemotherapy, and radiotherapy generally show a low objective response rate (10%–20%), while the typical survival period remains under one year, and less than 10% of patients survive beyond five years. In contrast, using a single checkpoint inhibitor can achieve response rates of 30%–45%, prolong median survival to two or three years, and increase five-year survival up to 40%. Checkpoint inhibitors targeting molecules such as CTLA-4 and PD-1 have significantly transformed treatment paradigms for various cancers, notably advanced melanoma. Around half of these patients can now attain long-term tumor suppression and delayed disease progression. Despite this progress, immune-related adverse effects may necessitate additional therapies like glucocorticoids or other immunosuppressants to alleviate symptoms. Going forward, research should delve deeper into strategies for enhancing patient responsiveness, developing combinatorial regimens, and exploring new immune-based therapeutic pathways.

Keywords: Immune checkpiont inhibitor, ipilimumab, nivolumab, drug combination, adverse reaction

1. Introduction

Melanoma is a highly aggressive malignant tumor with a rising global incidence and a very high fatality rate. Although surgery, radiotherapy, and chemotherapy are effective in some patients, melanoma has a strong resistance to traditional treatment methods, and the long-term survival prognosis for patients remains poor. Therefore, more effective treatment methods are urgently needed.

Recently, immunotherapy has become a focus of cancer research, and the discovery of immune checkpoints is of great significance. Programmed death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4)/B7 are key immune

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checkpoints that maintain immune homeostasis under normal physiological conditions. However, tumor cells can use these pathways to decrease T cell function and avoid immune system responses in malignant tumors like melanoma. By inhibiting the PD-1/PD-L1 or CTLA-4/B7 signaling pathways and removing the inhibition on T cells, immune checkpoint inhibitors (ICIs) increase the anti-tumor efficacy by enabling T cells to identify and lyse cancer cells. As of right now, ICIs like nivolumab and ipilimumab are authorized for the treatment of melanoma and have greatly enhanced patient survival. However, there are still research gaps in this field: the optimal regimens for the use of ICIs alone or in combination, the differences in efficacy, and how to reduce adverse reactions during combination therapy all require further investigation.

This article systematically retrieved studies related to immune checkpoint inhibitors and melanoma from the PubMed database and selected 11 studies published in recent years (2010-2024). It focuses on analyzing the clinical effects and safety of ICIs used alone and in combination. This study can serve as a guide for physicians creating treatment plans, assisting them in selecting the best medication for each patient's unique condition. At the same time, it can offer suggestions for the future development of immune checkpoint inhibitors that are more effective and less harmful, encouraging the study and development of immunotherapy medications for melanoma and helping to address this medical issue while also increasing the survival rate and quality of life for melanoma patients.

2. Concept and mechanism of immune checkpoint inhibitors

This study can serve as a guide for physicians creating treatment plans, assisting them in selecting the best medication for each patient's unique condition. At the same time, it can offer suggestions for the future development of immune checkpoint inhibitors that are more effective and less harmful, encouraging the study and development of immunotherapy medications for melanoma and helping to address this medical issue while also increasing the survival rate and quality of life for melanoma patients [1]. For example, the PD-1/PD-L1 model shows that interaction between T cell surface ligands PD-L1 and PD-L2 and PD-1 on T cell surfaces initiates inhibitory signaling pathways that prevent T cells from becoming more activated and multiplying. ICIs are a class of drugs that treat cancer by blocking the immune checkpoint signaling system and restoring the anti-tumor function of T cells [2]. By selectively blocking negative regulatory receptors (PD-1\CTLA-4) and their ligands (PD-L1\B7, etc.) on the surface of immunological or tumor cells, ICIs can alleviate T cell immunosuppression and improve anti-tumor immune responses. Immune checkpoint drugs that target the PD-1/PD-L1 pathway, for example, can reduce T cell inhibition, restore their ability to proliferate, and restore their effector function by blocking PD-1 and its ligands from binding. This allows T cells to effectively recognize and destroy tumor cells. Among the newly approved medications for clinical usage are monoclonal antibodies against cytotoxic T-lymphocyte-associated antigens (ipilimumab and tremelimumab), programmed cell death 1 (nivolumab and pembrolizumab), and programmed cell death ligand 1 (atezolizumab) [2]. The following section will mainly address the clinical therapeutic effectiveness of ipilimumab and nivolumab.

3. Clinical application of immune checkpoint inhibitors in the treatment of melanoma

3.1. Effect of monotherapy

Immune checkpoint medications have demonstrated exceptional effectiveness in treating individuals with metastatic melanoma, particularly those with anti-CTLA4 and anti-PD-1 antibodies. Significant

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tumor progression has been verified, and some patients may even experience long-term disease control. The two most often used and approved medications at the moment are ipilimumab, which inhibits CTLA-4/B7 binding, and nivolumab, which inhibits PD-1/PD-L1 binding. Ipilimumab, a human monoclonal IgG1 antibody against CTLA-4, is the first immune checkpoint inhibitor in the world to be approved for the treatment of metastatic melanoma [1]. In a phase III randomized clinical trial, the administration of immune checkpoint inhibitors significantly prolonged the overall survival of patients suffering from advanced melanoma [3].

Between 2008 and 2012, intravenous nivolumab demonstrated a median response duration of around two years, while the objective response rate reached 31% in those with advanced melanoma. Notably, in 12% of individuals, the therapeutic effects persisted for more than 16 weeks even after treatment withdrawal [4]. In a global double-blind phase III trial, patients with unresectable, metastatic, or treatment-resistant melanoma received nivolumab on a four-week schedule. The results of this study indicated that the median progression-free survival (PFS) was 4.6 months (95% CI: 3.4–5.6), and the proportion of patients who remained progression-free at 12 months was 36.0% [5]. Based on these results, ipilimumab can clearly help patients with growth disorders live longer and have a higher survival rate [6]. Further evidence showed that combining ipilimumab with dacarbazine significantly extended the overall survival duration compared to dacarbazine alone (11.2 vs. 9.1 months, $P < 0.05$). This combination also yielded higher survival rates at one, two, and three years [7].

In comparison to immunotherapy, conventional treatments such as radiotherapy or chemoradiotherapy alone offer limited long-term outcomes for melanoma patients—particularly those in stage IV, where the 5-year survival rate remains below 20%, and for stage III, where it typically ranges from 20% to 40%. The average duration of progression-free survival under these traditional methods generally spans two to four months. In contrast, the introduction of immune checkpoint inhibitors, notably nivolumab and ipilimumab, has markedly enhanced both progression-free intervals and overall survival rates in individuals with advanced melanoma. Nivolumab, for instance, has demonstrated a durable clinical response in a subset of patients, with response durations extending up to two years. Additionally, for those newly diagnosed with metastatic or inoperable melanoma, the application of immunotherapy has resulted in significantly prolonged progression-free survival when compared to standard care. These improvements are evident when evaluating outcomes such as median survival time and disease control, where immunotherapy—alone or in combination—consistently outperforms traditional chemotherapy-based regimens. Collectively, such findings underscore the distinct therapeutic benefits that immune checkpoint inhibitors offer in the treatment of advanced-stage and metastatic melanoma.

However, ICI resistance can also be found in clinical treatment, and the therapeutic effect decreases with the increase of the number of drugs used. Possible distant causes include reduction or loss of MHC molecules by tumor cells, which directly evade recognition by the immune system and render the drug ineffective. Or T cell exhaustion, which is the exhaustion of T cell function caused by long-term tumor antigen stimulation. Even if nivolumab eliminates immune checkpoint inhibition, the exhausted T cells are difficult to restore to effective killing function.

3.2. Strategy and effect of combined treatment

In clinical settings, it is common for patients to develop resistance to immune checkpoint inhibitors after prolonged treatment, leading to diminished therapeutic outcomes with increased dosage frequency. To address this challenge, researchers have explored combination therapies involving multiple immune checkpoint inhibitors. Compared to monotherapy, dual-agent immunotherapy has

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demonstrated enhanced clinical benefit, as it not only helps overcome resistance to single-agent inhibitors but also substantially extends progression-free survival and enhances objective response rates.

Current clinical evidence shows that the co-administration of nivolumab and ipilimumab provides more promising outcomes than monotherapy. Specifically, this combination appears to improve the progression-free survival (PFS) and response durability in individuals with stage III or IV melanoma. At a 4-year follow-up, the median PFS was reported to be 11.5 months in the ipilimumab plus nivolumab cohort, compared to 6.9 months for nivolumab alone, 2.9 months for ipilimumab alone, and a shorter duration for other treatment variations. Furthermore, neoadjuvant therapy using ipilimumab and nivolumab combined with surgery resulted in a longer event-free survival time than using nivolumab alone after surgical intervention.[8].

Long-term follow-up studies, such as the 6.5-year evaluation of CheckMate 067, have further confirmed the clinical value of the nivolumab plus ipilimumab regimen. In this trial, patients with advanced melanoma who received the dual-agent protocol showed more favorable survival outcomes compared to those treated with ipilimumab alone [9]. Additionally, retrospective analyses support the superiority of combined immunotherapy over single-agent regimens. In one randomized controlled trial with a 1:1:1 design, patients with untreated stage III or IV melanoma were allocated to three groups: one receiving ipilimumab with nivolumab, another nivolumab with a placebo, and the third ipilimumab with a placebo [3]. Results showed that the combination group achieved the best outcomes across multiple survival measures: higher median progression-free survival, improved 2-year and 3-year survival rates, and notably enhanced 4-year overall survival [3].

In summary, when compared to conventional treatment approaches, nivolumab in combination with ipilimumab provides better disease control and elicits stronger immune responses. This dual therapy has proven especially beneficial in advanced melanoma, offering more durable and comprehensive clinical advantages.

4. Adverse effects and management of immune checkpoint inhibitors

Ipilimumab (IPI) was discovered to have a number of dose-dependent inflammatory adverse effects in the aforementioned controlled tests. These side effects primarily affected the skin, liver, endocrine organs, and gastrointestinal tract, and their occurrence may reach 56%. In certain extreme situations, they could even be fatal [3]. Numerous clinical studies have revealed that 90% of patients receiving anti-CTLA-4 medication and 70% of patients receiving anti-PD-1/PD-L1 treatment experience immune-related adverse events (irAEs) [10]. These adverse events vary among patients, can involve any part of the body, and usually worsen as the disease duration progresses.

The mechanisms of IrAEs mainly include T cell activation, cross-reaction between anti-tumor T cells and similar antigens on healthy cells, increased secretion of cytokines, amplification of autoantibodies, or direct binding of monoclonal antibodies to normal tissues. Clinical data show that adverse reactions caused by combination therapy are usually stronger than those caused by monotherapy [11]. For example, among individuals diagnosed with untreated metastatic or unresectable melanoma, a high proportion—97.2% and 94.4% in two respective groups—developed adverse events (AEs) after receiving combination therapy with nivolumab and relatlimab, with a median treatment duration of 5.6 months, slightly longer than the 4.9 months observed for the nivolumab monotherapy group. Common treatment-related adverse events (TRAEs) associated with the combination, particularly those with an incidence above 15%, included fatigue (23.1% vs. 12.8%), pruritus (23.4% vs. 15.9%), and rash (15.5% vs. 12.0%), all of which occurred more frequently compared to nivolumab alone [5].

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Therefore, regular examination and symptom assessment are necessary for patients taking immune checkpoint inhibitors. If the adverse reaction is serious, it is usually controlled by interrupting the treatment, and glucocorticoids can be added in severe cases. When the adverse reactions are controlled, the use of immune checkpoint inhibitors can be resumed, or different immune checkpoint inhibitors can be changed.

5. Conclusion

Extensive clinical research has validated the remarkable efficacy of immune checkpoint inhibitors in the clinical management of melanoma. Immunocheckpoint inhibitors provide melanoma patients fresh hope by considerably extending their survival time, improving their five-year survival rate, and lowering their chance of recurrence, according to research findings.

Comprehensive clinical investigations have been conducted to evaluate the therapeutic efficacy of immune checkpoint inhibitors, and findings have affirmed their effectiveness in melanoma treatment, both as monotherapy and in combination strategies. Immunocheckpoint inhibitors alone produced some improvement in the patient population during the experiment; however, when combined with other therapies (like chemotherapy and targeted therapy), the treatment response rate was further enhanced, tumor shrinkage was more noticeable, and progression-free survival was noticeably extended.

Despite its remarkable efficacy, immune checkpoint inhibitors have also exposed some problems in the treatment process. Due to the weakening of its inhibitory effect on T cells, T cells excessively attack their own tissues and then cause adverse symptoms similar to autoimmune diseases, such as skin inflammation, thyroid dysfunction, enteritis, etc. These adverse symptoms affect the quality of life of patients and the subsequent treatment process to a certain extent.

In summary, immune checkpoint inhibitors have improved melanoma treatment, although more refinement of their therapeutic strategies is still needed. The following areas should be the focus of future research: first, increasing the rate at which patients respond to immune checkpoint inhibitors; second, using genetic testing and other methods to screen for patients who might respond well to immune checkpoint inhibitors; and third, creating targeted conditioning regimens is essential to enhancing the therapeutic effect. Second, there may be a synergistic impact between immune checkpoint inhibitors and targeted medications, which could enhance the therapeutic efficacy and lower the likelihood of side effects. In addition, continuous research on new immune checkpoints to provide more effective targets and therapeutic strategies for melanoma treatment is also an important direction for future research.

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