

Research Progress of Immune Checkpoint Inhibitors in Melanoma

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Abstract: Melanoma, also known as malignant melanoma, is a malignant tumor originating from melanocytes that is highly malignant, aggressive, and has a poor prognosis. Although melanoma accounts for about 10% of skin cancers, melanoma is the leading cause of death from skin cancers. Thus, it is essential to study the treatment of melanoma. Immunotherapy has produced durable clinical responses with long-term remissions in melanoma. In this article, we present a review of immune checkpoint inhibitors in melanoma treatment, and will introduce CTLA-4 inhibitors, PD-1 inhibitors, and PD-L1 inhibitors.

1. Introduction

As a malignant tumor with high degree of malignancy and high mortality rates, melanoma has become the deadliest form of skin cancer. The treatments for melanoma include surgical resection, chemotherapy targeted therapy and immunotherapy [1]. Different treatment modalities should be used for patients at different stages. Surgical resection of primary melanoma (PM) has promising efficacy and is the ideal treatment for primary malignant melanoma. However, melanoma progresses rapidly, and once metastasis occurs the survival rates drop significantly. Conventional radiotherapy and chemotherapy have poor therapeutic effect in metastatic melanoma and do not improve the overall survival of patients. With the development of immune checkpoint inhibitors (ICIs) and molecular targeted therapy, the prospect of patients with advanced melanoma has changed greatly. Because melanoma is one of the most immunogenic tumors, immunotherapy has sustained efficacy and is clinically proven to be highly tolerable over chemotherapy and targeted therapy [2,3].

Over the past decade, immunotherapy has emerged as the most promising form of tumor treatment. As early as 2011, the U.S. Food and Drug Administration (FDA) approved the immune checkpoint inhibitor ipilimumab for advanced melanoma, as shown in Table 1. Since 2015, monoclonal antibodies against other immune checkpoint molecules (PD-1 and its cognate ligand PD-L1) have also been approved by the pan-Canadian Oncology Drug Review (pCODR) for use in a variety of tumor types, including melanoma [4]. The development of immune checkpoint inhibitors also holds promise for the treatment of melanoma.

The interplay between tumors and host defense is complex and involves a balance of the immune

system: suppressing and promoting tumor growth [5]. Immune checkpoints are protective molecules in the human immune system that act like brakes to prevent inflammatory damage caused by over-activation of T-cells under normal conditions [6]. Tumor cells take advantage of this characteristic, inhibit the response of the human immune system and escape from human immune surveillance and killing via upregulating the expression of immune checkpoint molecules, thus promoting the growth of tumor cells [7,8]. Therefore a promising way to against cancer is to block immune checkpoints, the mechanism by which cancer cells disguise themselves as regular components of the human body.

Table 1: Immune Therapies for Melanoma

Immune Checkpoint Therapy		
Ipilimumab	Anti-CTLA-4 monoclonal antibody	Unresectable/metastatic melanoma (regardless of BRAF status) Adjuvant treatment of resected stage III melanoma (regardless of BRAF status)
Nivolumab	Anti-PD-1 monoclonal antibody	Unresectable/metastatic melanoma (regardless of BRAF status) Adjuvant treatment of resected stage III melanoma (regardless of BRAF status)
Pembrolizumab	Anti-PD-1 monoclonal antibody	Unresectable/metastatic melanoma (regardless of BRAF status) Adjuvant treatment of resected stage III melanoma (regardless of BRAF status)
Ipilimumab-nivolumab	Anti-CTLA-4 antibody+ anti-PD-1 antibody	Unresectable/metastatic melanoma (regardless of BRAF status)

2. Immune checkpoints

To date, several new immune checkpoint targets have been identified, such as lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), T cell immunoglobulin and ITIM domain (TIGIT), V-domain Ig suppressor of T cell activation (VISTA), and so on. However, only anti-programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) and anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) monoclonal antibodies (mAbs) are FDA-approved and in widespread use [9] (Figure 1). In this paper, the monoclonal antibodies against CTLA-4 and PD-1/PD-L1 for the treatment of melanoma are reviewed.

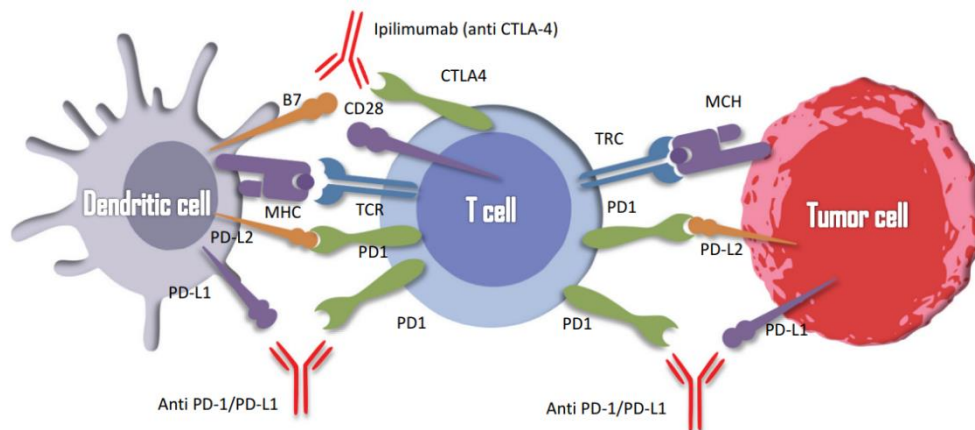


Figure 1: Anti CTLA-4 and PD-1/PD-L1 therapy

2.1. Cytotoxic T-lymphocyte antigen 4 (CTLA-4)

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) is a membrane glycoprotein expressed by activated effector T cells (Teffs) and participates in the repression of T cell proliferation, cell cycle progression and cytokine production [10]. CTLA-4 (CD152) and CD28 are homologous receptors expressed by both CD4+ and CD8+ T cells, which mediate opposing functions in T cell activation [11]. CTLA-4 is a co-inhibitory receptor for T cell activation and is regulated by co-inhibitory signaling [12]. CTLA-4 exerts its inhibitory effects through multiple mechanisms protecting tumor cells from T-lymphocyte attack, including negative signaling and competitive antagonism of CD28:B7-mediated costimulation [13]. Currently, antibodies against CTLA-4 are Ipilimumab and tremelimumab.

2.1.1. Ipilimumab

Ipilimumab was the first FDA-approved antibody for melanoma, and has been proved to have a long-term survival advantage for patients with advanced cutaneous melanoma [14]. A prospective real-world study of ipilimumab and non-ipilimumab treatment in patients with advanced melanoma showed that the 3-year OS rate was 28% in the ipilimumab-treated cohort and 25% in the non-ipilimumab-treated cohort [15]. This demonstrates that although ipilimumab is no longer commonly used as first-line monotherapy for patients with advanced melanoma, ipilimumab still gains benefit and has no detrimental impact on long-term quality of life (QoL). Although with the introduction of anti-PD-1 antibodies, ipilimumab is not as effective as PD-1 antibodies as a first-line monotherapy, the combination of nivolumab and ipilimumab led to better objective response rates, progression-free survival, and OS than ipilimumab and is approved in several countries for the first-line treatment of patients with advanced melanoma [16].

2.1.2. Tremelimumab

Tremelimumab is an immunoglobulin (Ig) G2 cytotoxic T lymphocyte-associated antigen-4 (CTLA4) –blocking monoclonal antibody. A phase III study of tremelimumab and chemotherapy in patients with advanced melanoma showed that tremelimumab as first-line therapy failed to improve OS compared with chemotherapy [17]. However, a phase I study found promising clinical activity with an acceptable toxicity profile using CP-870,893 (CD40) and tremelimumab to treat patients with metastatic melanoma, the median OS was 23.6 months, 1-year OS was 72.0%, and 2-year OS was 48.7% [18]. It suggests that tremelimumab has great potential in the treatment of metastatic melanoma and warrants further studies.

3. Programmed cell death protein-1 and its cognate ligand (PD-1 and PD-L1)

Programmed cell death protein-1 (PD-1), also known as CD279, is a member of the CD28/CTLA-4/ICOS costimulatory receptor family. PD-1 and the other receptors in this family are all type I transmembrane glycoproteins composed of an Ig Variable-type (V-type) extracellular domain, a transmembrane domain, and a cytoplasmic tail responsible for the binding of signaling and scaffolding molecules [19]. PD-1 is mainly expressing on the membrane of antigen-stimulated T cells, but it is also expressing on T cells, B cells, tumor infiltrating lymphocytes (TIL), dendritic cells (DCs), macrophages and natural killer (NK) cells [20]. PD-1 is mainly regarded as an inhibitory receptor, which is involved in the regulation of immunological tolerance. This inhibitory receptor signaling inhibits T cell activation under normal conditions, suppresses lymphocyte function, induces apoptosis, enhances autoimmune tolerance, and prevents autoimmune diseases [21]. Tumor cells may escape immune activation by up-regulating their own PD-L1/PD-L2 molecules, thus inhibiting the activation

of T cell, promote tumor growth [22]. PD-1 has two binding receptors, PD-L1 and PD-L2. The expression of PD-L2 is mainly in activated macrophages, DCs, mast cells and a few tumors, while PD-L1 is widely existed in activated T cells, B cells, macrophages, DCs and tumor cells [20]. Studies have found that PD-L1 is highly upregulated in many murine and human tumors and its expression is associated with poor outcome for patients with certain epithelial cancers [23]. Therefore, research focuses on PD-1: PD-L 1 blocking as a strategy for cancer immunotherapy.

3.1. PD-1 monoclonal antibody

3.1.1. Nivolumab

Nivolumab is human IgG4 monoclonal antibody, which inhibits the PD-1 immune checkpoint protein, and has been approved by the FDA in 2014 for the monotherapy of patients with advanced or unresectable cutaneous melanoma [24]. A prospective observational study of the efficacy of nivolumab in Japanese patients with advanced melanoma showed that the objective response rate and median survival time in Japanese patients treated with nivolumab were lower in daily practice than the >30% and >30 months, respectively, seen in global phase III trials [25]. Although the reasons for these differences are unclear, the efficacy of nivolumab monotherapy in real-world clinical practice does not appear to be particularly high. The authors of the study also concluded that the results of the trial may be related to the limitations of the trial design, but it also suggests that nivolumab monotherapy should be improved and that combination therapy may be able to achieve better treatment results. Further research could be done on other combination treatments besides combining ipilimumab.

3.1.2. Pembrolizumab

On December 18th, 2015, the US FDA awarded pembrolizumab for treatment of patients with unresectable or metastatic melanoma based on results of two randomized, open-label, active-controlled clinical trials [26]. A phase III trial of adjuvant pembrolizumab versus placebo in resected stage III melanoma found that Compared with placebo, pembrolizumab, as adjuvant therapy for resected patients with high-risk stage III melanoma, has a longer Relapse-Free Survival (RFS) and does not lead to a significant clinical decrease in health-related quality-of-life(HRQOL) [27]. Besides previous studies have found that pembrolizumab has a lower number of reported grade 3 or more serious adverse events than ipilimumab. This all demonstrates the efficacy and relative safety of pembrolizumab in the treatment of melanoma.

3.2. PD-L1 monoclonal antibody

3.2.1. Durvalumab

Durvalumab binding to PD-L1 with high affinity and specificity, thereby inhibiting its interactions to PD-1 and CD80. In 2017, durvalumab was approved by the FDA for the treatment of patients with urothelial carcinoma (who progressed during or after platinum-based chemotherapy, including those who had disease progression within one year of treatment with a platinum-based regimen in the neoadjuvant or adjuvant setting followed by surgical resection [28]. Although durvalumab is not approved for the treatment of melanoma at this time, but a single phase I clinical trial confirmed that the triplet combination of dabrafenib, trametinib, and durvalumab is feasible in patients with BRAF-mutant advanced melanoma(including patients who had previously progressed on anti-CTLA-4 therapy)and induces robust and sustained immune modulation [29]. Studies have shown that Durvalumab still has potential in the treatment of melanoma and could be an important drug for adjuvant therapy.

3.2.2 Avelumab

Although avelumab is not approved for melanoma treatment at this time, a phase 1b data from patients with previously treated patients with unresectable stage IIIC or IV melanoma showed that of all enrolled patients, the confirmed ORR was 21.6 and 31.4% in patients with non-ocular melanoma and 7 of 16 patients (43.8%) with ocular melanoma had a best overall response of stable disease with avelumab [30]. This trial attests avelumab has durable responses, promising survival outcomes, and an acceptable safety profile in patients with previously treated metastatic melanoma.

4. Limitations of immune checkpoint therapy

4.1. Immune-related adverse events (irAEs)

Immune checkpoint blockade therapy has become a popular tumor treatment at this stage due to its wide use, less adverse effects and good efficacy. Promoting T-cell activation by ICIs agents can lead to good anti-tumor immune responses. Immune checkpoints act as molecules that maintain immune homeostasis, preventing T cell overactivation from triggering inflammation, whereas ICIs lead to an imbalance in immune tolerance, creating an unwanted immune response. The adverse events of the programmed cell death protein 1 and its ligand and of the cytotoxic T-lymphocyte-associated protein 4 are similar. Immune-related adverse reactions may involve many body organs, such as thyroiditis, dermatitis, pneumonia, colitis, hepatitis, pituitary gland inflammation, uveitis, polyneuritis, pancreatitis, etc. Cutaneous toxicity is the most frequent and precocious, 30-50% of patients treated with ICIs for melanoma experience adverse skin reactions [31]. The most common cutaneous toxicities are maculopapular exanthema and pruritus, but other more specific adverse effects (e.g. lichenoid or psoriasiform reaction, vitiligo, sarcoidosis, among others) or located in the oral mucosa and/or adnexa are underreported [32,33].

IrAEs range from mild to severe, and in some severe cases can be life-threatening, and not all patients taking ICIs will develop the same irAEs, therefore it is necessary to extract patient-level irAEs, which may be affected by patient genetics, disease characteristics, demographics, co-occurrent drugs, among others [34]. These patient-level irAEs are important for tailored personalized ICI treatments and irAE management [35]. Standard treatment algorithms for irAEs have been developed that utilize immune-modulating medications including corticosteroids, antihistamines, antitumor necrosis factor medications and calcineurin inhibitors, which may quell the inflammatory response, without eliminating the antitumor immune response [33]. Some studies have also shown that most irAEs are not caused by the drug's off-target effects, therefore, if we want to minimize and mitigate the adverse effects of ICIs, it is important to identify and understand how the off-target of ICIs is involved in irAEs. Furthermore different of these ICIs have preferences for side effects, personalized selection of ICI therapy and management of irAEs is important.

4.2. Drug resistance

While immune checkpoint inhibitors targeting the CTLA-4 and PD-1 receptors have significantly improved the prognosis of many patients with metastatic melanoma, there remains a group of patients who demonstrate no benefit [36]. These non-responding patients can be categorised into two main groups: (1) Congenital or primary resistance, which means people who have no response to the blocking of immune checkpoint at all or whose diseases have been stable for less than 6 months before disease progresses (about 20–40% patients); (2) Secondary or acquired drug resistance refers to patients who relapse after the initial response to immunotherapy and develop into diseases (about 20–30% patients) [36-38]. Drug resistance is the biggest obstacle limiting the use of immune checkpoint therapy in the treatment of melanoma, so in-depth research is necessary to investigate drug resistance.

Immune checkpoint inhibitors only improve the prognosis of some patients, and the molecular

mechanisms of lack of responses are being studied. There is growing evidence that altered expression levels of microRNAs (miRNA)s induce drug-resistance in tumor cells and that restoring normal expression of dysregulated miRNAs may re-establish drug sensitivity [39]. Veronica Huber [40] described a set of microRNAs (miR-146a, miR-155, miR-125b, miR-100, let-7e, miR-125a, miR-146b, miR-99b) that are associated with myeloid-derived suppressor cells (MDSCs) and resistance to treatment with immune checkpoint inhibitors in melanoma patients, higher circulating levels of these miRs cluster with shorter PFS and OS in patients receiving ipilimumab and nivolumab, but not in those treated with BRAF/MEK inhibitors. It is reasonable to foresee that combining miRNAs with different immune checkpoint targets could mimic and possibly improve the effect of combined immune checkpoint blockade therapies [39,41].

5. Conclusions

With the in-depth study of immune checkpoints, more and more immune checkpoints have been discovered, such as LAG3, TIGIT, TIM3, adenosine A2A and CD47[31]. Research on these newly discovered immune checkpoints is also ongoing, in anticipation of the development of new immune checkpoint inhibitors that will hopefully help melanoma patients.

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