Clinical effects of immune checkpoint inhibitors in metastatic advanced melanoma

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Abstract: Immune checkpoint is a kind of immunosuppressive molecules, which regulate the immune response, so as to avoid damage and destruction to healthy tissues. In some special tumors, immune checkpoints are the main reason for their immune tolerance. The immune checkpoint inhibitor reactivates the anti-tumor immune response and promotes the clearance of immune-mediated tumor cells by blocking the co inhibitory signal pathway. Melanoma is a disease in which malignant cells are formed in melanocytes. Immune checkpoint inhibitor is one of the current drugs for the treatment of metastatic melanoma. It mainly includes 3 types of drugs, which are ipilimumab, pembrolizumab and nivolumab. Ipilimumab belongs to CTLA-4 blocker, pembrolizumab and nivolumab belong to PD-1 / PD-L1 blocker. They have different clinical effects and adverse reactions in the treatment of metastatic melanoma. In this review, the effects and adverse reactions of these three drugs in the clinical treatment of metastatic melanoma were systematically introduced.

1. Introduction (Heading 1)

Melanoma rates have doubled due to an ageing population, increased UV exposure in the sun, the continued use of tanning beds and increased awareness and testing. Although melanoma accounts for only 1% of all diagnosed skin cancer cases, it is by far the deadliest, killing an estimated 10,000 people in the US in 2018.Due to the possible biological effects of UV radiation and melanin, most patients' melanoma cells contain a relatively large number of mutations in their DNA [2]. Melanoma is the third most common source of brain metastases after non-small cell lung cancer (NSCLC) and breast cancer [3]. Considering that the incidence of malignant melanoma is much lower than that of non-small cell lung cancer or breast cancer, the tendency of metastatic malignant melanoma to the central nervous system becomes apparent. Therefore, melanoma is most likely to metastasize to the brain. The risk of brain metastases in metastatic melanoma increases with the duration of the disease. Melanoma brain metastases (MBM) are found at autopsy in 75% [4] of patients with metastatic melanoma. As a result, the battle to treat melanoma in its later stages is on, and scientists have discovered drugs associated with immune checkpoint inhibitors, opening the door to attacking the disease.

In addition to targeted treatment options, immune checkpoint inhibitor immunotherapy had also made a huge contribution to this development. Immune checkpoint inhibitors with anti-CTLA-4 and anti-PD-1 antibodies are the standard treatment for metastatic melanoma. Anti-PD-1 (pembrolizumab and nivolumab) and anti-PD-L1 (atezolizumab and avelumab) antibodies have been approved for the treatment of several other advanced malignancies, including NSCLC, urinary tract cancer of the skin, carcinoma of the stomach and classical Hodgkin lymphoma [5]. For melanoma, what succeeded up till now are PD-1 antibody monotherapy can achieve a response of 26-32%, and the combination of PD-1 antibody and CTLA-4 antibody achieve a response up to 60% [6-7]. Some of patients achieve durable responses with PD-1 antibody monotherapy and do not require combined immune checkpoint inhibitors.

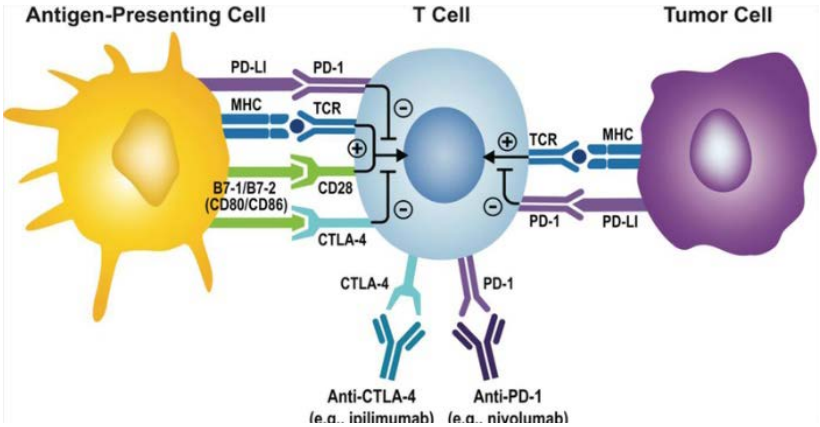

Fig 1. The structure of typical checkpoint inhibitors [1].

However, until recently, most clinical studies have ruled out patients with melanoma brain metastases (MBM), and their prognosis remains poor, with survival typically within a few months if untreated. Despite significant improvements in MBM treatment, a large number of patients continue to progress and die due to MBM [8]. Despite the great success of immune checkpoint inhibitor therapy, it does not produce a lasting response in all patients. Different entities and patients respond differently. The challenge we face today is that there is still a need to find reliable biomarkers to help identify patients who will benefit from immune checkpoint inhibitors, as well as those who are predominantly resistant [9]. Biomarkers are also needed to help identify the type of first-line treatment. In addition, MBM is the cause of death in most patients with advanced melanoma.

In this review, the current status immune checkpoint inhibitors treatment for melanoma are reviewed and concentrated on the effect of the corresponding antibodies. It focused on some of the drugs used by patients with advanced metastatic melanoma, to figure out the effects of the drugs on this cancer, and compared these effects. Furthermore, the properties, functions, mechanisms, clinical effects and comparison of the three drugs, as well as adverse reactions were introduced. In the future, prospective studies of patients with melanoma with MBM are urgently needed, focusing on treatment combination and sequence, and developing new treatment strategies and biomarkers for treatment response. In addition, further research is needed to decipher the brain's specific treatment resistance mechanisms.

2. The Typical Drug：IPILIMUMAB

Ipilimumab is an all-human monoclonal IgG1 antibody that blocks cytotoxic T lymphocyte antigen-4 (CTLA-4) expressed on T cells. Ctla-4 usually binds to the B7 receptor on the surface of antigen-presenting cells in lymph nodes, an endogenous mechanism that inhibits t-cell-mediated immune responses and promotes tolerance [10]. By blocking this immune checkpoint, IPilimumab can effectively activate and prolong the body's anti-tumor immunity, and has produced good therapeutic effects in some patients, including a small number of patients with undetectable disease [11].

2.1 The Clinical effect and application of ipilimumab

Ipilimumab's Phase I study showed an 11.7% response rate [12]. In a Phase II trial, 217 patients who had previously received stage III or IV melanoma were randomized to a fixed dose of ipilimumab followed by maintenance therapy every 3 months, showing a positive correlation between response rate, toxicity, and increased drug concentration [13]. There were 676 patients in a Phase III trial, in which tumors cannot be treated with surgical excision alone. Doses of Ipilimumab were calculated based on body weight, 3mg per kg of body weight, and administered every 3 weeks, up to 4 times as much [14]. The results showed that the 1-year survival rate of Ipilimumab monotherapy was 39.3% and the 2-year survival rate was 24.2% [13]. In addition, the long-term efficacy of ipilimumab was analyzed by late survival analysis, and the 1-year survival rate was 45.6%, and the 2-year survival rate

was 23.5%. These data suggest that ipilimumab significantly improves overall survival in patients with metastatic melanoma.

2.2 The Adverse reactions of ipilimumab

With the wide application of ipilimumab in the treatment of metastatic melanoma, many patients benefit from it. However, everything has two sides. Ipilimumab also has many adverse reactions in clinic, even causing death, which is called immune-related adverse events (irAEs). IrAEs range from minor to potentially life-threatening events and may involve many systems, including dermatological, gastrointestinal, liver, endocrine and lung.

2.2.1 The treatment of ipilimumab in Dermatological field

Pruritus During the treatment of ipilimumab, pruritus appears to be a direct result of CTLA-4 inhibition and subsequent enhanced immune system activation [15]. A recent meta-analysis showed that nearly 31% experienced pruritus after treatment with ipilimumab, but only 1% experienced the highest grade if pruritus [16]. Fortunately, in most cases, it is possible to treat the pruritus without changing Ipilimumab's treatment plan.

Maculopapular Exanthema During the treatment of ipilimumab, this kind of rash is a common symptom. Approximately 47–68% of patients are reported to develop it in 2–4 weeks of treatment after the treatment [17]. It is shown as red macules or patches intermixed with papules and plaques typically involving the trunk, arms, or legs although any region of skin may ultimately be affected [18]. In most cases, using medium potent topical corticosteroid or calcineurin inhibitor can reduce the inflammation [19], and anti-histamines are administered to address pruritus without stopping the treatment [20-21]. In severe cases, a gradual tapering course of oral prednisone 1–2 mg/kg per day, in addition to withholding or cessation of ipilimumab may be required [20-22].

Vitiligo-Like Melanoma-Associated Hypopigmentation Vitiligo occurs in 2-11% of patients treated with ipilimumab, but it is a sign of benign treatment [23]. Vitiligo is characterized by asymptomatic stains or plaques, usually around the site of primary melanoma or metastases, but may be limited or widespread. Depigmentation differs from depogmentation, a common post-inflammatory side effect, It is important that Vitiligo does not disappear after removal [24].

Other inflammatory skin disease caused such as neutrophilic dermatoses, acute generalized exanthematous pustulosis, and pustular acneiform eruptions [17].

2.2.2 The treatment of ipilimumab in Gastrointestinal field

The most common irAEs was diarrhea, which occurred at any grade in 27-31% of patients who treated with Ipilimumab [11]. And early use of corticosteroids can reduce the occurrence of immune-related adverse events [11].

2.2.3 The treatment of ipilimumab in Liver

Liver disease occurs in 10% of patients treated with these drugs, usually 12-16 weeks after the third dose. Symptoms are asymptomatic or accompanied by fever [25].

2.2.4 The treatment of ipilimumab in Endocrine

Typically, hyperthyroidism/ hypothyroidism, hypophysitis, adrenal insufficiency and diabetes may develop after 9 weeks of treatment with ipilimumab, which is characterized by fatigue, anorexia, nausea and headache and is therefore difficult to diagnose [25].

2.2.5The treatment of ipilimumab in Lung

Pneumonia, pleurisy and sarcoid-like granulomatosis can occur in patients treated with these drugs, and pneumonia being the most common, occurring in about 1% of patients [16].

3. The typical drug：PEMBROLIZUMAB

With A resolution of 2.3-A, Pembrolizumab can clearly be seen as A compact molecule with A Y-shape, consistent with the presence of A short hinge region. The Fc domain is glycosylated at the CH2 domain level of both chains, but the conformation of the CH2 domain is rotated 120° compared to all structures reported so far, and its glycan chain faces the solvent [27].We can only assume that the new conformation is driven by a shorter hinge. This structure illustrates the role of S228P mutation in blocking IgG4 arm exchange. Furthermore, this unusual Fc conformation suggests that the IgG subclass may be structurally diverse, and due to molecular flexibility, the use of isolated antibody fragments may mask potentially important interactions [28].In addition, the evaluation of pharmacokinetic/pharmacodynamic (PK/PD) characteristics also plays an important role in the early clinical development of pembrolizumab [29].

3.1 The Clinical effect and application of Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody directed against programmed death receptor 1 (PD-1). PD-1 is a key immunosuppressive checkpoint protein that is involved in down-regulating anti-tumor immune responses. This intravenous medication is suitable for the treatment of advanced melanoma which are unresectable or metastatic. These studies were conducted in patients who were ipilimumab naive or who had previously received ipilimumab and evaluated different regimens of pembrolizumab, all of which determined the level under a recommended dosage. In trials using active control drugs, compared to ipilimumab-naive patients, pembrolizumab significantly improved progression-free survival (PFS), and significantly improved overall survival (OS) and overall response rate (ORR). Improvement in PFS and ORR Compared to chemotherapy in patients with refractory ipilimumab, if the BRAF mutations are positive, these patients also receive treatment with a BRAF / MEK inhibitor. Pembrolizumab is tolerated and immune-system related adverse events are generally controllable or reversible. Therefore, pembrolizumab is an attractive treatment option for patients with advanced melanoma, including those who have progressed following treatment with ipilimumab and BRAF/MEK inhibitors [30].In another experiment, the researchers randomly assigned 834 patients with advanced melanoma to different groups. Patients in the experimental group received pembrolizumab (10mg/kg body weight) every 2-3 weeks. These results suggest that pembrolizumab not only prolongates the progression-free survival and overall survival of patients with advanced melanoma [31], but also has low and high toxicity.

3.2 The Adverse reactions of Pembrolizumab

Adverse effects of Pembrolizumab in treating diseases affect on different organs. It has been associated with side effects like fatigue, pruritus, and decreased appetite, and renal toxicity was not seen in initial reports [32]. Some patients can even have some acute kidney injury during hospitalization for chest and abdominal pain [33]. However, renal adverse effects are rare with Pembrolizumabs, even with checkpoint inhibitors [34]. The overall incidence of acute kidney injury was reported to be 2.2% among 3695 patients on a checkpoint inhibitors [35]. Sometimes the side effects can occur in the lungs.

4. The typical drug：Nivolumab

T cell checkpoint inhibition has profound implications for cancer treatment. Nivolumab is an immunotherapy cancer treatment drug, also Nivolumab is the generic name for the trade drug named Opdivo®. It is considered a targeted therapy, a PH-1 blocking antibody. Nivolumab is considered one of the lead molecules of the cancer immunology therapeutic revolution. It is considered an IgG4 subclass. Due to its low affinity for Fc and C1q receptors, complement and cell activation can only be weakly reduced, therefore it basically cannot activate host effector functions [37].

4.1 The Clinical effect and application of Nivolumab

Approximately 1.6 million new cases of lung cancer are added each year, and unfortunately, about 87% of cancer patients die. First of all, if the cancer is at an early stage and has not spread, the traditional cancer treatments are surgical treatment and radiotherapy, but these are all local treatments that can only treat early-stage cancer. Once the cancer is in the advanced stage, chemotherapy or targeted drugs can be used. Bone marrow transplantation can also be used for blood-related cancers. Even though modern technology has different ways to treat cancer, chemotherapy and targeted therapies are advancing rapidly. But the survival rate of cancer patients is still very poor [38]. Modern research on immunotherapy and the development of immunological drugs seem to be the possibility of effective treatment of cancer.

Nivolumab is a fully human monoclonal antibody against programmed death receptor, a negatively regulated checkpoint molecule with immunosuppressive effects. The medicine is given intravenously. Nivolumab approved in Japan for relapsing malignant melanoma. According to the study, the clinical benefits of the drug are long-lasting. Patients will need two milliliters of Nivolumab every three weeks. Patient who received the treatment lived significantly longer. The study is the first to demonstrate the potential of nivolumab as an intravenous treatment for advanced malignancies such as melanoma. Therefore, nivolumab is a new and promising option for the treatment of malignant melanoma [39].

4.2 The Adverse reactions of Nivolumab

Base on the phase Ib study, the result shown nivolumab was well tolerated. 41% percent of the patients were having adverse reactions, however, only 6% of the patients were considered grade 3 or 4 adverse reactions (toxicities). The common adverse reaction among lung cancer patients was skin toxicities, about 31% of the patients in the phase lb study were suffering from skin toxicities. 12% had a skin rash, 9% had pruritus and 3% had vitiligo. 11% of the patients had gastrointestinal toxicities such as diarrhea. 3% had pneumonitis, but only 1% having classified as a grade 3 pneumonitis. Other adverse reactions included abnormalities in transaminases, infusion-related reactions, and thyroid dysfunction [38]. According to a Japanese study on the Nivolumab, less than 18% of patients had elevated γ-glutamyltransferase, which was classified as a grade 3 or 4 adverse event [39].

5. Conclusion

In summary, three checkpoint inhibitors ipilimumab， pembrolizumab and nivolumab worked well in clinical trials in melanoma. The combination of ipilimumab and nivolumab has also had impressive success. These studies also lay the foundation for the clinical application of this method in other tumors. As a monotherapy, ipilimumab has a low response rate and significant activity in long-term survival [40]. A pooled analysis of more than 1,800 clinical trial patients showed 20% long-term survivors. Pembrolizumab and nivolumab outperformed ipilimumab as first-line treatment and progression to ipilimumab. But long-term follow-up is needed to see if it can achieve long-term survival, as ipilimumab has demonstrated. The combination of ipilimumab and nivolumab is the most active immunotherapy to date for metastatic melanoma. However, while the effect of immune checkpoint inhibitors in advanced melanoma is impressive, there are several points that need special attention. It is important to note that specific immunological and clinical training is necessary for optimal management of these drugs, and longer follow-up of ongoing trials is still needed to clarify their effects. Future challenges with immune checkpoint inhibitors include the development of drug resistance mechanisms that may lead to new therapeutic combinations (such as anti-PD-1 /PD-L1 drugs and CD73 inhibitors), as well as the possibility of anti-PD-1, if treatment is discontinued, and the optimal timing of treatment with an effective drug. Additional data suggest that these conditions occur in patients with melanoma with brain metastases. In addition, new potential therapeutic combinations, including combination of anti-PD-1 therapy with IDO inhibitors or new anti-Rag-3 checkpoint inhibitors, have been identified and will continue to be developed in the future to study their specific effects.

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