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Application of immune checkpoint inhibitor in melanoma treatment

Yutong Chen

The High School Affiliated to Renmin University of China, Beijing, 100000, China

1812100101@mail.sit.edu.cn.

Abstract. Since ipilimumab was approved by FDA in 2011 as the first immune checkpoint inhibitor (ICI) to treat melanoma, the development of immunotherapy had a huge break through. These inhibitors can block the checkpoint proteins, which include CTLA-4 and PD-1, and resulting in the reactivation of T cells. Their promising effect on suppressing cancer growth is proved once they were used in cancer treatments. One of the greatest contributions of the ICIs is the improvement of melanoma treatment. Melanoma is the most aggressive skin cancer since its death rate is the highest among all the skin cancer. Their application on melanoma patients is shown to improve patients' overall survival and response rate with durable responses. Furthermore, they can treat metastatic melanoma which former therapies were struggling with. Although they still faced the problem of severe side-effects that damage patients' lives, many new combinations of therapies had been invented to overcome these drawbacks. The results of using combined therapies are anticipated in further clinical trials.

Keywords: Immune checkpoint inhibitor, melanoma, application, adverse events.

1. Introduction

As a fatal skin cancer, melanoma was well-known for its aggressiveness. The disease had gained people's attention to a great extent in recent years, which includes cutaneous melanoma, mucosal melanoma and ocular melanoma. Although not really considered as a type of melanoma, metastatic melanoma had also been concerned by many people because it is dangerous. The presence of metastatic melanoma indicates that the tumor had spread from original site to other places. One effective way to avoid death is to detect the tumor as early as possible and use surgery to remove it. However, at the same time, it was also difficult to find the tumor out before getting to later stage. Data had shown that melanoma accounts for nearly 75% of skin cancer death despite that there are only about 4% of it among all skin cancer cases [1]. There are various treatments for melanoma which had been proved to be useful to some extent. The main treatment is through surgery, which ended up as disappearance of both tumor cells and the healthy tissue surrounding it. Despite its directness, surgery faced its problem when it comes to metastatic diseases. This problem can be solved by chemotherapy, but the considerable amount of toxicity and side effects caused by it made it a less favored choice. Before 2011, melanoma had been determined to be a deadly disease which almost lack any possibility to cure after 18 months of diagnosing within the help of chemotherapy [2].

Although early detection of the cancer is always the priority for everyone, in some cases, tumor was found in relatively late stage, so an effective therapy for melanoma was still necessary [1].

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Targeted therapies can also be a good treatment, but patients who have this treatment are likely going to gain resistance within a short period of time. Under this circumstance, a new immunotherapy named immune checkpoint inhibitors (ICIs) came out with significant effect on melanoma. ICIs work by acting against checkpoint proteins or their partner proteins, which are the ligands, in order to activate the immune response. In this way, cancer cells can't escape from immune response and T cells will be able to attack them. In 1987 and 1992 respectively, gene encoding for two immune checkpoints named cytotoxic T lymphocyte 4(CTLA-4) and programmed cell death protein 1(PD-1) were discovered. In 2011, the first ICI, ipilimumab, was approved by the FDA as an immunotherapy that aimed at treatment of melanoma. This was a big breakthrough in the history of treating melanoma. It was approved for more diseases in the following years. Also, PD-1 inhibitors were also important for melanoma treatment, as they showed their usefulness of increasing the overall survival rate in patients [1]. It was demonstrated by the prominent improvement of five-year survival rates in melanoma patients, especially metastatic melanoma, comparing to former patients' survival rates.

ICIs had been proved as successful immunotherapy for melanoma, but its unique advantages that stand out from other therapies and potential disadvantages are still studied incompletely. The investigations on ICIs' benefits and risks are necessary for melanoma patients to better understand whether ICIs better fits their needs for treatment. This research will emphasis on both ICIs' strengths and risks.

2. Types of the ICIs

Physiologically, it is common among all human that the human immune system will protects its host if it detects attack that damage the body. This process is done with cooperation of different kinds of immune cells, and an important part of this cooperation is the immune checkpoint [3]. T cell constitutes a big part of people's immune system. It is a type of leukocyte that is in charge of deciding the specific immune response in human body, consisting helper T cells, toxic T cells, regulatory T cells (Treg) and memory T cells. ICIs function by blocking the immune checkpoints in human body. However, strong immune responses caused by T cells will sometimes damage healthy cells, so the immune checkpoint existed as a part of people's immune system, which may prevent the strong immune response that hurt the healthy cells in the body.

Despite immune checkpoints' essential function to prevent over immune response, a growing number of evidences show that cancer cells use immune checkpoints as a way to stop immune responses toward tumor. The checkpoint proteins such as PD-1 and CTLA-4 on all types of T cells bind to their ligands which trigger dephosphorylation of T cell receptors, thus the reducing activation and proliferation of T cell was caused [3]. As a result, T cell are disable to kill cancer cells. In order to overcome this problem, ICIs are created to bind to either checkpoint proteins or the partner proteins on the cancer cells, leading to the reactivation of T cell.

CTLA-4 is an immunosuppressive molecule, or in other words, checkpoint protein, that can reduce the T cell inflammatory response by a negative regulation. Different from PD-1, CTLA-4 works mainly in lymph nodes, controlling proliferation of T cells. In contrast, PD-1 suppresses the activity of T cells in peripheral tissues [4]. CTLA-4 suppresses the immune response by competing with CD28 for its ligands. CD28 is a molecule presenting on T cells' surfaces that led to the activation of T cells' function, then blocks its pathway. However, CD28 has less binding affinity to the ligands thus CTLA-4 has a greater chance to stop immune response.

Another checkpoint protein named PD-1 is an immunosuppressive molecule, or in other words, checkpoint proteins, presented on all T cells. Under usual circumstances, PD-1 immune checkpoint takes some control of the immune system. This part is done by facilitating T cells' apoptosis. Furthermore, PD-1 can slow the death of regulatory T cells, which can inhibit immune responses in cells and decrease inflammatory responses. PD-L1 and PD-L2 are ligands of PD-1, which in this case, are presenting on the cancer cells. PD-1's ligand, PD-L1 can combine with it and induce the suppressive response toward T cells. When they banded, it will start to decrease T cell's production of IFN-γ, which is a cytosine that can positively help with PD-L1's expression after recognizing the

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cancer's antigen, and inhibit T cell's activation [5]. Mainly through JAK-STAT pathway, IFN-γ can regulate PD-L1 expression in tumor cells. PD-L1 also occurs on surface of its derived exosomes, which was directly related to IFN-γ in a similar way. Since PD-L2 wasn't studied as clear and deep as other checkpoint proteins, it didn't have a prominent impact in development of ICIs.

3. Mechanism of checkpoint in melanoma

When it comes to melanoma, which has a special mechanism that makes it hard to cure, ICIs can still play an important role on improving treatment of the disease. Melanoma can't be easily destroyed spontaneously despite its immunogenicity, which is the ability to cause immune response when foreign molecules enter the body. The tumor can even develop ways to suppress or adapt to the immune response caused by its immunogenicity [6]. This adaptive resistance can be further reinforced by more immune feedback. As the general mechanism shows, expressed melanoma cells have PD-L1/2 that can send the "off" signals to stop the original positive T cells signals. These signals are delivered by MHC-I and MHC-II, the surface proteins that help antigens binding to T cells, antigen-presentation routes. Mainly through the expressing MHC-II, melanoma is able to attract molecules that can inhibit immune response. There are studies showing that melanoma cells are capable of activating Treg cells in order to enhance the immunosuppressive response. In this case, Treg cells are increasing in a wide range of places including blood vessels and lymph nodes [6].

Ipilimumab, as one of the CTLA-4 inhibitors, works by blocking the receptors that locate on effector T cells and diminish the Treg cells thus improve T cells' anti-tumor immunity. Ipilimumab is a member of IgG and the result of its usage on melanoma patients reveals that the increasing expansion of T cell clones is almost constituted of those which weren't seen before the therapy, and only a few amount of T cell clones presenting before using therapy rises [7]. The result inclined ipilimumab's ability to enlarge repertoire of T cells that target melanoma cancer cells.

Nivolumab and pembrolizumab are two checkpoint inhibitors that impede the combination of PD-1 and its ligands. They were invented based on the successful result after blockage of PD-1/PD-L1. Tests on animals had shown that impeding PD-1/PD-1's combination to T cells led to the restoring function of T cells [8]. As an antibody, Nivolumab binds to PD-1 and distracting it from binding to its ligands, which are most likely to be PD-L1 and PD-L2. Pembrolizumab is also similar to nivolumab which is demonstrated by its type of antibody, and FDA had approved to use it on advanced melanoma.

4. Application of ICIs

ICIs are one of the early developed therapy that was shown to improve survival rate of advanced melanoma patients. Although not all the patients respond to the therapy, there's still a considerable amount of people benefited from ICIs which can be seen by the long-term disappearance of the late stage tumor [8].

The CTLA-4 inhibitor ipilimumab was the first ICI that make a big breakthrough. The breakthrough was demonstrated by the extension of the median overall survival of advanced melanoma patients. Ipilimumab elongated the overall survival for about 3 months longer than patients taking vaccine that is specific for melanoma [9]. Further evidences include a III phase study on metastatic melanoma, and patients who were at late stages of cancer received ipilimumab. Patients receiving ipilimumab alone lived for around 10.1 months and median living length was 10.0 months for those who had both ipilimumab and gp100. Comparing with 6.4 months for patients who only received gp100, it was a big improvement. In those patients who had metastatic melanoma and didn't take any previous therapy, a research was done by using both ipilimumab associated with dacarbazine and dacarbazine with placebo. The overall survival was significantly better in the first group, which is 11.2 vs. 9.1 months [10]. These results demonstrated that receiving ipilimumab can increase patients' overall survival rate, and this encouraging conclusion also resulted in FDA's approval of ipilimumab used in patients who are at late stage, unresectable melanoma [8]. Furthermore, Ipilimumab have a consistent and durable responses on patients. Analysis on patient treated with ipilimumab had been done, and the data revealed that the median overall survival of patients is 11.4 months and survival

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curve was becoming steadier after 3 years, with a plateau about 21% survival rate, indicating the durability of ipilimumab in advanced melanoma patients [11].

PD-1 inhibitors including nivolumab and pembrolizumab had also showed activity in increasing survival rate in melanoma patients. In a clinical trial, nivolumab was compared by dividing patients into 3 groups of untreated melanoma patient who received different therapies. The median progression free survival for patients who only had nivolumab was 4 months longer than those who took ipilimumab alone. However, the result also showed that receiving both nivolumab and ipilimumab seemed to increase the progression free survival the most, indicating the possibility of combination treatment. Also, the overall response rate of patients after receiving nivolumab had a dramatic increase. A phase III trial including melanoma patients who didn't well response to prior ipilimumab or BRAF inhibitor therapy proved this point strongly. Without affecting by the presence of BRAF mutations, nivolumab improved the response rate from 10.7% to 31.7%, comparing to patients who take chemotherapy. Pembrolizumab was tested in clinical trial for melanoma patient too. The patients who had taken ipilimumab or BRAF inhibitors before were treated with pembrolizumab, and the progression free survival of them had improved under 2mg/kg every 3 weeks. Worth mentioning, pembrolizumab was proved to be more efficient compared with ipilimumab. This was shown by an overall advancement on the 1-year overall survival, response rate along with progression free survival [7]. This reflected pembrolizumab priority on treating advanced melanoma comparing with ipilimumab and some targeted therapies [10]. FDA had approved pembrolizumab with this doses based on the result of trial. From the above data, it was obvious that PD-1 inhibitors' effect on melanoma patients mostly overcame CTLA-4 inhibitors including ipilimumab when it comes to survival rate. In metastatic melanoma patients, the response rate of pembrolizumab was about 38% while therapies with nivolumab demonstrating nearly 40% response rate. A combination of ipilimumab and nivolumab treatment has resulted in 57% response rate, indicating it was the better therapy to use in order to increase response rate [2].

5. Immune-related adverse events

While the promising effect of ICIs had improved melanoma patients' condition evidently, there are also side-effects with ICIs, which can be severe and even damage patients' lives. These side effects are also called immune-related adverse events (irAEs), which are mostly caused by over- activated immune system and proliferating T cells after receiving ICIs. Since ICIs had disrupted the function of immune checkpoints and led to proliferation of T cells, T cells tended to be more aggressive and widely harmed healthy tissues under a lack of suppression. The presence of irAEs is unpredictable and it often varies, but it was known that most of them happened within 12 weeks induction period after receiving ipilimumab and nivolumab [12]. Also, studies show that different doses of ICIs can affect irAEs to some extent. For patients who received ipilimumab, their doses varied from 0.3mg/kg, 3mg/kg, to 10mg/kg, and the total amount of patients experiencing irAEs' increased from 19 out of 72 to 46 out of 71 and finally to 50 out of 71, indicating the more doses given to the patients, the more chances of having irAEs after the treatments [13].

A considerable portion of melanoma patients receiving ipilimumab, the CTLA-4 inhibitor, had experienced irAEs which led to various serious outcomes. The data from a Phase III study can prove the point. The advanced melanoma patients received ipilimumab, and result showed that around 10.2 to 14.5% of them had irAEs. In addition to this number, 50% of patients were dead because the severe irAEs related to treatment [8]. The severity of irAEs is considerable and it can also be shown by a more specific example, enterocolitis mediated by immune system. In a III phase trial of ipilimumab, 6.7% of the patients with metastatic melanoma had deadly immune-mediated enterocolitis, and 5.5% of them had moderate enterocolitis. Finally, presences of severe enterocolitis contributed to 5.1% of patients going to hospital and 0.4% of them dead [14]. The serious diseases caused by ICIs are an obvious potential threat to the patients.

When it comes to PD-1 inhibitor, pembrolizumab also has toxicity and causes irAEs. The basic mechanism of causing irAEs of anti PD-1 inhibitors are similar to anti CTLA-4 inhibitors, but the

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former one had less toxicity and danger comparing with the latter one. Multiple clinical trials compared ipilimumab and pembrolizumab, and results indicate that patients treated with pembrolizumab had a prominent lower chance to experience irAEs [15]. Also, a therapy with both nivolumab and ipilimumab had increased the irAEs despite their effect on increasing clinical efficiency, indicating a need for balance between toxicity and effectiveness of ICIs [8]. Overall, PD-1 inhibitors' advantages on improving safety had made it a more preferable choice for melanoma treatment comparing with ipilimumab.

Although irAEs is a potential threat to the melanoma patients, it didn't negatively affect the various benefits including increased survival rate brought by ICI. In a study, data from those patients who received ICIs and didn't continue because of severe irAEs were collected. Surprisingly, half of them were still alive after 5 years, meaning their overall survival still didn't decrease much. The durability of immune responses caused by ICIs is proved and ICIs are shown to be effective within those patients who experienced irAEs and give up ICI therapy for a relatively long time [12].

6. Combined therapy with ICIs

In order to enhance the therapeutic effect of ICIs on melanoma patients, combinations of different therapies were tested and shown promising effect. The mechanism behind the successful combination was studied. Despite the similarity of CTLA-4 and PD-1's mechanism of suppressing T cells from activating, they had different mechanisms that are not overlapping, which contribute to various effects on different T cells population during different phases. To be more specific, CTLA-4 worked during priming stage, in contrast, PD-1 worked during effector stage. Consequently, combining them together became reasonable and further experiments proved it. A Phase III study was conducted by dividing melanoma patients into three groups, consisting a group receiving only ipilimumab, a group receiving only nivolumab, and a group with both of them. The result showed that group that had both ipilimumab and nivolumab therapy had greater improvements in both survival and response rate in comparison [7].

Another powerful combination in both clinical rationale is the combination of targeted therapies and ICIs. The mechanism is that the targeted therapy that targets the specific positions may add a substantial impact on immune system attacking the tumor along with usage of ICIs [16]. An example is an oncogene named BRAF can be targeted in a targeted therapy, but the effect is not ideal. There is only a limited control on tumor without being durable enough. However, BRAF targeted therapy can help to increase the amount of antigens in the tumor microenvironment, demonstrating the possibility to help ICIs as a supporting therapy in treatment of melanoma.

7. Conclusion

As a revolutionized development in the cancer treatment, ICIs had been used in many cases and was proved to be effective for a considerable amount of patients. It brought the most benefits to melanoma patients since melanoma was known for its high death rate, and the presence of ICIs had improved their unpromising situation by evidently increasing the survival and response rate. Both CTLA-4 and PD-1 inhibitors had been developed and tested in many clinical trials, which further reinforce that ICIs' effect on melanoma patients is promising. However, at the same time, ICI faced difficulties on dealing with serious side-effect that can harm patients' lives, making it a riskier choice for treatment. In the future, there are still difficulties including toxicity waiting for people to solve.

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