Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/16/20240599

The current progress of PD-1 / PD-L1 mAb applications in melanoma immunotherapy

Jianing Dang

School of Life Science, Shanxi University, Shanxi, 237016, China

202101304506@email.sxu.edu.cn

Abstract. In recent years, the most serious skin cancer is malignant melanoma, metastatic melanoma has always been poor, and in recent years because of the immunogenicity of melanoma, Anti-programmed killing antibody (PD-1) therapy has become standard practice for many immunotherapy means, primarily the development of the programmed killing of cells 1 (PD-1) protein and its ligand (PD-L1). Meanwhile, nivolumab and pembrolizumab have been approved by the FDA (US Food and Drug Administration), both of which are very active and have controlled toxicity. While some progress has been made, there are still many obstacles to overcome, including patient predictors, innate medication resistance, and other issues. This review briefly summarizes the current state of the available research and introduces the background and evolution of PD-1 / PD-L1 monoclonal antibody in the field of immunotherapy, recent scientific backing experiments, and limitations in clinical practice. It also discusses the relevant topics of PD-1 / PD-L1 monoclonal antibodies in the field of melanoma immune therapy in detail. The shortcomings and issues with the previous research are noted, and the importance and objectivity of the present study are validated.

Keywords: Melanoma, PD-1 / PD-L1, Immunotherapy.

1. Introduction

Melanoma (MM), usually referred to as malignant melanoma, originates in melanocytes and mainly affects the skin. Exposure to ultraviolet light from the sun is the primary cause of melanoma, and exposure to ultraviolet light can damage DNA in cells, causing cell cycle arrest and, if the DNA cannot be repaired, apoptosis [1]. Small tumors are more likely to spread and are harder to cure later on. Malignant melanoma rates and fatalities have been rising steadily in the past few years. Despite having a lower mortality rate when compared to other tumors that are solid, skin cancer is a particularly dangerous type of cancer [2], with removal by surgery being the primary treatment option in many cases. Although good outcomes following surgical resection have been demonstrated, this has only been seen in cases with stage IV melanoma, and metastasis to sites such as lymph nodes is uncommon. As a result, systemic therapy is typically used to treat unresectable metastatic melanoma [1]. Therefore, among the systemic therapy treatments for malignant melanoma, radiation therapy is one of the most common treatments for cancer, which uses high-energy rays or radioactive substances to kill tumor cells and prevent them from proliferating and dividing is the basis for the treatment [3], but some healthy tissues are inevitably exposed. Radiation therapy often makes patients feel physically and mentally tired after

DOI: 10.54254/2753-8818/16/20240599

a few weeks because radiation destroys some healthy cells as well as cancer cells. Usually, fatigue worsens as the course of treatment continues [4].

However, immunotherapy provides a benefit beyond conventional radiation treatments because of how the immune system functions. The human being's own defenses against infection, which can block immune responses that target tumors to halt tumor growth, development, and survival, is the goal of immunotherapy rather than tumor cells and organs [5]. Generally speaking, compared to other tumor treatment methods (including radiotherapy, chemotherapy, and surgery), it is safer to use immunotherapy with PD-1/L1 stopping, because it is non-invasive and natural, and the treatment mechanism enhances the ability of autoimmune cells to resist tumor formation [6]. Therefore, immunotherapy comes with fewer side effects. In 2013, Science magazine rated cancer immunotherapy as an annual breakthrough [7]. Among them, PD-1/PD-L1 monoclonal antibody is the main clinically available immune checkpoint therapy in the use of antibodies that block immune regulatory checkpoints and has made substantial progress in recent years [8], however, there are still shortcomings in melanoma, which can cause unfavorable immune-related effects. Therefore, this article analyzes the application and PD-1/PD-L1's shortcomings in monoclonal antibody immunotherapy for melanoma during recent years, providing reference suggestions for future research in this field.

2. Application of PD-1 / PD-L1 mAb immunotherapy in melanoma

2.1. Summary of the pathways

Immune checkpoint inhibitors target the chaperone PD-L1 or the immune checkpoint protein PD-1. Some cancers suppress the T cell reaction by overproducing PD-L1.

2.1.1. PD-1. In 1992, interleukin-3 (IL-3)-depleted mouse progenitor cells from the bloodstream and mouse T-cell hybridoma detection cell types were the first to exhibit the presence of PD-1, which is also referred to as CD279. It is 288 amino acids, 55 kDa transmembrane protein with two terminal bases that are at the amino and carboxyl sides of its extracellular N-terminal domain (lgV-Like), membrane-permeable area, and cytoplasm tail. By encoding receptors that are inhibitory on T cells's activation and B lymphocytes, as well as cell types such as macrophages, dendritic cells (DCs), and single cells, PD-1 inhibits both innate and adaptive immune responses. Notably, melanoma-specific T lymphocytes exhibit significant PD-1 description levels. A T cell's activity is suppressed, T cell resistance is brought on, T cell development is slowed down, and cell death is brought on by binding to either ligand [9].

2.1.2. PD-L1. In general, macrophages, activated cells such as T cells and B cells, DC, and certain epithelial cells are known to exhibit PD-L1, particularly in autoimmune conditions. Additionally, tumor cells express PD-L1 in an immunological mechanism to circumvent immune responses that are anti-tumor. According to studies, PD-L1 is linked to an immunological milieu that is abundant in CD8 T cells (cytotoxic T lymphocytes), Th1 cytokines (helper T cells that promote other cell types in the immune cells, including antigen-presenting cells), the production of chemical factors, and the expression characteristics of interferon and specific genes, IFN-y (interferon Y interferon-gamma, a cytokine with antiviral, anti-tumor, and immune regulatory effects) can cause upregulation of PD-L1 in melanoma cells, which is the cause of disease progression. The production of PD-L1 on the outermost regions of cells of focus, including cells from tumors, is triggered by the simultaneous secretion of IFN-y by T and NK cells. By attaching to proteins and turning on signaling pathways that promote growth and the continuation of life, PD-L1 has a role as a tumor-promoting agent with malignant tumors. PD-L1 is additionally known to have nonimmune growth impacts on several tumor sorts of cells. For instance, PD-L1 causes the epithelial-mesenchymal transition (EMT) and originates cell-like behavior in kidney cancer cells, demonstrating how the basic route of PD-L1 enhances the growth of many malignancies [10].

DOI: 10.54254/2753-8818/16/20240599

2.2. With the PD-1 / PD-L1 monoclonal antibody

Impressive PD-1/PD-L1 monoclonal antibodies used in research studies have provided an alternative path for immunotherapy against cancer. Nivolumab, pembrolizumab, natalizumab, Avezumab, and durvalumab are the latest permitted by the FDA PD1 pathway [11].

PD-1 and PD-L1 inhibitors have been shown to contribute to the treatment of many different types of cancer. The greatest clinical benefit has been observed in melanoma patients since the introduction of PD-1 / PDL-2014 blocking agents, which are now considered first-line therapy for melanoma patients and have been displayed to enhance life expectancy more than traditional agents like dacarbazine. Along with melanoma, PD-1 / PD-L1 medicines showed promising outcomes in follicular B cells, both solid and liquid malignancies, and lymphoma other than Hodgkin's. Nivolumab and pembrolizumab raised survival rates as well as effectiveness in NSCLC patients in contrast to pharmaceuticals [9].

2.2.1. Nivolumab. Intravenous injection of nivolumab (Opdivo(®)) The PD-1 roadblock blocker is one of the initial to be authorized for usage. Certain cancer cells have PD-L1 on their outermost layer, and when PD-1 on T cells binds to PD-L1, the T cells become inactive. By inhibiting PD-1 from adhering to PD-L1, nivolumab can stop T cell inactivation and trigger the body's immune response to assault cells from tumors [12]. Nivolumab is often used in combination with ipilimumab. In a randomized, double-blind phase III test, the monotherapy of apizumab and nivolumab in individuals with unresectable aggressive melanoma was evaluated, and the results showed that compared to single-drug apizumab, single-drug nivolumab had a higher progression-free survival (6.9 months VS 2.9 months) and an Objective Response Rate (43.7% VS 19.0%). In the same Phase III study, more than 82% of participants who were on nivolumab experienced any immune-related adverse events (AEs), and 16.3% of patients reported AEs of severity level 3 or 4 [1]. In addition, in patients treated with imatizumab alone, both indicators were lower than the total number (86.2%; 27.3%; grade 3 or 4). Therefore, nivolumab may have a lower tolerance to patients.

2.2.2. Nivolumab was combined with ipilimumab. Ipilimumab is an antibody with a monoclonal structure that blocks the activity of the CTLA-4 protein (IgG1, an anti-cytotoxic T lymphocyte antigen-1), and it is the treatment of choice for people with metastatic melanoma. It prevents tumor cells from being able to resist the reaction of the immune system, which was already mentioned [1]. In initial research, people with advanced melanoma may also experience a long-lasting skeptical answer after receiving nivolumab. Initial clinical testing has demonstrated that inhibiting PD-1 and CTLA-4 together results in stronger anticancer efficacy than preventing each of them separately [2], so the combination is often chosen clinically. Patients who have severe melanoma are recommended to have nivolumab as a starting treatment, either by itself or in conjunction with ipilimumab [3]. Recent trial data show that in individuals with severe melanoma, no substantial decline during or after therapy with nivolumab + ipilimumab or nivolumab alone, physical well-being of life was observed, and the 5-year long-term survival rate was more than half of it in the nivolumab enlarge ipilimumab group, 44% in the group of nivolumab, and about 20% in the group of ipilimumab [4]. With longer progression-free survival and life expectancy, nivolumab can be more effective than ipilimumab or nivolumab alone, increasing the probability of survival. Ipilimumab is an antibody with a monoclonal structure that blocks the activity of the CTLA-4 protein (IgG1, an anti-cytotoxic T lymphocyte antigen-1), and it is the treatment of choice for people with metastatic melanoma. It prevents tumor cells from being able to resist the reaction of the immune system, which was already mentioned [1]. In initial research, people with advanced melanoma may also experience a long-lasting skeptical answer after receiving nivolumab. Initial clinical testing has demonstrated that inhibiting PD-1 and CTLA-4 together results in stronger anticancer efficacy than preventing each of them separately [13], so the combination is often chosen clinically. Patients who have severe melanoma are recommended to have nivolumab as a starting treatment, either by itself or in conjunction with ipilimumab [14]. Recent trial data show that in individuals with severe melanoma, no substantial decline during or after therapy with nivolumab + ipilimumab or nivolumab alone, physical well-being of life was observed, and the 5-year long-term survival rate was more than

DOI: 10.54254/2753-8818/16/20240599

half of it in the nivolumab enlarge ipilimumab group, 44% in the group of nivolumab, and about 20% in the group of ipilimumab [15]. With longer progression-free survival and life expectancy, nivolumab can be more effective than ipilimumab or nivolumab alone, increasing the probability of survival.

2.2.3. Pembrolizumab. Pembrolizumab is similar to nivolumab. Pembrolizumab significantly improves the patients with stage-aggressive melanoma life expectancy and has relatively low toxicity [9]. An IgG1 antibody is responsible for preventing the PD-4/PD-L pathway. This is the first PD-2014 antibody for melanoma with advanced stages that the FDA has approved; nivolumab received approval shortly after [1]. Fully transformed anti-PD-1 monoclonal antibody known as pembrolizumab has undergone extensive testing in melanoma patients who have already used and received treatment with ipirizumab. Additionally, it is also a well-tolerated drug with positive therapeutic effects [16] and can specifically bind to T cell PD-1 receptors, which restricts them from interacting with tumor cell PD-L1 targets. The approach, which is frequently utilized in other cancers, can help to destroy cancer cells and avoid tumor tolerance [13].

According to the above description of the three monoclonal antibodies, the three monoclonal antibodies have an irreplaceable effect on melanoma therapy for severe disease. However, the likelihood that the three monoclonal antibodies will survive in melanoma patients and the treatment of NSCLC are different. It can be seen that the efficacy between pembrolizumab and nivolumab is very similar, and the implications on life expectancy and survival without disease progression are same in patients who have severe melanoma. That's shown in the data in Table 1, although the three monoclonal antibodies have been used the same number of times in clinical practice, pembrolizumab and nivolumab reduced high-level toxicity events and significantly prolonged the progression-free survival and overall survival of advanced melanoma patients compared to ipilimumab. At the same time, in NSCLC, a cross-trial comparison showed that the efficacy of pembrolizumab and nivolumab were different. Pembrolizumab has been demonstrated to increase the lifespan in individuals with aggressive NSCLC [17], not only Ipilimumab does not increase the beneficial impact of pembrolizumab when used with it but also more toxic than pembrolizumab monotherapy for the first-line treatment of metastatic NSCLC. And the current information does not support the combination of pembrolizumab-pilimumab instead of monotherapy with pembrolizumab [18]. However, nivolumab data have not demonstrated that it increases the lifespan in individuals with aggressive NSCLC [17]. Among those suffering from metastatic NSCLC, studies show that nivolumab, when used along with ipilimumab, can increase the odds of surviving the disease [19]. The above trials also show that there are indeed some differences in efficacy between the two monoclonal antibodies.

At the same time, as shown in Figure 1, it is also clearly seen from the protein structure that these antibodies seem to differ from the contact surface of PD-1, but they are both on the same side of PD-L1 and similar to contact PD-1's surface. This screened these antibodies for competitive binding to PD-L1.

Table 1. Survival rates for melanoma patients with advanced stages following 12 months of treatment are compared [1].

Treatment regimen	Survival probability(%)	FDA-approved indications for melanoma
Ipilimumab	46	Melanoma along with a treatment (2011)
Nivolumab	72.9	Melanoma along with a treatment (2014)
Pembrolizumab	74.1	Melanoma along with a treatment (2014)

DOI: 10.54254/2753-8818/16/20240599

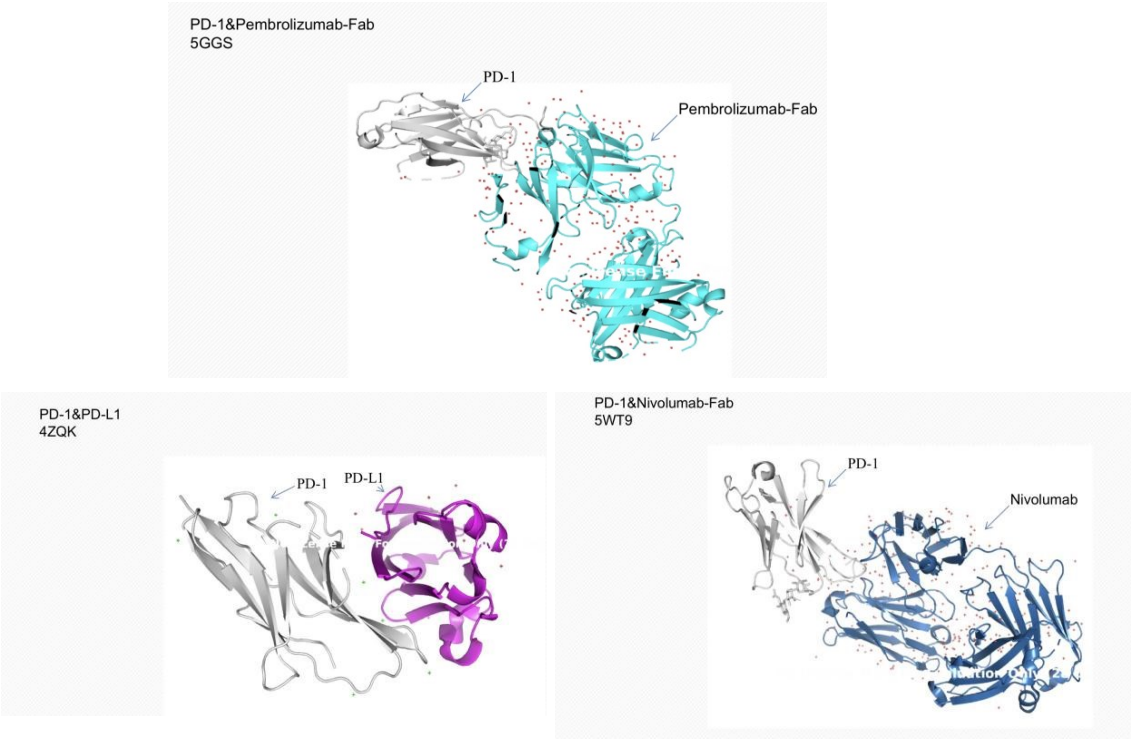

Figure 1. Peptides binding between PD-1, PD-L1, nivolumab, and pembrolizumab.

3. The defects of PD-1/PD-L1 monoclonal antibody immunotherapy melanoma

One of the disadvantages of this chemotherapy for tumors is that it can cause immune-related adverse events (irAEs) that can result in the autoimmune destruction of different organs in a particular population [9]. The most frequent irAE is skin toxicity, which manifests as different types of rashes. Other irAEs tend to involve colitis, which is respiratory infections, liver disease, and issues with the endocrine system affecting the thyroid system, hypothalamic/pituitary, and glands of the adrenal [13]. Others may also be impacted in extremely rare circumstances. Anti-PD-L1 therapy patients can experience infusion-related reactions (IRR). These IRRs, which typically range from grade 1 to 3, appear as a chilly feeling, and a high temperature and are most inclined caused by natural immune system stimulation due to the presence of a region of fragment crystallizable (a constant region of Fc antibodies in which the sequence of amino acids exhibits the same state in different antibodies and different types of antibodies, further determined by the specific structure of the antibody Fc fragment). These negative side effects often happen during or following the first four treatments and impact about 25% of patients [20]. At the same time, efficient treatments for this side effect are to lower the infusion rate, temporarily halt the infusion to be giving earlier paracetamol and antihistamines, or, if necessary, provide low-dose steroids [21].

4. Conclusion

This review allows researchers to understand the current progress and dilemmas in this field, provides researchers with relevant recommendations, gives an overview of the PD-1/PD-L1's history, development as a therapeutic target, the range of biomarker and their limits in clinical practice and potential future enhancements to the results of therapy. This review provides an overview of the current finding of a PD-1/PD-L1 antibody that is mono in the branch of study of melanoma immunotherapy. Identified specific adverse immune reaction limitations and problems associated with some patients using monoclonal antibodies in the ongoing study. This review confirms the significant progress made by PD-1/PD-L1 antibodies that are mono in the last ten years in the medical care of melanoma, as well as their crucial role in other cancer treatment fields. The comparison with PD-1/PD-L1 an antibody that is mono medicines' effectiveness. However, doesn't constitute an all-inclusive. Over the next decade, as

DOI: 10.54254/2753-8818/16/20240599

technologies evolve, they will play an increasing role in different settings and melanoma combined with other models. Additionally, further study is required to determine the patient group that answers best with these medications. In the end, to create more potent medicines, subsequent studies ought to zero in on other immunological and pathogenic pathways.

References

[1] Sood. S R Jayachandiran and S Pande 2021 Integr Cancer Ther 20
[2] Russo I et al 2018 Scientifica (Cairo) 2018
[3] Gianfaldoni S Gianfaldoni R Wollina U Lotti J Tchernev G Lotti T 2017 Scientifica (Cairo) 5 521-525
[4] Majeed H Gupta V 2023 StatPearls
[5] L Tang Z Huang H Mei and Y 2023 Signal Transduct Target Ther 8 306
[6] A Constantinidou C Alifieris and D T Trafalis 2019 Pharmacol Ther 194 84-106
[7] A Ribas and J D Wolchok 2018 Science 359 1350-1355
[8] Y Jiang M Chen H Nie and Y Yuan 2019 Hum Vaccin Immunother 15 1111-1122
[9] R. Makuku N Khalili S Razi M Keshavarz-Fathi and N Rezaei 2021 J Immunol Res 2021
[10] Y Han D Liu and L Li 2020 Am J Cancer Res 10 727-742
[11] X. Wu, Z. Gu, Y. Chen, B. Chen, W. Chen, L. Weng, et al 2019 Comput Struct Biotechnol 17 661-674
[12] J. D. Wolchok, V. Chiarion-Sileni, R. Gonzalez, P. Rutkowski, J. J. Grob, C. L. Cowey, et al. 2017 N Engl J Med 377 1345-1356
[13] S. Sahni, G. Valecha and A. Sahni 2018 Cureus 10
[14] F. S. Hodi, S. J. O'Day, D. F. McDermott, R. W. Weber, J. A. Sosman, J. B. Haanen, et al. 2010 N Engl J Med 363 711-23
[15] J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J. J. Grob, P. Rutkowski, C. D. Lao, et al. 2019 N Engl J Med 381 1535-1546
[16] J. Martin-Liberal, T. Kordbacheh and J. Larkin 2015 Expert Opin Drug Saf 14 957-64
[17] J. C. Moser, G. Wei, S. V. Colonna, K. F. Grossmann, S. Patel and J. R. Hyngstrom 2020 Acta Oncol 2020 59 434-437
[18] M. Boyer, M. A. N. Sendur, D. Rodriguez-Abreu, K. Park, D. H. Lee, I. Cicin, et al. 2021 J Clin Oncol 39 2327-2338
[19] T. Cascone, W. N. William, Jr., A. Weissferdt, C. H. Leung, H. Y. Lin, A. Pataer, et al. 2021 Nat Med 27
[20] pK. Kelly, J. R. Infante, M. H. Taylor, M. R. Patel, D. J. Wong, N. Iannotti, et al. 2018 Cancer124 2010-2017 504-514
[21] J. Naidoo, X. Wang, K. M. Woo, T. Iyriboz, D. Halpenny, J. Cunningham et al. 2017 J Clin Oncol 35 709-717