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Progress in immune-targeted combination therapy for melanoma

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Abstract. Melanoma is a type of skin cancerous tumor that develops from melanocytes and often appears on the skin's surface, however it can also spread to other areas like the eyes and mucous membranes. Research on it has made significant progress in recent years. Immunotherapy has become an important means of treating melanoma. The use of anti-CTLA-4 and anti-PD-1/PD-L1 antibodies has achieved significant success, so some patients have achieved long-term survival. benefit. Secondly, there have been breakthroughs in targeted therapeutic drugs targeting specific molecular targets such as BRAF and MEK. It has the ability to successfully stop melanoma cells from growing and spreading. Despite significant advances in immunotherapy and targeted therapies, drug resistance remains a serious problem; metastasis of melanoma is one of the main causes of its lethality, but little is known about how melanoma cells metastasize to other organs There are still many unanswered questions about the mechanism. This article compares the benefits of immune-targeted combination therapy with immunotherapy alone. It also immunotherapy and targeted therapy alone. It comes to the conclusion that combination therapy is the best course of action. The mechanism of action, effectiveness and drawbacks of drug resistance of the targeted therapy drug Vemurafenib were also introduced, further confirming the 1+1>2 treatment plan. Combination therapy provides new ideas for future cancer medicine, but the drug resistance of some targets needs to be solved, and subsequent research can focus on the development of new targets.

Keywords: Mitogen-activated Protein Kinase, BRAF gene, Vemurafeni, combination therapy.

1. Introduction

Melanocytes are cells that are mostly located in the choroidal layer of the eye, mucosal surfaces, meninges, basal epidermis, and hair follicles. These cells are derived from the neural crest. Melanocytes contain melanocytes that specifically produce melanin. When the skin is exposed to ultraviolet light, it acts as a response to ultraviolet-induced DNA. Skin horn cells secrete melanocyte-stimulating hormone in reaction to damage. This hormone binds to melanocortin receptor 1 on melanocytes, causing the melanocytes to generate and release melanin, which causes the skin to darken.This is the so-called sunbathing. The pigment produced by melanocytes is transferred to other cells in the skin, thereby protecting their DNA from sun damage. Ultraviolet radiation, a component of sunlight, damages the DNA of cells and causes mutations that may lead to the formation of skin cancer. Skin cancer often originates from mutations in melanocytes. Ultraviolet rays cause thymine dimers to form in the DNA of

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melanocytes, disrupting their protein synthesis. Cell division is out of control, malignant tumors form, and the risk of cancer is increased. Tumor cells can be transferred to other parts of the body, including organs, through the blood circulation and lymphatic circulation, and these tumor cells can lead to further tumor formation. One of the most common human diseases to metastasize is malignant melanoma, in which a T1 submillimeter-sized primary tumor with approximately 106 cell populations may have significant metastatic potential, whereas most solid cancers, with 10-9 cell populations T1 tumors that are twice the size but similar may not have metastatic potential. Due to changes in the global atmosphere, ultraviolet exposure to the skin has gradually increased, and the incidence of melanoma has also increased. Although there are currently various treatments, preventive measures are essential. People can isolate part of the skin through means such as parasols and sunscreen. UV rays reduce the risk of disease. Among all melanomas, a higher proportion of mucosal melanomas are found in the head and neck (52%), gastrointestinal tract (28%), female genitalia (9%), conjunctiva (6%), and other sites (5%) [1]. The ALM subtype of cutaneous melanoma accounts for 41%, the NM subtype accounts for 20%, the SSM subtype accounts for 19%, the LMM subtype accounts for 7%, and unknown or unclassified cases account for 13% [2].

Patients with melanoma may live longer and enjoy better quality of life thanks to new treatments,such as immunotherapy and improved surgical technique. Secondly, the use of innovative therapies such as CART cell therapy and immune checkpoint inhibitors (ICI) in melanoma treatment has promoted progress in the field of immunotherapy. These advances will not only benefit melanoma patients, but may also provide therapeutic implications for patients with other types of cancer. Traditional malignant tumors need to be cured by radiotherapy and chemotherapy, which are often accompanied by severe side effects. By studying the biological and genetic characteristics of melanoma, scientists can better understand the development mechanism of this disease and identify potential therapeutic targets. This will help develop more effective treatment strategies and reduce reliance on traditional treatments. The development of new vaccines, such as the study of the combination vaccine of mRNA-4157 (V940) and Keytruda, has demonstrated the potential to prevent relapse and improve patient survival rates. This marks an important advance in vaccine therapy in the field of cancer treatment, particularly in achieving long-term control and potential cure of the disease.

2. Immunotherapy approaches for melanoma

One of the most effective treatment strategies for melanoma is immunotherapy because this tumor is highly immunogenic. Immunotherapy works primarily on specific targets of the immune response's counter-regulatory system. One is an immune system-based vaccination strategy. Vaccine virus is one of them. It has a good oncolytic agent. It can infect cells and elicit an immunological response. The cytokines and other immune regulatory molecules it produces activate the tumor immune system. Based on viruses including adenovirus, HSV and reovirus,a number of oncolytic viruses have been created [3]. Studies have shown that the HSV can selectively proliferate in the melanoma tissues of naked mice and can induce in vitro cellular death in human melanoma cell lines [4]. Clinical experiments have demonstrated the safety of injecting oncolytic viruses intraperitoneally into individuals with melanoma. This is because the replication of oncolytic viruses not onlyworks on tumor cells forthright, but the therapeutic agent also spreads further through the tumor tissue, making it safe and efficient. Another discovery of antibodies against specific targets is based on the immunological origin of malignancy, known as ICI. Kill cancer cells by reactivating T cells and prolong survival time.

Research shows that the main power of cancer treatment lies in drugs combination. The victory of clinical trials is inseparable from the combined use of chemotherapy, radiotherapy, ICI and targeted molecular therapy. Although the target of melanoma targeted therapy is easy to be inactivated, it is highly targeted and is an indispensable treatment method at the moment. Gene mutations in melanoma cells are mainly concentrated in the mitogen-activated protein kinase pathway (MAPK). Stimulating factors activate the downstream MAPK pathway by binding to receptors on the cell membrane. Ultimately, MAPK can phosphorylate a variety of downstream targets, transmit extracellular signals into cells, and regulate physiological and pathological processes of cells. The main genes involved in

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this pathway are BRAF, NRAS and KIT.T he BRAF gene mutation is one of the most common gene mutations in melanoma. The following will describe the pathogenesis and treatment ideas by introducing the mechanism of action of the main research target BRAF.

3. Activation of MAPK pathway caused by BRAF gene mutation

The BRAF gene is a proto-oncogene located on chromosome 7q34. Encodes a serine/threonine-specific kinase. Because it belongs to the subfamily of MAPKKK, it plays a key role in the mitogen-activated protein kinase pathway. By taking involvement in the cell surface stimulation of melanocortin receptors, it participates in the proliferation and differentiation process of melanocytes. Studies have found that overexpression of mutant BRAF gene products can increase the activity of downstream extracellular regulated protein kinase ERK, reduce the expression of melanoma antigens Melan-A/MART-1 and glycoprotein 100 recognized by T cells, and cause obstacles to immunotherapy. The MAPK pathway combined with the STAT3 signaling and transcriptional activator pathway can cause melanoma cells to produce a variety of immunosuppressive factors, leading to immune evasion.

The most common cause of MAPK signaling is RTK dimerization in response to GF binding. This results in the phosphorylation of certain tyrosine residues in the cell's cytoplasmic tail. The MAPK pathway's activation promotes long-term cell proliferation and prevents programmed cell death. The global MAPK pathway is made up of three layers of protein kinases that are activated in order during the MAPK pathway's cascade reaction. The majority of upstream levels consist of a group of kinases known as MAPKKKs, which, upon activation, phosphorylate and dimerize MAPKKs, which is a class of downstream dual-specificity serine/threonine kinases. MAPKKs sequentially phosphorylate the most downstream effector serine/threonine kinase group, namely MAPKs.

4. Inhibitory effect of vemurafenib on BRAF

An oral mutant BRAF inhibitor called vemurafenib prevents kinase activity, which overactivates the MAPK pathway. Experimentally, vemurafenib was demonstrated to improve survival with a 48% effectiveness rate and manageable toxicity when compared to the standard-of-care drug dacarbazine.
Mutation testing for metastatic melanoma has become important with the invention of vemurafenib. The prospective test is highly suitable for all patients with thick melanomas or local lymph node involvement after resection, and can significantly reduce the risk for systemic treatment of metastatic disease in the future. In melanoma, V600E and its codon-associated mutations activate the MAPK pathway. Vemurafenib is a small molecule kinase inhibitor which selectively attacks activated BRAF V600E andIt is utilized to suppress the mutant serine-threonine kinase BRAF. By engaging with the ATP binding site of BRAF V600E kinase specifically, it suppresses its activity. Murafenib's biochemical affinity for mutant BRAF results in a strong suppression of ERK phosphorylation and BRAF mutant cell line growth. Vemurafenib reduced tumor growth in cells with the BRAF V600E mutation in animal models. Clinical trials using venemofenib in patients with metastatic melanoma that was incurable and had BRAF V600E mutations showed impressive response rates from the range of 50% to 80%.The median progression-free survival time was increased in the vemurafenib group, as well as the median overall survival time. About 25% of individuals receiving vemurafenib developed corneal acanthoma-type cutaneous squamous cell carcinoma with little invasive potential and no metastases. BRAF mutations are also found in other solid cancers such as papillary thyroid cancer. Vemurafenib has also been tested in these entities with good results.

5. Disadvantages of vemurafenib – drug resistance

One significant issue is that most patients become resistant to vemurafenib within a few months of treatment, and there are various ways in which resistance can arise. Its epigenetic mechanisms include DNA methylation, non-coding RNA, histone modifying enzymes and histone modifications. Furthermore, a key factor in resistance to BRAFi is the tumor microenvironment.Drug resistance has been linked to intratumoral fibroblasts and macrophages, according to recent research. Cancer-associated fibroblasts (CAFs) is different of normal fibroblasts in that CAFs upregulate the expression

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of vimentin, fibroblast activation protein-1 (FAP1), α-smooth muscle actin (SMA), and PDGFR and TGFβ signaling [5]. According to reports, CAFs permit BRAFi's therapeutic escape.

Melanoma cells have an aggressive character in the presence of CAFs. Following BRAFi treatment, melanoma cells continue to exhibit high levels of mTOR activity signaling, which encourages the synthesis of proteins, cell division, and the uptake of nutrients in the surrounding environment [6]. Additionally, they react to cytokines and growth factors generated by CAFs, including as VEGF and TGF-β, which encourage cell growth and survival [5]. Vemurafenib directly stimulates fibroblasts to release hepatocyte growth factor (HGF), triggers the signaling pathways PI3K/AKT and MAPK/ERK, and reduces the expression of genes that promote apoptosis [7]. Interestingly, senescent fibroblasts associated with senescent melanoma secrete sFRP2 and are more invasive, which suppresses the production of MITF and apurinic endonuclease (APE1), and makes the cells resistant to BRAFi [8]. Additionally, CAFs release components of the extracellular matrix (ECM), and resistance to BRAFi is promoted by integrin signaling induced by the ECM. In terms of interaction, TGF-βis released by BRAFi-resistant melanoma cells, which encourages CAF formation and raises the expression of ECM components, eventually resulting in the emergence of BRAFi resistance [9].

6. Combination therapy is considered the best option

According to clinical trials, patients with braf-mutant melanoma now get standard targeted therapy consisting of vemurafenib and cobimetinib, which has been shown to have a greater response rate, an improved overall survival of around two years, and reduced skin damage. Combined inhibition of PI3K/AKT and MAPK can enhance BRAF mutant melanoma's perception to BRAFi or MEKi, and the two have a synergistic effect in inducing apoptosis [10]. As uveal melanoma with activating Q209 L/P mutations was studied, the pan-PI3K inhibitor GSK2126458 and the MEKi GSK1120212 together significantly increased apoptosis as compared to when each pathway was inhibited alone [11]. By combining PI3K/AKT inhibitors, the effectiveness of MAPK inhibitors can be increased while also potentially overcoming resistance. According to one study, drug-resistant melanoma did not exhibit decreased phosphorylation of AKT and MAPK downstream target S6, indicating that AKT pathway hyperphosphorylation may play a role in drug resistance. This is corroborated by the fact that BRAFi, MEKi, and an AKT inhibitor restored melanoma cell resistance to vemurafenib [12]. Similarly, dafinib or trametinib plus the PI3K inhibitor GSK2118136 will postpone the onset of resistance.

The clinical effectiveness of BRAFi or MEKi in combination with PI3K/AKT inhibitors has been underwhelming, despite strong preclinical findings. Only few melanomas reacted in a phase 1 clinical trial evaluating the safety of trametinib in conjunction with the AKT inhibitor afresertib.

ICIs include PD-1 and CTLA-4 receptor inhibitors (i.e., pembrolizumab, nivolumab, and ipilimumab), which exhibit longer-lasting effects than BRAFi but lower response rates. The combination of BRAFi and MEKi with ICIs may be able to overcome the drawbacks of each type and produce responses that are more persistent, according to preclinical and translational studies [13]. According to mechanistic research, BRAF inhibitor treatment, either by alone or in combination with MEK inhibitors, has been associated with increased T cell toxicity, increased CD8+ T cell infiltration, and decreased production of immunosuppressive cytokines, such as IL-6 and IL-8. Immunotherapy's potential in conjunction with BRAF/MEK inhibitors [14].

Clinical trials are currently being conducted on dual-target MAPK inhibitors in conjunction with ICIs for the treatment of melanoma. COMBI-i had the most effective rate, at 78%, according to the results of Keynote-022, IMspire 150, and COMBI-i. For the dual-target group and the three-drug group, there was no statistically significant difference in the objective effective rates across the three experiments. According to the data, the dual target's efficiency has achieved its peak. For the treatment of melanoma, dual-target MAPK inhibitors are presently undergoing clinical trials in combination with ICIs. Based on Keynote-022, IMspire 150, and COMBI-i findings, COMBI-i had the highest effective rate, at 78%. The objective effective rates for the three experiments did not differ statistically significantly for the dual-target group or the three-drug group. The data indicates that the efficiency of the dual target has peaked [15].

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7. Conclusion

This article explores the pathogenesis of melanoma and compares various treatment methods through statistical analysis of clinical data of melanoma patients. Research results show that the occurrence of melanoma is related to gene mutations such as BRAF, NRAS and KIT. This article mainly explores the impact of BRAF gene mutations on the MAPK pathway to cause tumors, as well as the pros and cons of vemurafenib targeted treatment of melanoma. Numerous studies have found that trametinib plus targeting PD-1, PD-L1, or CTLA-4 may be a more effective anti-tumor combination therapy than either of the two alone. This is because blocking the MAPK pathway and immune checkpoint signaling at the same time may be beneficial.This means that combined immune and targeted therapy is by far the best solution. However, we still have a long way to go to deal with the inevitable drawbacks of tumor drug resistance and the easy failure of targets. It is hoped that future research can focus on the development of new targets, which will be conducive to the development of innovative drugs and personalized medicine. It may also reduce drug side effects and drug resistance and other aspects of problems. It will promote basic medical research and brings new hope for disease treatment.

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