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Treatment of Melanoma: Current Status and Prospects

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Abstract: Melanoma is a tumor caused by the deterioration of melanocytes. Both genetic factors and environmental factors contribute to the occurrence of the disease. Melanoma accounts for about 1% to 3% of all malignant tumors, and its prevalence is increasing year by year at the rate of 3% to 5%. With the exception of early surgical resection, there is a lack of specific treatment for patients with melanoma, and many of them have poor prognosis. Treatment strategies for advanced melanoma have been developing rapidly in recent years. Many new therapeutic drugs have emerged and are being tested in recent years. This review focuses on the current development of melanoma treatment (specifically, gene targeted therapy and immunotherapy) and discusses future treatment possibilities.

Keywords: Melanoma; Genetic mutations; Targeted therapy; Immunotherapy

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1. Introduction

Originated from melanocytes, melanoma is the "king of cancer" and has a high level of malignancy. Melanoma mainly affects the skin, mucosa, and internal organs, accounting for about 3% of all tumors. It is commonly seen in middle-aged to elderly people and can affect any part of the body. The incidence of melanoma has risen rapidly with an annual growth rate of 3% to 5% over the last 50 years. Many institutions around the world have been studying the disease's mechanism and exploring effective treatments for it. The scope of research is not limited to understanding the epidemiology of the disease, but also the discovery and testing of new therapies as well as improving the diagnostic aspect, in order to promote early detection. Except for a few early-stage cases, most patients with advanced melanoma require further systemic treatment to minimize the risk of recurrence. Targeted therapy and immunotherapy are still the two main methods for treating melanoma. The gene targeted therapy has certain specificity, which can cut off the signal transduction induced by mutant genes and inhibit the proliferation of tumor cells. Biological immunotherapy can help resist, inhibit, and kill tumor cells by enhancing or inducing the patient's own immune response. We will discuss both approved and experimental drugs in gene targeted therapy and immunotherapy.

2. Current drugs and efficacy

2.1. Gene targeted therapy

2.1.1. Gene targeted therapy

The BRAF gene is located on chromosome 7q34, and it encodes serine/threonine protein kinase, which activates the mitogen-activated kinase pathway. Mutations to this gene would lead to unrestricted cell

growth and proliferation. It has been reported that nearly half of all patients with melanomas have mutations in the BRAF gene. Majority of BRAF mutations occur at codon 600 (V600), among which the most common being V600E (90%) (substitute glutamic acid for valine), followed by V600K (5-6%) (substitute lysine for valine) and V600R/M/D (5%) [1]. Vemurafenib (Zelboraf), dabrafenib (Tafinlar), and encorafenib (Braftovi) are the main drugs that directly attack mutated BRAF proteins. Vemurafenib (Zelboraf) is a kinase inhibitor that specifically targets and binds mutated BRAF kinase. In 2011, it was approved as the first targeted therapeutic drug for metastatic melanoma by the FDA. A clinical trial conducted on 43 patients with BRAF mutations showed that the median progression free survival (PFS) was 6.48 months and the median overall survival (OS) was 11.47 months after receiving vemurafenib. Specifically, vemurafenib improved the OS (11.47 months) of patients with V600 mutation [1]. Compared with vemurafenib, encorafenib showed stronger efficacy in the treatment of melanoma in view of its distinct pharmacological properties [2]. As a reversible ATP-competitive inhibitor, dabrafenib can selectively target and inhibit BRAF V600E kinase, resulting in decreased ERK phosphorylation and inhibition of cell proliferation. MEK is a kinase located downstream of BRAF in the MAPK cascade. Drugs that selectively target MEK1/2 include cobimetinib (Cotellic), trametinib (Mekinist), and binometinib (Mektovi). Cobimetinib is an inhibitor of MEK1/2, which is a protein in the cellular signaling pathway that helps control cell growth and survival. Cobimetinib is used in conjunction with vemurafenib to treat cases that are not surgically treatable or have metastasized. A study of 495 patients with BRFA V600 mutation showed that the combination of cobimetinib and vemurafenib (PFS: 9.9 month) significantly improved PFS and OS compared with vemurafenib alone (PFS: 6.2 months). Besides, the rate of complete or partial response was higher in the combination group (68%) than the control group (45%) [3]. Along with encorafenib, binimetinib was also approved by the FDA in 2018 for treating melanoma, especially for patients with BRAF V600E/V600K mutation. A previous study on 577 patients revealed that the combination of encorafenib and binimetinib (PFS: 14.9 months) also improved the progression-free survival compared with encorafenib alone (PFS: 9.6 months). The median OS was 33.6 months in the combination group, whereas that of the control group was 23.5 months [4].

2.1.2. c-KIT gene

KIT is a tyrosine kinase that can promote cell growth and proliferation. KIT mutations are usually present in mucosal and acral melanoma. Thirty-two studies, which included 5,224 patients, reported 497 cases (9.5%) with KIT mutations that are closely related with age, anatomic location, and chronic sun damage (CSD) [2]. KIT exon 11 and exon 13 mutations appear to be highly sensitive to KIT inhibition, whereas KIT exon 17 mutations appear to have relatively less sensitivity [5]. Imatinib is a targeted therapeutic drug, which has shown significant clinical responses among melanoma patients with c-KIT gene mutation. A previous study conducted on 295 patients with melanoma (51 with c-KIT mutation) showed an overall response rate (ORR) of 16%, median PFS of 12 weeks, and median OS of 46.3 weeks [6]. Another study conducted on 25 patients (8 with c-KIT mutations) showed an ORR of 29% and an overall disease control rate of 50% [6]. The findings substantially confirm the efficacy of imatinib. Dasatinib was also approved for treating patients with c-KIT mutations. The E2607 trial conducted on 30 patients with melanoma (KIT+) showed a PFS of 2.1 months and a median OS of 7.5 months [7]. Due to multiple mutation sites on c-KIT gene, the overall effectiveness of the treatment in c-KIT mutations is lower compared with that in BRAF mutations. Researchers have been trying to explore new KIT inhibitors in order to obtain better curative effect.

2.2. Immunotherapy

2.2.1. CTLA4

Cytotoxic T lymphocyte antigen-4 (CTLA-4) is a 223-amino-acid protein receptor that acts as an immune

checkpoint and downregulates immune responses. Anti-CTLA-4 antibody can maintain T cell activation by releasing a signal that inhibits T cell activation. Ipilimumab (Yervoy) is the first anti-CTLA-4 monoclonal antibody approved for the treatment of tumors. A study conducted on 1,861 patients with advanced melanoma treated with ipilimumab revealed that the median OS was 11.4 months, and the 3-year overall survival rate was 22% [8]. Another study found that ipilimumab, as adjuvant therapy, can prolong the 5-year overall survival rate of patients with advanced melanoma (65.4%), compared with 54.4% in the control group [9].

2.2.2. PD-1

Nivolumab is the first PD-1 monoclonal antibody with melanoma indication and was approved by FDA in 2020. The most prominent clinical study (CheckMate 067) confirmed that nivolumab (single drug) is better than ipilimumab (single drug) in the treatment of advanced melanoma (medial OS: 37.6 months in the nivolumab group versus 19.9 months in the ipilimumab group) [10]. The study also revealed the use of nivolumab in conjunction with ipilimumab significantly improved the overall effective rate and prolonged the overall survival rate. Compared with 34% overall survival rate (3 years) in the ipilimumab group, the nivolumab-plus-ipilimumab group showed 58% OSR, while the nivolumab group showed 52% OSR. However, the side-effects were as high as 56% in nivolumab-plus-ipilimumab group, compared with 21% in the nivolumab group and 28% in the ipilimumab group [10].

As one of the PD-L1 immunotherapy, pembrolizumab helps to detect and fight tumor cells by improving the immune system. It blocks the interaction between PD-1 and PD-L1/PD-L2 and relieves the inhibition of immune response mediated by PD-1 pathway. Previous research has revealed that blocking PD-1 activity can inhibit tumor growth in homologous mouse models. In 2014, pembrolizumab (Keytruda) was approved in the treatment of advanced melanoma. A study (KEYNOTE-001) recruited 655 patients with advanced melanoma, and pembrolizumab injections were administered to these patients. The result showed that patients with advanced melanoma can benefit from long-term survival with a 5-year OSR of 34%; the complete remission (CR) rate was 15%, and the median OS time was 23.8 months [11]. In terms of adverse reactions, pembrolizumab was well tolerated by the patients.

3. Prospects

3.1. NRAS gene

The NRAS (neuroblastoma) gene is responsible for encoding N-Ras, which is a protein that regulates genetic transcription by participating in the RAS-RAF-MEK-ERK pathway. This pathway is closely related with cell proliferation. When pathogenic mutations occur in the NRAS gene, the N-Ras protein encoded by the gene will be continuously activated, resulting in uncontrolled cell proliferation and tumor formation (predominantly at codon 61). Tumors with NRAS mutations are known to be aggressive and are closely related with patient survival. Currently, there is no approved targeted therapy specifically designed for NRAS-mutated melanoma. The current therapies for NRAS-mutated melanoma are still limited. Patients with NRAS mutations are usually given MEK inhibitor (binimetinib) or standard dacarbazine chemotherapy. Previous clinical trials have shown that the efficacy of MEK inhibitor (MEKI) in patients with advanced melanoma is about 20% [12]. The study initiated by Professor Reinhard Dummer (NEMO study) that specifically focused on patients with NRASQ61 mutation showed a median PFS of 2.8 months with binimetinib (MEK162) and 1.5 months with dacarbazine; the rates of effectiveness were 15.2% and 6.8%, respectively, while the total disease control rates were 58% and 25%, respectively [12].

3.2. NOL7 gene

The protein coding gene NOL7 was shown to be strongly linked to the development of melanoma. A study

revealed the novel tumor-promoting capacity of NOL7 gene in melanoma. NOL7's expression increases with disease progression from benign nevus to metastatic melanoma. The knockdown of NOL7 is highly associated with decreased levels of certain cell cycle regulators, such as CDK2 and cyclin A/E, and with increased levels of certain cell cycle inhibitors, such as p21 (CDKN1A) and p27 (CDKN1B) [13]. The study also revealed that NOL7 knockout significantly decreased the growth of tumors in mouse models [13]. These results suggest the significance of NOL7 in regulating apoptosis, cell adaptation, and protection against adverse conditions in melanoma. In terms of mechanism, hypoxia inducible factor HIF-1α can promote the transcription of NOL7 and then transduce the signal to PI3K/AKT/ERK signaling pathway through HRAS, thus further activating downstream cyclin, apoptotic protein, and EMT protein, which finally promotes the growth and metastasis of melanoma.

3.3. CKD pathway

Currently, patients with BRAF mutation are generally prescribed with BRAF inhibitors alone or BRAF inhibitors in conjunction with MEK inhibitors. Previous literatures have revealed that many patients with BRAF mutations have CDK pathway abnormalities (such as CDKN2A gene mutation or deletion). It could be more effective if drugs are designed to co-target CKD pathway and BRAF together. The study published at the 2016 ASCO Annual Meeting deduced that CDK pathway could be an important therapeutic target for acral melanoma in the future. The study reported that among 428 patients with acral melanoma, almost 80% of patients have genetic abnormalities in the CDK pathway. Patients with acral melanoma may need individualized targeted therapy.

4. Conclusion

Clearly, despite the fact that many novel medications have been developed and evaluated for the treatment of melanoma, some of them are ineffective. Although gene targeted therapy has high effectiveness, many patients develop resistance to it after use. Immunotherapy has a relatively slow effect, but the overall benefit is relatively longer. Besides, certain drugs may cause serious side effects, including fatigue, rash, and pruritus. Hence, it is difficult for patients to continue taking these medications. Researchers should also pay attention to alleviating the side effects of drugs in future research, which can largely benefit patients. We should expect to see an increasing number of high-efficiency drugs developed and listed in the future.

Disclosure statement

The author declares no conflict of interest.

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