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Malignant Melanoma: Molecular Targets and Current Therapy

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Abstract

Melanoma is one of the most malignant tumors, mainly due to their ability to rapidly metastasize. Currently, the global incidence of melanoma is increasing at a faster rate than other cancers (1.7% of newly diagnosed cancers), despite the fact that malignancy accounts for only 4% of all malignant skin tumors. They are responsible for up to 80% of deaths in affected patients. The incidence of cutaneous melanoma varies between populations, with the disease being more common in Caucasians in Australia and New Zealand. In Europe, melanoma claims the lives of more than 20,000 people each year, placing a significant burden on the public health care sector.

Keywords: Melanoma; Immunotherapy, Melanoma risk factors

Introduction

Melanoma therapy varies depending on the stage of the disease and may include surgical excision, immune checkpoint inhibitor treatment, targeted therapy, radiotherapy, or chemotherapy [1]. Despite a reduction in mortality rates over the last decade as a result of the approval of new targeted therapies such as BRAF inhibitors, MEK inhibitors, and immune checkpoint inhibitors, many of the currently available treatments are costly and toxic [2-4]. Furthermore, despite significant therapeutic advances, some patients develop acquired drug resistance and experience disease relapse. As a result, developing new, less toxic treatments for melanoma patients is critical.

Incidence of Melanoma

Melanoma is one of the deadliest skin cancer diseases, and its incidence has steadily increased over the past decades. Prior to the development of immunotherapy, this diagnosis was associated with a high mortality rate, with less than 10% of patients surviving for more than 5 years. The first immune checkpoint inhibitor was approved for the treatment of malignant melanoma

in 2011 [5,6]. This breakthrough sparked a revolution, increasing patients' 5-year survival rate to 44%, transforming what was once a "death sentence" into a more manageable diagnosis [7].

Malignant melanoma has an annual incidence of 3-5 cases per 100,000 people in Mediterranean countries, 12-35 cases per 100,000 people in Scandinavian countries, 20-30 cases per 100,000 people in the United States, and possibly up to 50 cases per 100,000 people in Australia and New Zealand [8]. Differences in melanoma incidence between countries are attributed to population-specific factors such as skin type and length of sun exposure. Melanomas, when compared to other solid tumors, primarily affect people in their twenties and thirties, with a median age of 57 years. When analyzing melanoma incidence by gender, women have a higher occurrence of the disease [9].

Risk Factors for the Development of Melanoma

UV radiation, particularly in the UV-B spectrum, is the primary environmental risk factor for the development of melanoma [10]. Intense and prolonged sun exposure and sunburn during a person's lifetime are linked to an increased risk of melanoma development. Chronic sun exposure, on the other hand, is a cause of keratosis and non-melanoma skin cancer [11]. UV-A radiation from artificial sources is another risk factor for melanoma. Individuals who use tanning beds and patients undergoing phototherapy for conditions such as psoriasis are especially vulnerable [12]. Many studies and meta-analyses highlight the growing public health concern about tanning bed use, particularly among children [13]. UV radiation has thus been officially designated as a carcinogen [9].

Furthermore, patient-specific risk factors play an important role in the development of melanoma. The number of congenital and acquired melanocytic nevi, genetic susceptibility, and a positive family history are among the risk factors [14]. According to studies, nearly 25% of melanoma cases are caused by pre-existing nevi. Not only the number of nevi, but also their size and type, are associated with an increased risk of melanoma development in this context [9].

Another risk factor is an individual's genetic susceptibility, specifically the polymorphism of the melanocortin 1 receptor gene (MC1R), which is responsible for variations in skin pigmentation in humans. Individuals with fair skin, red hair, and other distinguishing characteristics are more vulnerable to UV radiation [15].

In 5-10% of melanoma cases, a positive family history is confirmed [16]. The disease is passed down through families due to genetic mutations. True hereditary melanoma is uncommon at the moment. Melanoma incidence, on the other hand, rises in families predisposed to certain cancers, such as familial atypical multiple mole melanoma (FAMMM) syndrome and melanoma-astrocytoma syndrome (MAS). The most common genetic abnormalities identified in these families are cyclin-dependent kinase inhibitor 2A (CDKN2A/p16) and, to a lesser extent, cyclin-dependent kinase 4 (CDK4) mutations [17]. Other inherited melanoma risk factors include xeroderma pigmentosum, familial retinoblastoma, Lynch syndrome type II, and Li-Fraumeni syndrome [9].

The primary goal of cancer research is to identify biological markers that will aid in the selection of specific therapies for individual patients. BRAF mutations, particularly BRAFV600E, are common predictors of RAF inhibitor response. After some time, the disease progresses in some of these patients, while in others, primary resistance to BRAF (+/- MEK) inhibitors may be observed. Genetic mutations in the RAS-RAF-MEK-ERK and PI3K-AKT-mTOR signaling pathways have been linked to resistance to chemotherapy and targeted therapies in melanomas [18].

Resistance to BRAF (+/- MEK) inhibitors can be classified as genomic (20% NRAS/KRAS mutations, 16% BRAF-associated variants, 13% BRAF amplification, 7% bypass-track mutations), immunological (epigenetic and transcriptomic changes in molecules involved in antigen-presenting mechanisms), or a combination of both [19]. The detection of mechanisms responsible for BRAF and MEK inhibitor resistance is not currently standard clinical practice, but the development of non-invasive procedures for determining tumor mutational status may lead to changes in pharmacotherapy management [20].

Current Pharmacological Therapies for Melanoma

The majority of new melanoma cases are diagnosed in their early stages, and the majority of these cases are curable, with surgical removal of the melanoma being the preferred treatment [21]. However, in some patients, the disease may reappear in a disseminated form after a certain period of time. Melanomas in advanced stages (about 10%) cannot be surgically removed. Approximately one-third of patients experience visceral or brain complications during stage IV of the disease, with a poor prognosis and a low likelihood of a positive response to therapy [22]. Melanoma is regarded as one of the most difficult cancer types to treat due to the development of drug resistance [23].

The most effective cytotoxic agents in the treatment of malignant melanoma are dacarbazine, temozolomide, and cisplatin, but the positive response to this treatment remains low [24]. Since 2011, several important drugs for the treatment of advanced-stage melanomas have been approved, including kinase inhibitors (RAF and MEK inhibitors) and immune checkpoint inhibitors (anti-CTLA4 and anti-PD1). In the treatment of advanced stages of the disease, anti-PD1 (nivolumab, pembrolizumab), anti-CTLA4 antibodies (ipilimumab), and BRAF inhibitors (vemurafenib, dabrafenib), either alone or in combination with MEK inhibitors (kobimetinib, trametinib), have shown promising results [25,26].

In clinical practice, the presence of BRAFV600E mutations is currently required for selecting an appropriate treatment strategy. Although the impact of NRAS, NF1, KIT, CDKN2A, and PTEN proteins is not yet standard clinical practice, identifying changes in genes encoding these proteins is critical for experimental progress in clinical trials [9].

Targeted Therapy

Targeted therapy refers to drugs and other substances that slow or stop the progression of cancer by binding to specific (target) molecules. Mutations in signaling pathway genes, as well as mutations in the MAPK signaling pathway, are important in the pathogenesis of melanomas. These mutations cause tumor cells to proliferate and improve their survival and invasiveness. The BRAF gene mutation is a significant mutation in this pathway in melanoma pathogenesis [27].

In recent years, significant progress has been made in the use of BRAF and MEK inhibitors, particularly in BRAFV600E melanomas. The combination of these inhibitors resulted in a high response rate (70%), rapid induction, and symptomatic control, as well as a 12-month extension of patients' lives [28].

Vemurafenib is an orally administered, highly selective competitive inhibitor of BRAF kinase with the V600E mutation. The FDA approved a drug containing this inhibitor in 2011. Vemurafenib is the first-line therapy for patients with this mutation who have metastasis.

Dabrafenib is a reversible, selective inhibitor of BRAFV600E. The FDA approved a drug containing this inhibitor in 2013. Many studies are still being conducted to look into the activity of vemurafenib and dabrafenib, both alone and in combination with various cytotoxic and biological agents, as well as their potential use in adjuvant therapy for early-stage melanoma [23].

Trametinib is a MEK-1 and MEK-2 selective inhibitor. It is prescribed to patients who have metastases and mutations in the BRAFV600E and BRAFV600K genes. The drug was approved by the FDA in 2013 [29]. Trametinib and cobimetinib are mostly used as single agents. Clinical studies, however, show increased clinical activity when these substances are combined with BRAF inhibitors [23].

One of the major challenges of targeted therapy is the emergence of drug resistance. In 15% of patients, primary resistance has been observed. The majority of patients develop secondary resistance, which is characterized by disease progression following initial improvement [30].

Immunotherapy

Immunotherapies boost the immune system's antitumor response by inhibiting immune checkpoint molecules [31]. Ipilimumab (IgG1) binds to CTLA-4, a surface antigen expressed on activated CD4+ and CD8+ T cells. CTLA-4 inhibits T cell antitumor activity under physiological conditions. The binding of ipilimumab inhibits the interaction between CTLA-4 and its target ligands CD80/CD86, stimulating the immune response of T cells [32]. Ipilimumab is a monoclonal antibody that was approved by the Food and Drug Administration in 2011 [29]. It is approved to treat malignant melanoma and was recently recommended as adjuvant therapy for cutaneous melanoma after complete surgical removal, with a treatment duration of up to 3 years [23].

Nivolumab and pembrolizumab are PD-1-binding IgG4 antibodies. This receptor is expressed on T cells, which inhibits the interaction of the PD-L1 and PD-L2 ligands. The PD-1 signaling pathway mediates the immune escape mechanism, and inhibiting it increases T-cell immune response, leading to T-cell activation and proliferation. Both drugs are approved for the treatment of melanomas that cannot be surgically removed or that have spread [32]. Nivolumab and pembrolizumab are mostly used as single agents [29]. Nivolumab is also approved for the treatment of BRAFV600-positive unresectable melanomas or metastases in combination with ipilimumab. Pembrolizumab is used to treat melanomas that are resistant to ipilimumab therapy [23].

Adjuvant Therapy

In studies, interferon-α (INF- α) alone as adjuvant therapy did not show significant antitumor activity. The addition of a 12kDa polyethylene glycol chain (peginterferon-2b) to the pharmacokinetics of INF-2b protects the INF molecule from proteolytic cleavage and increases its half-life. In a European clinical trial of patients with stage III melanoma, patients with nodular metastases and ulcerated tumors had the best results with peginterferon-2b. Peginterferon-2b was approved by the FDA in 2011. Peginterferon-2b administration did not improve overall survival in patients, but it did improve the survival of patients who experienced disease recurrence [33,34].

Conflicts of Interest

The authors declare no conflict of interest.

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