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Treatment of malignant melanoma - a review of the literature

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Abstract

Melanoma is caused by genetic mutations in melanocytes, pigment-producing cells found in the skin, eye, inner ear, and soft meninges. Sun exposure, atypical nevi, previous history of melanoma, and the presence of multiple (≥40) common nevi were found to be associated with an increased risk of melanoma detection (OR: 1. 3; 95% CI: 1. 1-1. 6). Its prevalence is highest among light-skinned populations and in regions of lower latitudes. Significance of family history of melanoma and presence of congenital nevi were excluded. For localized primary melanoma, the dominant prognostic factors for survival are lesion thickness, ulceration, and lymph node involvement Understanding the pathogenesis of melanoma has been crucial in developing new therapeutic approaches. The characterization of oncogenic signaling pathways and interactions has made it possible to identify new targets for clinically effective therapies, such as pathway inhibitors and antibodies to immune checkpoints or the use of phototherapy. In this article we describe the main signaling pathways which are deregulated in melanoma. We also mention how it has become a viable and crucial strategy for melanoma therapy and then thoroughly review the safety, clinical efficacy and progress regarding PDT- promising alternative therapy and the immunotherapies of melanoma in especially advanced metastatic stage basing on published clinical data and registered clinical trials, most of which are in phase III.

Key words: malignant melanoma; immunotherapy; photodynamic therapy

Introduction

Characteristics

Melanoma is caused by the presence of genetic mutations in melanocytes, pigment-producing cells that can be found in the skin, eye, inner ear, and soft meninges [1- 4]. The incidence of melanoma worldwide has increased dramatically over the past 50 years. Its prevalence is highest among light-skinned populations and in regions of lower latitudes. The incidence is higher in geriatric populations, but melanoma is also one of the most common cancers found in adolescents and young adults. In fact, it is one of the leading cancers with an average number of years of life lost to death from the disease. [5]

However, the value of population-based melanoma screening is still controversial. In retrospective studies, when converted per screen-detected melanoma, the number of missed melanomas is 0. 15 (95% CI: 0. 12-0. 18) in the age-based approach and 0. 22 (95% CI: 0. 19-0. 26) in the risk-based approach [6].

Multivariable analysis showed that sun exposure, atypical nevi, previous melanoma history, and the presence of multiple (≥40) common nevi were associated with an increased risk of melanoma detection (OR: 1. 3; 95% CI: 1. 1-1. 6). Significance of family history of melanoma and presence of congenital nevi were excluded. [6]

For localized primary melanoma, the dominant prognostic factors for survival are lesion thickness, ulceration, and lymph node involvement. In metastatic melanoma, the most important prognostic factors are the location of the metastases and the presence of elevated serum lactate dehydrogenase. [7]

Results of retrospective studies suggest that 13. 4% of patients with high-risk primary melanoma will relapse within 2 years. [8] It has also been shown that clinicopathological characteristics, particularly anatomical localization on the head, neck, hands, feet, genitalia or lower extremities, and diagnostic partial biopsies, identify melanomas with an increased risk of recurrence. [9]

Distinct genetic alterations associated with melanoma have been identified. For example, families with melanoma that have germline mutations in CDKN2A show a confirmed predisposition, but the vast majority of sporadic melanomas have mutations in the mitogen-activated protein kinase cascade, the pathway with the greatest oncogenic and therapeutic relevance to this disease. BRAF and NRAS mutations are usually found in cutaneous

melanomas, whereas KIT mutations are mainly observed in mucosal and acral melanomas, and GNAQ and GNA 11 mutations predominate in uveal melanomas. [10]

Understanding the pathogenesis of melanoma has been crucial in developing new therapeutic approaches. The discovery of the PI3K-AKT-PTEN pathway and the immune checkpoint pathway was important. The discovery that protein 1 ligand 1 of programmed cell death (PDL1) and PDL2 are expressed by melanoma cells, T cells, B cells, and NK cells has led to the recent development of antibodies specific for protein 1 (PD1) of programmed cell death (e. g. , nivolumab and pembrolizumab). Together with other new drugs - namely BRAF inhibitors (vemurafenib and dabrafenib) and MEK inhibitors (trametinib and cobimetinib) - these agents hold great promise and have been shown to significantly improve the prognosis of patients with advanced metastatic disease [10].

Understanding the pathogenesis of melanoma has been crucial in developing new therapeutic approaches. Characterization of oncogenic signaling pathways and interactions has enabled the identification of new targets for clinically effective therapies, such as pathway inhibitors and antibodies to immune checkpoints or the use of phototherapy. [1, 10]

Immunotherapy

The immunological features of melanoma have been accurately characterized in the past, so patients with this condition are now routinely treated with checkpoint immunotherapy, which has revolutionized both the treatment and prognosis of melanoma. [11] Long-term remissions are now said to be possible with a 5-year survival rate of 35%, and many patients who have received immune therapy have been completely cured of their condition. [12] Melanoma has long been considered an immunogenic neoplasm due to the fact that a significant subset of tumors are infiltrated by lymphocytes. Most immunotherapy treatment strategies aim to intensify the immune response against the tumor; the first group consists of immune checkpoint inhibitors; antibodies directed against specific targets, such as antiprogrammed cell death 1 (PD-1) and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). [13, 14]

The second group is based on adoptive cell therapy; it involves the use of so-called LAK (lymphokine-activated killer) cells, tumor infiltrating lymphocytes (TIL) and other specific lymphocytes. [15] [16] The third includes biological drugs such as interferons, cytokines, and granulocyte and monocyte colony-stimulating factors. A fourth group is vaccines based on a peptide, whole protein, virus, DNA, or DC [17, 18] Although immune checkpoint inhibitors have been a breakthrough in the treatment of melanoma, a significant group of patients do not respond to these drugs, and a subset exhibits secondary immunity. Side effects can be very serious and the treatment itself requires a lot of money, so research is underway to find biomarkers that can predict whether a patient will respond positively to the therapy. [14, 19, 20]

Checkpoint inhibitor immunotherapies are monoclonal antibodies directed at disrupting the programmed cell death protein 1 (PD1/PDL1) pathway or the cytotoxic T lymphocyte-associated antigen 4 (CTLA4) pathway. There are currently seven FDA-approved cancer

immunotherapies, which include ipilimumab (CTLA4), pembrolizumab (PD1), nivolumab (PD1), cemiplimab (PD1), atezolizumab (PDL1), avelumab (PDL1), and durvalumab (PDL1). [13, 15]

Numerous studies have been conducted to prove the high efficacy of this group of drugs: the first randomized phase III study was MDX010-020, which was presented at the annual meeting of the American Society of Oncology. The study was designed to demonstrate improved overall survival (OS) for the ipilimumab-containing arms compared with the gp100 vaccine. The study was unique in that a dose of 3 mg/kg and only 4 cycles were used, whereas the conventional dose was 10 mg/kg and 4 cycles, with a maintenance phase of 10 mg/kg every 3 months. Demonstrated improvement in os in metastatic melanoma. Observation, which lasted nearly 10 years, showed a persistent plateau in overall survival, and the FDA is allowing ipilimumab to be sold as a treatment for metastatic melanoma. [12, 21]

CheckMate-066- nivolumab therapy showed a ~40% response rate with a 12-month overall survival rate of 73% compared to 43% of patients treated with dacarbazine). Another phase III trial, Keynote-006 (using pembrolizumab), also showed that monotherapy with a PD-1 inhibitor results in an objective response rate of approximately 40%-45% and relatively well-tolerated side effects, approximately 17% grade 3-4 adverse events (AEs).

PD-1 inhibitor monotherapy is therefore now widely used. Treatment with iplimumab showed durable survival of up to 10 years in 20% of cases; compared to a median survival of less than one year in stage IV melanoma patients, and this is a major advance. [20] The Checkmate-067 trial combining CTLA-4 and PD-1 inhibition (ipilimumab and nivolumab, respectively) further increased OS to 52% and resulted in 11. 5 months of progression-free survival in patients with asymptomatic brain metastases. [17, 22]

Careful dosing and sequential therapy may help maximize objective responses while mitigating systemic toxicity.

Analysis of pooled data from multiple phase II and phase III clinical trials in patients with metastatic melanoma treated with anti-PD-1 showed an objective response rate of 34% (598/1773 patients) and a grade 3-4 toxicity rate of 14% (256/1773 patients). Currently, there are no good biomarkers to help decide who should receive PD-1 inhibitors versus combining PD-1 and CTLA-4 inhibitors. [19]

The American Society of Clinical Oncology has shown that elevated serum levels of interleukin-6 and C-reactive protein indicate worse outcomes in patients treated with immunotherapy. A prospective study of a combination of an interleukin-6 inhibitor (for example, tocilizumab) and a PD-1 inhibitor in this population is currently underway. [12]

It is impossible not to mention the adverse effects of immunotherapy: there is a serious debate about the mechanism of Immune-related adverse events (iRAE). One potential explanation is a tolerance disorder that is tissue specific. Tissue-resident Treg cells carrying

CTLA-4 often inhibit tissue-specific autoreactive T cells to maintain homeostasis. Lichenoid dermatoses are seen in patients treated with PD1 inhibitors. And the most common cutaneous iRAE from ipilimumab is spongiform eruption. When analyzing systemic iRAEs, anti-CTLA-4 therapy is associated with colitis and pituitary, while anti-PD therapy is associated with pneumonia and thyroiditis. [14, 19, 20]

However, anti-PD therapy is far from perfect, as only a subset of patients respond, and some patients experience significant toxicity, albeit less than other immunotherapies.

The basis of adoptive cell transfer (ACT) and chimeric antigen-receptor T^ cells (CAR-T) is the induction of antitumor immunity, adapting the patient's T cells to recognize specific cell surface markers on melanoma. [22, 23] Currently, ACTs can be divided into three different groups, each with an individual mechanism of action, namely T cell receptor (TCR) gene therapy ACTs, tumor infiltrating lymphocyte (TIL) ACTs, and chimeric antigen receptor (CAR) modified T cell ACTs. In TIL, T cells present in the tumor are isolated and proliferate ex vivo after surgical removal of the tumor. TILs are then further multiplied in a rapid expansion protocol (REP). Prior to intravenous transfer of cells to the patient, the patient is treated with an apheresis conditioning regimen. In ACTs in which genetically modified peripheral blood T cells are present, CAR gene therapy and TCR gene therapy can be distinguished. For both treatments, peripheral blood T lymphocytes are isolated by leukapheresis. Lymphocytes are then transduced by viral vectors to express a specific TCR or CAR, respectively. [15, 16]

The strength of TCRs and their ability to distinguish infected or abnormal cells from each other depend on their interaction with the major tissue compatibility complex (pMHC). Additional costimulatory signals are often needed to make the most of T cell function. The main costimulatory signals are CD8 on the surface of cytotoxic T cells (CTL) binding to MHC I and CD4 on the surface of helper T cells (Th) binding to MHC II [17]

One major difference between CAR and TCR therapies is that CAR-T can recognize antigens in an MHC-independent manner, but is limited to antigens on the cell surface. Unlike CARs, TCRs are able to recognize all proteins in the cell, so CARs are limited to surface antigens, which can be problematic to define in solid tumors, and research is underway to improve this technique. [25, 26]

The NY-ESO-1 trial (NCT00670748) of TCR demonstrated objective clinical responses in 55% of melanoma patients. The estimated overall 3- and 5-year survival of melanoma patients in this study was 33%, which is comparable to treatment with some immunotherapeutics. [15, 17]

Several oncolytic viruses have been developed based on viruses such as adenovirus, herpes simplex virus (HSV), reovirus, retrovirus, vesicular stomatitis virus and measles virus. Replication-capable HSV, in which neurovirulence is inactivated, leads to cell death in human melanoma cell lines in vitro. A key advantage of oncolytic viral therapy is that viral replication not only acts directly on the cancer cells, but also spreads the therapeutic agent

further through the tumor tissue. The goal of ongoing research is to enhance the virus' ability to selectively replicate and its ability to stimulate the immune system. [17, 18]

Photothermal therapy

Photothermal therapy (PTT) has been developed as an effective approach to cancer therapy. It is believed to remove cancer cells using heat generated from absorbed near-infrared (NIR) light energy with minimal side effects to the patient. [27] Meanwhile, NIR (l= 700-1100 nm) laser-based PTT is preferred due to the large depth of tissue penetration of NIR light, which can reach several centimeters. [28] Many variations of photothermal agents have been selected, including noble metal nanostructures [29].

Inspired by these facts, the authors of one of this year's studies attempted to deliver an Ag NP-based PTT agent for in vivo cancer therapy [30]. In order to avoid the side effect from external media, there is a need to introduce a protective layer on the outside of Ag NPs such as Au, [31] self-organized monolayers (SAMs) of organic thiols [32] and silica or titanium [33]. The ideal coating should provide adequate protection against environmental interference but should not significantly alter the characteristics of the plasma, and titanium dioxide meets these conditions. The preparation was tested in B16-F10 cells containing a melanoma prototype and C57BL/6J mice. The product was injected into the tumor and irradiated with an 808 nm laser at 2 W/cm2 for 1 minute.

Ag@TiO2 have high photothermal conversion efficiency: 60% of the cells experienced cell necrosis and the tumors shrank after laser irradiation for 1 min, a shorter time than in other experiments. The designed silver nanoparticles coated with titanium dioxide (TiO2) layer did not undergo silver nanoparticle aggregation, showed good chemical stability and good biocompatibility. Oxide coatings have not only increased the stability of Ag nanoparticles, but may also provide a binding site for targeting and tagging molecules in future studies [30]

In another study utilizing the therapeutic properties of precious metals, researchers synthesized and applied platinum nanoparticles (PtNPs) for anti-cancer therapy using 808 nm laser light and X-rays or a combination thereof [H]. Two laser power densities (1. 0 and 1. 5 W/cm 2) and three X-ray doses (2, 4 and 6 Gy) were chosen to irradiate the line b16/F10 cells at 24 and 72 hours after treatment.

Photothermal conversion activity was observed in a concentration-dependent manner at 72 h after treatment. In addition, further investigation up to 72 hours showed that PtNPs act as a good sensitizer for photothermal therapy and radiotherapy and induce effective death in melanoma cancer cell line. Laser light irradiation before RT to PtNP-containing cells led to deeper treatment and greater production of oxygen free radical ROS compared with laser light or X-ray light alone. PtNPs may therefore act as a novel dual absorber of laser light and X-rays for melanoma treatment. The results of this study may be considered after further clinical trials in tumor treatment. [34] For aggressive cancers such as melanoma in which chemotherapy and radiotherapy are ineffective, the efficacy of immunoprotective photodynamic therapy (PDT) as an adjuvant in surgery is also being investigated [35],

especially since this therapy has been successfully used to treat patients with non-melanoma skin cancer [36], esophageal cancer [37], head and neck cancers [38], breast cancer [39] and lung cancer [40, 41]. Towards the development of specialized photosensitizers (PS) for the treatment of pigmented melanomas, nine novel near-infrared (NIR) absorbing photosensitizers based on divalent rubidium compounds have been investigated [35]. Three compounds showed high potency toward melanoma cells. Furthermore, PDT treatment with compound 2 from the study induced immunogenic death of B16F10 placed mouse melanoma tumor cells and proved safe for in vivo administration (maximum tolerated dose ¼ 50 mg/kg) [35]. Furthermore, female and male mice with implanted B16F10 cells that were treated with PDT in combination with compound 2 exhibited 80 and 55% protection, respectively, against growth tumor, which led to a significant prognosis of survival [35]. Treatment with light-activated photosensitizers (photodynamic therapy, PDT) has shown limited tumor killing efficacy in pigmented melanoma, mainly due to light scattering and poor light penetration in this tissue [42]. To increase the treatment efficiency by reducing light scattering, an optical clearing agent (OCA) was applied to a mouse model of cutaneous melanoma shortly before the application of single and dual photosensitizer PDT [43].

This treatment appeared to have minimal therapeutic effect on the control in this study, non-pigmented cutaneous melanoma cells. In pigmented tumors, on the other hand, optical clearing significantly improved therapy for both single and, in particular, dual agent PDT for which the tumor was not detectable in vivo 10 days after treatment. This was evidenced by the absence of S100 and Ki67 immunoblotting in pigmented melanomas, which confirmed the killing of the tumor cells used in the study. The preclinical in vivo experiments described here support the hypothesis that the use of combined cellular and vascular PDT improves therapeutic response compared to single-agent PDT and that optical clearance results in improved tumor response to both single- and dual-agent PDT. The results also indicate the potential of PDT therapy with OCA enhancement in the treatment of pigmented lesions, including melanoma [43].

Summary

The presence of distant metastases in patients with malignant melanoma is still associated with a poor prognosis. Studies that have proven the high efficacy of immunotherapy open a window to better treatment prospects with checkpoint inhibitors, adoptive cell therapy (ACT), as well as oncolytic vaccines. Careful dosing and sequential therapy may help maximize objective responses while mitigating systemic toxicity.

If chemotherapy and radiotherapy are ineffective, the efficacy of immunoprotective photodynamic therapy (PDT) as an adjuvant to surgery is also being investigated. The results indicate the potential of PDT therapy with OCA enhancement in the treatment of pigmented lesions, including melanoma.

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