Treatment of Cutaneous Melanoma

Subjects: Dermatology
Contributor: Cristian Ionut Orasanu , Bogdan Marian Caraban , Mariana Aschie , Mariana Deacu , Georgeta Camelia Cozaru , Mihaela Butcaru Pundiche , Raluca Ioana Voda

Cutaneous melanoma is a public health problem. Pathogenic pathways and the tumor microclimate are key to the development of therapeutic methods. Revolutionary therapies like targeted therapy and immune checkpoint inhibitors are starting to replace traditional therapeutic methods. Targeted therapy aims at a specific molecule in the pathogenic chain to block it, stopping cell growth and dissemination. The main function of immune checkpoint inhibitors is to boost cellular immunity in order to combat cancer cells.

cutaneous melanoma | immune checkpoint inhibitors | targeted therapy

1. Introduction

Despite advances in the field of research, skin melanoma remains a worrisome pathology for health [1]. Efforts to reduce incidence continue to be ineffective, as rates keep increasing [2]. Incidence rates vary across continents: there are <0.5 cases/100,000 in Asia, 1/100,000 in Africa, 13.2/100,000 in Europe, 21.6/100,000 in the USA, and 48/100,000 in Australia. However, on a global scale, the number of cases is steadily rising by 2.6% every year [3][4]. Melanoma is the twelfth most common cancer globally, with higher rates in Europe (seventh) and the USA (fifth) [1][4]. The age-standardized incidence rate observes similar proportions of 3/100,000 women and 3.8 per 100,000 men [5].

Over the years, tremendous efforts have been implemented to decrease the number of cases through primary and secondary prevention programs. Primary prevention consists of avoiding the main risk factor attributed to melanoma's development: exposure to ultraviolet rays (UV) [1][6]. Worldwide, there have been campaigns to raise awareness of the risk of developing melanomas due to exposure to ultraviolet rays. After observing the favorable outcomes of the 1980s campaign in Australia, other countries like the USA embraced this trend as well, exemplified by "The Surgeon General's Call to Action to Prevent Skin Cancer" [1]. The United States Preventive Services Task Force strongly advises against sunlight exposure and the use of tanning beds. They also recommend using sunscreen with a sun protection factor of ≥15, and wearing sunglasses, hats, and sun-protective clothing. Also, behavioral counseling is offered to all people aged 6 months and up. These measures involve collaborating with the US Food and Drug Administration to provide information and guidance on sun protection lotions, partnering with the Environmental Protection Agency to offer information, widgets, and weather warning smartphone applications, and working with the Community Preventive Services Task Force to develop policies aimed at promoting preventive behavior [6]. In Germany, the national skin cancer screening program, covered by insurance, has been in action since 2008. Thus, dermatologists and general practitioners must visually examine the entire skin of the patient [7].

Secondary prevention refers to any method that aims to identify high-risk populations, and screening strategies [1]. Secondary prevention is based on the early identification and treatment of pre-lethal injuries. Every person should be educated on self-examination and how to identify signs of concern, giving them access to a healthcare system that can diagnose melanoma early and provide the necessary treatment. Detection programs have been tried in Australia, Belgium, France, Germany, and the USA. The conclusion of the screening programs was a beneficial one, but the evidence was not strong [8]. However, the United States Preventive Services Task Force did not identify sufficient evidence to recommend routine skin screening, even if screening by total body examination of the high-risk population is safe, cost-effective, and efficient (5.2 quality-adjusted life years per 1000 people screened annually). These aspects can lead to overdiagnosis and a potential increase in therapeutic costs with a limited mortality benefit [9]. In this regard, new technologies are being developed to help dermatologists and primary care physicians. They can rely on artificial intelligence, with the most notable examples being multispectral digital skin lesion analysis, image-analysis software, and total body mole mapping [8][9].

Even if the prevention results were favorable (identifying cases at an early stage or reducing the frequency in certain population groups), they did not bring significant improvements, and the frequency of melanomas increased year by year [1][7]. There are undeniable advantages to early detection. This approach minimizes disfigurement by reducing the size and extent of surgical excision, mitigates adverse effects caused by systemic therapy, potentially saves the lives of patients who may not benefit from advanced systemic treatments, and lowers overall healthcare costs [10]. Another strength of early detection resides in the association with patient survival. Melanomas limited to the epidermis (in situ) pose no risk of death, and the likelihood of metastasis is low for thin melanomas [11]. The issue of overdiagnosis is a significant problem, as it does not bring any benefits to the patients. Instead, it can cause them to suffer as a result of both the diagnosis itself and the treatment they will undergo [12]. Overdiagnosis occurs when a tumor is diagnosed as malignant, but would not actually lead to the patient's

death if left untreated. In Australia, a study found that overdiagnosis occurred in 54% of melanoma cases in women and 58% of melanoma cases in men. Thus, although useful, early detection programs are less than 100% effective. This means that for every lesion diagnosed as melanoma, there are other undiagnosed melanocytic lesions [13]. In a study conducted by Kurtansky NR et al., which analyzed nine registries of the Surveillance, Epidemiology, and End Result Program, the authors identified evidence (discrepancies between the relative increase in incidence compared to mortality) that suggested overdiagnosis, especially in middle-aged people and young women [12]. This overdiagnosis not only harms the patient but also the health system through increased costs and use of resources. Unfortunately, it is difficult to determine which melanomas are overdiagnosed or overtreated. Due to this challenge, doctors face significant difficulty in determining the precise adjustments needed in their practice to enhance the overall well-being of their patients [14]. So far, one way to prevent overdiagnosis is to include histopathological parameters like tumor thickness, ulceration, invasion, or mitotic rate in the report. In advanced stages, molecular biology examinations are added [15].

Primary and secondary prevention, along with new therapies, have proven their effectiveness in terms of mortality. In the USA, the mortality rate had an initial evolution of a slight increase—despite a solid prevention program—but after the new treatments were initiated, the mortality rate was a decreasing one [16]. In Europe, mortality differs between regions, with a maximum rate of 3.2:100,000 inhabitants in Norway and 1:100,000 inhabitants in Romania. This aspect represents a paradox given that Northern European countries benefit from much more extensive secondary prevention programs than Central or Eastern European countries [4]. Contrary to these measures, the International Agency for Research on Cancer estimates that the mortality of cases diagnosed with melanoma will increase by 56.92% until 2040 [17].

Without underestimating the role of prevention, studies have shown that the contribution of new immunological therapies is superior [16][18]. In this regard, the most important therapies are represented by immune checkpoint inhibitors (ICIs): anti-CTLA-4 monoclonal antibodies and anti-PD-1 monoclonal antibodies [19][20]. Anti-CTLA-4 medications act by directly inhibiting CTLA-4 with CD80/CD86 ligands, which causes CD28 co-stimulation and T-lymphocyte activation. The immunosuppressive effect in melanoma is partially mediated by Treg recruitment (highly expressed CTLA-4). Anti-CTLA-4 medication causes a reduction in tumor infiltration and circulating Tregs after therapy. In contrast to the modulation of immune function during the initial phase of T-lymphocyte activation, anti-PD-1 therapy functions by halting cell activity during the effector phase. This consists of reducing the number of phenotypically exhausted cytotoxic CD8+ lymphocytes. Also, a response to anti-PD-1 drug treatment is dependent on a T lymphocyte response in the tumor microclimate [21]. Normally, PD-1 binding inhibits the proliferation of T lymphocytes, reduces their overexpression, and inhibits the production of (IFN-γ), tumor necrosis factor-α, and IL-2. Thus, anti-PD-1 medication acts on these immune checkpoints, restoring or increasing the antitumor immune response to achieve tumor regression [22]. The advantages of these therapies consist of the extension of their increased efficiency to metastatic melanomas, or those with a high risk of recurrence [20]. These therapies prove their effectiveness in the advanced stages where surgical excision has limited curative potential. Thus, until stage III, surgery is the first line of treatment [19].

2. Treatment of Cutaneous Melanoma

The first-line treatment in early melanomas (stages 0-IIA) is surgical. The National Comprehensive Cancer Network suggests different excision margins based on the thickness of the melanoma: 0.5 cm for melanoma in situ, 1 cm for melanomas up to 2 mm thick, and 2 cm for thicknesses over 2 mm [23][24]. In the case of invasive melanomas, it is recommended to perform wide local excision, which should include excision of the subcutaneous tissue up to the level of the fascia to ensure thorough removal. Of course, if invasion of the fascia is observed, it and the underlying tissue will be excised. In acral melanomas, depending on their invasiveness, amputations can be reached [24].

Surgical excision can be performed in almost all cases only with local anesthesia. If the surgical margins are not free of the tumor, re-excision is required. Extended surgical margins are not recommended in the case of free histological margins. Surgical excision is generally not performed under two circumstances: when the patient explicitly declines the procedure or when the patient's overall health is severely compromised [25]. Complete lymph node dissection has the role of preventing the expansion of tumor cells and increasing the accuracy of the melanoma stage diagnosis. However, the German Dermatologic Cooperative Oncology Group Selective Lymphadenectomy (DeCOG), Multicenter Selective Lymphadenectomy Trial (MSLT-2), and other studies, did not observe a benefit in terms of overall survival or melanoma-specific survival of patients. Moreover, the rate of complications was higher compared to the cases biopsied for SLN or the observational groups [25][26].

Adjuvant therapy is essential for advanced melanomas, particularly those in stages IIB to IV and those with a thickness beyond 2 mm. This therapy offers a range of treatments including interferon, IL-2, targeted therapy, and/or immunotherapy [23]. A special mention should be made regarding stage III treatment with a combination of immune checkpoint inhibitors (anti-PD-1) and targeted therapy (BRAF + MEK inhibitor). In the study conducted by Helgadottir H et al., adjuvant therapy highlighted a net benefit in terms of recurrence-free survival. Apparently, in terms of overall survival, the results did not have the expected positive results [27].

Interferon has proven its effectiveness through its multiple mechanisms. It possesses an immunomodulatory effect, augmenting the expression of class I of the histocompatibility complex, inhibiting proliferation, triggering apoptosis, and diminishing VEGF secretion. Furthermore, its impact extends to immune cells, as it stimulates the conversion of helper 2 lymphocytes into Th1 cells, suppresses regulatory T lymphocytes, enhances the cytotoxic activity of T lymphocytes, boosts the survival rate of dendritic cells, and amplifies the cytotoxic activity of natural killer cells [28]. These effects result in medication with interferon α-2b reducing the risk of recurrence, but have minimal benefits for survival [29]. The pegylated form (PEG-IFN) offers enhancements such as an optimized pharmacokinetic profile, prolonged half-life, and weekly administration [30]. Regrettably, there is no disparity in terms of overall patient survival between the two forms [29]. Clinical trials were performed to highlight the difference between low doses and high doses of IFN α-2b. The low doses did not bring obvious improvements, and the increased ones caused increased toxicity and numerous adverse reactions. Thus, interferon therapies have a moderate efficiency, not reflecting a major effect [31].

Treatment with cytokines (IL-2) stimulates the production of lymphokine-activated killer cells. Also, IL-2 potentiates the growth factors of T cells and the cytolytic effect of natural killer cells [32][33]. Optimal treatment necessitates higher doses and, by extension, close monitoring of the patient. This is due to the many adverse reactions it possesses. The most common are represented by fever, hypotension, oliguria, dyspnea, tachypnea, neurotoxicity, pruritus, neutropenia, and thrombocytopenia. However, the advantages of this treatment include an impressive response rate of 15–20%, a notable complete response rate of 5–10%, and a remarkably favorable survival rate. Monotherapy treatment is becoming less common these days. It is now more common to either replace it with immunological therapy or use it in combination with this [34].

Treatment with alkylating agents has been a common method directed against advanced melanoma since the 1970s. The most used chemotherapeutic agent is Dacarbazine. This is a prodrug whose activation is initiated by the liver. The objective response rate is up to 15%; most responses are partial, and only approximately 3–5% are complete. It is relatively well tolerated, with its toxicity being grade 3 or 4 in about 18% of patients. The most frequent adverse effects include nausea, vomiting, fatigue, and myelosuppression [35][36]. Other chemotherapies used are represented by temozolamide and fotemustine. These are chosen especially in cases of cerebral metastasis [35][37].

A therapeutic advance in contrast to chemotherapy is the use of targeted therapy. It has greater specificity and different side effects compared to alkylating agents [38]. Targeted therapy involves using specific substances to target and block the growth and spread of cancer cells by focusing on certain molecules. This concept is based on good knowledge of the physiopathogenesis of the tumor for which it is used. Therapy can act on cancer cells and/or on the tumor microclimate. Within these therapies, you can use small molecules, therapeutic monoclonal antibodies, gene therapy, or therapeutic cancer vaccines [39]. In the treatment of melanoma, the most used small molecules are directed against the BRAF gene (Vemurafenib, Dabrafenib, and Encorafenib) and/or MEK/MAPK (Binimetinib, Cobimetinib, Trametinib) [40].

Vemurafenib is a therapeutic agent directed against melanoma with BRAF V600E mutation in advanced stages. Clinical studies have observed a 63% reduction in the risk of death and a 74% reduction in tumor progression. Adverse effects are manageable and directly proportional to dose and exposure. The skin, liver, central nervous system, and joints are the areas most commonly impacted. Squamous cell carcinoma poses the most significant risk, likely due to a paradoxical activation of the MAPK pathway [41][42].

Dabrafenib is also directed against advanced-stage melanoma with BRAF mutation (V600E and V600K). In cases without brain metastases, the response rate is 50%. Progression-free survival and overall survival demonstrate a stable phase lasting 3 years, with a progression-free rate of 11–12% at 5 years. In the case of cerebral metastases, regardless of the local treatment performed or not performed, the efficiency decreases. The median survival for the V600E mutation is higher than for the V600K mutation, with 7.2–7.6 months compared to 3.7–5 months, respectively. In addition, the frequency of adverse reactions is also higher in the case of the presence of brain metastases. Common adverse reactions to the treatment include headache, hyperkeratosis, fever, arthralgia, hair loss, fatigue, and hyperkalemia [43][44].

Encorafenib is the most recently approved targeted agent against melanomas in advanced stages with BRAF mutation. Most treatment schemes associate it with the administration of an MEK inhibitor. Clinical studies have demonstrated an impressive 60% objective response rate, as well as a progression-free survival rate that outperforms the other two BRAF inhibitors. Grade 3 or 4 adverse effects are rare. Nausea, diarrhea, vomiting, fatigue, joint pain, and headache are among the most frequent reactions [45][46].

Binimetinib is a selective non-competitive ATP inhibitor of MEK1 and MEK2. It is often associated with Encorafenib, bringing improvements to both progression-free survival and overall survival. Its main adverse effects are rash, diarrhea, nausea, acneiform dermatitis, and fatigue [47][48].

Cobimetinib is an MEK1 and MEK2 inhibitor, allosteric, reversible, and non-competitive ATP. It is administered together with Vemurafenib. The combination of the two results in maximum efficiency, increasing apoptosis and inhibiting tumor growth. The majority of adverse reactions are mild to moderate, including symptoms such as diarrhea, nausea, vomiting, skin rash, arthralgia, and increased levels of creatine kinase. In the phase 3 clinical trials, an objective response rate of 68–87% was accomplished, with a remarkable 10% of participants showcasing a complete response. Notably, the average progression-free survival ranged from 9.9 to 13.7 months [49][50].

Trametinib is a non-competitive ATP-selective MEK1/2 inhibitor, approved both as a single agent and in combination with Dabrafenib. It decreases tumor proliferation by arresting the cell in G1 of the cell cycle, causing apoptosis. Treatment may need to be interrupted or delayed due to adverse effects such as cardiomyopathy, retinal pigment epithelial detachment, retinal vein occlusion, and febrile reaction. The association with Dabrafenib brings both antitumor benefits and the improvement of patients' quality of life. This association delivers a response rate of 64–67%, along with an average progression-free survival of 9.3 to 11.4 months [51][52][53].

Regarding other elements of the pathogenic chain, clinical studies' outcomes have not yielded the anticipated results for the targeted treatment. Despite being one of the first genes discovered in the development of melanoma, there has been no advancement in the development of an NRAS inhibitor until now. Drugs such as Binimetinib or farnesyltransferase inhibitors can be used on RAS mutations [33][54][55]. Due to the complex downstream protein shifting process, developing a drug against RAC1 is an extremely challenging task [33]. Medications against the KIT mutation exist on a large scale (Imatinib, Sunitinib, Dasatinib, Nilotinib), but in the case of melanomas, they have not proven their effectiveness [33][56][57].

Currently, immune checkpoint inhibitors are among the most used anti-melanoma medications. They can be administered as a monotherapy or in combination with targeted therapies. Their advantage lies in the ability to induce lasting control over the pathology [38][58]. The National Comprehensive Cancer Network recommends Ipilimumab, Nivolumab, and Pembrolizumab as adjuvant treatments for advanced melanomas [59].

Ipilimumab is a CTLA-4 inhibitory monoclonal antibody. It can be used alone or in combination with Dacarbazine (it has better survival rates alone than with Dacarbazine, but results in more frequent grade 3 and 4 adverse effects) or with Nivolumab (which presents synergistic effects). Monotherapy has a complete response rate of 6%, with an average survival of 19.9 months and a 5-year survival of 26%. In association with Nivolumab, the complete response rate rises to 22%, the average survival exceeds 60 months, and the 5-year survival is 52% [58][60].

Nivolumab was the second PD-1 inhibitory monoclonal antibody used in advanced melanomas. It is usually used as a second-line treatment, after anti-CTLA-4 or anti-CTLA-4 and BRAF inhibitor treatment [61]. The complete response rate is 19%, with an average survival of 36.9 months and a 5-year survival of 44% [58].

Pembrolizumab is a PD-1 inhibitory IgG4 monoclonal antibody. It has the role of potentiating the production of IL2, IL6, IL17, ɤ-interferon, and α-tumor necrosis factor. The most common adverse reactions are represented by pruritus, rash, diarrhea, arthralgias, and nausea. A disadvantage of using Pembrolizumab consists of immune-type adverse reactions (hypo- or hyperthyroidism and pneumonitis) [62]. A prediction score of immune events is CYTOX. It is composed of 11 circulating cytokines: IL-1a, IL-1B, IL-1RA, IL-2, IL-12p70, IL-13, IFN-α2, FGF-2, Fractalkine, G-CSF, and GM-CSF. Their increase has been associated with a severe risk of developing immune-type adverse reactions and requires the administration of immunosuppressive agents [63]. Unlike CTLA-4 inhibitors, this medication shows increases in progression-free survival and total survival [64]. Patients treated with Pembrolizumab have an average survival of 38.7 months, with a 5-year survival rate of 43%. An advantage also lies in the increased response rate (22%) in cases of brain metastases [58].

In the case of immune therapies, preclinical studies have shown that preoperative administration leads to increased survival. There are hypotheses suggesting that even a single dose of a PD-1 inhibitor could potentially stimulate the activity of cytotoxic lymphocytes [65]. Moreover, in the case of Pembrolizumab, randomized clinical trials have observed an increased efficiency of neoadjuvant administration. This involves activating lymphocytic infiltration in the tumor, exposing the antigen, and reducing the tumor size during surgery [60].

Currently, 20 clinical trials in phases 2 and 3 are ongoing and active with disseminated results, and are monitoring the effectiveness (objective response rate, survival rate, relapse, progression-free survival) of various therapies against cutaneous melanomas. Studies that aimed for response rate or clinical benefit over a time period are reported as percentages, and those that aimed for overall survival, progression-free survival, or recurrence-free survival are noted as time periods [66].

The factors that influence the response to treatment with immune checkpoint inhibitors are varied. The index that quantifies all tumor mutations is called tumor mutational burden. A correlation of this index with the response rate was observed in anti-PD-1 and anti-CTLA-4 therapies [67]. Another element that influences the treatment is represented by the major histocompatibility

complex (MHC). MHC I controls the function of CD8 lymphocytes, which directly target cancer cells, while MHC II facilitates the activity of CD4 lymphocytes, which promote an inflammatory response by producing ɣ-interferon [68][69]. MHC I activity serves as a predictor for anti-CTLA-4 therapy, while MHC II predicts the efficacy of anti-PD-1 therapy [67]. Nevertheless, the absence of the B2M protein from MHC I results in a resistance mechanism against both types of inhibitors [70]. Another predictor of response to anti-PD-1 therapy is represented by the immunohistochemical expression of its ligand (PD-L1). Positivity is determined by a threshold of either greater than 1% or greater than 5% of tumor cells [58][67]. However, currently, no study has identified differences in the overall survival of patients depending on PD-L1 expression. Therefore, quantifying the expression is optional and should not be considered when making therapeutic decisions for stage IV cases [71]. The gastrointestinal microbiota play an important role in the response to immune checkpoint inhibitors. The presence of a population rich in *Faeclibacterium* spp. shows a favorable clinical response, while the abundance of *Bacteroides* spp. is associated with a low response to ICI [67].

Two of the most prevalent factors in resistance to treatment with inhibitors targeting the PD-1/PD-L1 axis involve the depletion of T cells and the impaired function of tumor-infiltrating lymphocytes. The depletion of T cells in the tumor microenvironment is caused by damage to the immunoreceptor tyrosine-based inhibitory motif domain. The consequences consist of the impairment of PD-1 signaling and the activity of T lymphocytes. The overexpression of TIM-3 in regulatory T lymphocytes causes the dysfunction of tumor-infiltrative lymphocytes, leading to resistance to treatment [72][73]. Cells refractory to treatment have undergone mutations, losing their response to ɣ-interferon or MHC class I [74].

A series of investigations can be used to monitor the effectiveness of the treatment. The serum LDH test is the most easily accessible. Increased levels can serve as both a reliable indicator of recurrence, with a sensitivity of 72% and a specificity of 97%, and a surrogate for a high index of tumor mutational burden [63][67]. Increased basal levels of IL-6 were associated with a low therapeutic response and low patient survival [67]. Circulating tumor DNA detected in the patient's serum correlates directly proportionally with progression and tumor mutational burden. An additional indication of improved treatment adherence is reflected in the heightened presence of CD8-positive lymphocytes within the tumor microenvironment and the rise in T helper 9 lymphocytes in the bloodstream [74].

There are several other noteworthy treatments, such as T-VEC, ECT, and Treg inhibitors [75][76]. T-VEC is an oncolytic viral therapy that can be used in grade IIIB-IV melanomas. Because its effectiveness is not high, it is only used in specific subgroups of patients who have only local or regional cancer extension [75]. In phase III of the MASTERKEY-265 clinical trial, the combination of T-VEC and Pembrolizumab did not result in significant improvements in either progression-free survival or overall survival compared to the combination of Pembrolizumab and the placebo. Even though progression-free survival was higher by 5.8 months in T-VEC and Pembrolizumab, this was not reflected in overall survival [77]. ECT is a technique that uses high-intensity electrical pulses intending to deliver medication (cytotoxic, cisplatin, and bleomycin) to tumor cells. Following the action, the lymphatic vessels are destroyed, and the local recurrence rate is zero [76]. Treg inhibitors have the role of stimulating antitumor immunity. This treatment targets the tumor microenvironment to prevent the infiltration of regulatory T lymphocytes into the tumor tissue [78]. A particular aspect is represented by adoptive T-cell therapy. An increased number of lymphocytes are selected from the tumoral lymphocytic infiltrate. They are cultivated in vitro, and are capable of recognizing and performing antitumor functions. After that, they are re-administered [32].

Also, new therapeutic approaches regarding advanced melanomas are underway: anti-LAG3, GITR agonists, and anti-TIGIT. LAG-3 (lymphocyte activation gene 3) is an inhibitory receptor of the immune checkpoint of CD4+/CD8+ and Treg T lymphocytes. It suppresses the activation and proliferation of T lymphocytes. The coexistence of LAG-3 and PD-1 leads to the persistent stimulation and subsequent exhaustion of T lymphocytes, which may present a possible mechanism of resistance to immunotherapy [79][80]. GITR (the glucocorticoid-induced TNF receptor) is a member of the TNF receptor superfamily. Activating the GITR pathway stimulates antitumor activity by promoting proliferation and enhancing the effector functions of CD4+ and CD8+ T lymphocytes. Also, the effects downregulate the immunosuppressive activity of Treg lymphocytes [79]. TIGIT (T cell immunoreceptor with immunoglobulin and ITIM domain) binds to CD112 and CD155 ligands that downregulate the functions of T lymphocytes and natural killer cells. The inhibition of PD-1 and TIGIT potentiates the activity of tumor antigen-specific CD8+ T lymphocytes and tumor-infiltrating lymphocytes [79][81].

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