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Title

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Permalink

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Journal

Dermatology Online Journal, 26(7)

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Publication Date

2020

DOI

10.5070/D3267049551

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Current and emerging treatment options for metastatic melanoma: a focused review

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Abstract

Melanoma is responsible for nearly 9,000 deaths each year in the United States. Until the early 2000s, chemotherapeutic agents were the mainstay of treatment for metastatic disease. Currently approved treatments include therapies that block signal transduction pathways (BRAF inhibition), increase anti-tumor immune responses (CTLA-4 blockade), or stimulate tumor-infiltrating T cells (IL2). In recent years, various new strategies have emerged. Radiation therapy has been widely underutilized, but it can prime tumor cells that are distant from the field of radiation, a phenomenon termed the abscopal effect. Other therapies such as pembrolizumab disrupt the tumor cells' typical mechanisms of T-cell avoidance. Various other treatments involving imiquimod, adoptive T-cell therapy, and vaccines are currently being studied and can play a role in metastatic melanoma treatment in the future. Herein, we review the past treatment modalities, currently approved treatments, and potentially effective options for the future. We also provide strengths of recommendation and level of evidence for each treatment.

Keywords: metastatic melanoma, treatment, vemurafenib, radiotherapy, ipilimumab, vaccine, pembrolizumab

Introduction

Each year, over 65,000 new melanoma cases and nearly 9,000 melanoma deaths are reported in the United States [1]. Although melanoma rates have increased since 1980, mortality rates have remained relatively unchanged. In the absence of new

treatment options, it is projected that there will be 112,000 new melanoma cases in 2030 [1].

Melanoma survival rates vary widely depending on their stage at diagnosis. For example, the 5-year survival rate for localized melanoma is 98.3%, as compared to 16.0% for patients diagnosed with metastatic melanoma [2]. Melanoma staging is dependent on their depth of involvement and spread to lymph nodes and other parts of the body. Stage I and II involve neither lymph node involvement nor metastasis and instead are distinguished based on their chance of recurrence. Stage III melanoma involves metastases in local lymph nodes whereas Stage IV is characterized by the presence of distant metastases. Patients with Stage III and IV melanoma have the lowest survival rates that range from 5 to 23 months after diagnosis [3]. Long-term survival rates are approximately 10% for patients with metastatic melanoma [4].

For many years, chemotherapeutic agents were the mainstay of treatment for metastatic melanoma. However, their survival benefits were modest. Recent promising strategies have included blocking signal transduction pathways (BRAF inhibition) and/or increasing anti tumor immune responses (CTLA-4 blockade). Furthermore, various newer strategies including immunotherapy, vaccines, and kinase inhibitors have emerged in recent years. Therefore, a systematic review is necessary for clinicians to stay up to date on treatments for metastatic melanoma. We provide a review of past treatment modalities, currently approved treatments, and potentially effective options for the future. We also provide a strength of recommendation and level of evidence for each treatment (**Table 1**). Delineations for

strength of recommendation and level of evidence were adopted by the SORT grading scale (**Table 2**), [5].

Past Treatments

Chemotherapy

Chemotherapy was the mainstay of treatment for metastatic melanoma prior to the early 2000s. Dacarbazine was the first Food and Drug Administration (FDA) approved agent. Dacarbazine's mechanism of action includes alkylating bases in

DNA to prevent cells from replicating. Dacarbazine's response rate ranged from 19-28% in initial trials in the early 1970s [6, 7]. However, more recent large-scale trials from 2004 to 2006 only provide a response rate ranging from 5-12% [8-10]. Not only are the response rates low, but the long-term effects are mild, with only 1% of patients achieving a long-term chemotherapeutic response [11]. Large, randomized controlled trials have not shown improved survival in patients on dacarbazine monotherapy [12].

Table 1. Summary of Treatments with Strength of Recommendation and Level of Evidence.

Treatment	Overall Response Rate ¹	Notes	Level of Evidence	Strength of Recommendation
Chemotherapy Dacarbazine, Temozolamide, Fotemustine	5-28%	Long-term effects are mild Large-scale, randomized controlled trials have not shown survival benefit in patients taking dacarbazine	III	C
Surgical metastectomy	7.0-20.8%	Primarily used for symptomatic palliation Best when combined with systemic treatment	I	C
Systemic/Intralesional IL-2	16-78%	Systemic IL-2 can cause vascular leak syndrome Systemic IL-2 is first-line therapy for unresectable stage IV melanoma with "good performance status" Intralesional IL-2 reduces systemic symptoms	I	A
Anti-CTLA4 Ipilimumab	15.2%	Can be used for treatment-naïve or treatment-resistant patients Can be combined with dacarbazine for improved efficacy First-line therapy for BRAF-negative unresectable stage IV melanoma patients with "poor performance status"	I	A
BRAF Inhibitors Vemurafenib Dabrafenib	37-81%	Can be used for brain metastasis Nearly 25% of patients develop cutaneous squamous cell carcinomas (majority are keratoacanthomas)	I	A
Radiation Therapy	30%	Indicated for symptomatic palliation Exhibits abscopal effect	II	B
Anti-PD-1 Therapy Pembrolizumab Nivolumab	26-61%	Exerts synergistic effect with CTLA-4 inhibitors	I	A
Interferon Therapy	19.5-48%	Nearly 30% of patients discontinued due to intolerability Improved overall response rate but no improvement in survival	II	C
Imiquimod	82.3%	Based on case reports and one case series	III	C
Adoptive T-cell Therapy	29-49%	Challenging and laborious process	III	C
Vaccines	11-16%	Oncolytic vaccines exhibit abscopal effect	II	B

¹Overall response rates include complete and partial response.

Table 2. Strength of Recommendation and Level of Evidence Definitions [5].

Strength	Definition
A	Recommendation based on consistent and good-quality patient-oriented evidence
B	Recommendation based on inconsistent or limited-quality patient-oriented evidence
C	Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening
Level	Definition
I	Systematic review/meta-analysis of randomized, controlled trials with consistent findings; high-quality randomized, controlled trials; all-or-none study
II	Systematic review/meta-analysis of lower-quality clinical trials or of studies with inconsistent findings; lower-quality clinical trial; cohort study; case-control study
III	Consensus guidelines, extrapolations from bench research, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening

Various chemotherapeutic agents have been developed since dacarbazine. Temozolomide, a dacarbazine derivative, was approved in 2000 as an oral chemotherapeutic for metastatic melanoma. Because it can cross the blood-brain barrier, it was used primarily for brain metastases. Temozolomide was equally as effective in terms of overall survival (OS) as dacarbazine, but its oral formulation was associated with improved quality of life and physical functioning [13]. Fotemustine is a chloroethyl nitrosourea that, when compared to dacarbazine, has improved response rates (15.2% versus 6.8%), [8]. Overall, the aforementioned chemotherapeutic agents lacked significant improvement in survival, which is oftentimes the most valued metric in the management of melanoma. This led to the development of new therapies such as targeted immunotherapies and checkpoint inhibitors.

Surgical metastatectomy

In the past, surgery for advanced melanoma was reserved for three clinical scenarios: 1) symptomatic palliation for patients with diffuse stage IV disease, 2) patients with oligometastatic disease, and 3) patients with stage III melanoma. One study had superior survival benefits for a select group of stage IV patients undergoing surgery versus those receiving systemic treatment [14]. However, there has been considerable debate regarding the validity of these results owing to a non-randomized selection of patients with favorable biology who potentially had a survival benefit over a non-matched comparison group [15].

Surgery for metastatic melanoma to the gastrointestinal tract is a reasonable option for many patients. Interestingly, melanoma metastasis to the gastrointestinal tract has the greatest survival compared to melanoma metastatic to the liver, spleen, and pancreas. Specifically, the 1-year and 2-year survival for patients undergoing complete metastatectomy from the gastrointestinal tract were 52% and 41%, respectively [16]. Increasing age and the presence of ulceration are associated with worse overall survival. Patients with metastasis to the gastrointestinal tract have exhibited a longer mean survival when undergoing partial resection (8.9 months) or complete resection (23.5 months) as compared to those who did not resect (4.1 months), [17]. The benefit of total resection has been supported by other studies highlighting that it is safe, relieves gastrointestinal symptoms, and can prolong remission [18-20]. Lastly, surgery alone is commonly used for symptom relief, such as in the setting of bowel resection for bowel obstruction or cutaneous excision for pain control.

Surgery confers the greatest benefit when combined with systemic treatment. In the Multicenter Selective Lymphadenectomy Trial, patients who underwent surgery with or without systemic medical therapy had a longer mean survival and 4-year survival rate compared to patients undergoing systemic medical therapy alone (15.8 versus 6.9 months; 20.8% versus 7.0%, respectively), [14]. Furthermore, patients with M1a disease (distant skin, subcutaneous layer, or distant lymph nodes) experienced the greatest benefits in mean survival time and 4-year survival

rates. Surprisingly, in this trial, patients who received multiple operations for multiple metastases did not experience improved survival rates.

Surgery can be attempted for other sites of distant metastases, such as the adrenal glands, liver, or brain [21, 22]. Adrenalectomy resulted in a mean overall survival of 29.2 months as compared to nonoperative treatment of 9.4 months [23]. A 2015 study of the treatment of liver metastases suggest that there is no difference in overall survival between ablation and resection, although both can result in a mean overall survival of 25.9 months [24]. Operative management of cerebral metastases results in a mean survival time of 8.5 months from the time of diagnosis [25]. Current efforts are focused on reducing the morbidity associated with surgery in addition to combining surgery with systematic treatments. Such efforts have culminated in procedures such as laparoscopic inguinal lymph node dissection, neoadjuvant targeted and/or immunotherapy, and isolated limb infusion with systemic therapy.

Currently Approved Therapies

Systemic/Intralesional IL2

Interleukin-2 (IL2) is used for various cancers because of its ability to stimulate the proliferation and activation of tumor-infiltrating T cells [26]. IL2 administration results in an overall objective response rate of 16%, with 6% achieving complete response and 10% achieving partial response [27]. Systemic IL2 is currently considered a first-line treatment option for unresectable stage IV melanoma patients with "good performance status" irrespective of BRAF mutation status [28]. Because intravenous IL2 infusion can cause vascular leak syndrome, it is generally reserved only for relatively healthy patients, but can be second-line treatment for patients with "poor performance status."

To reduce systemic toxicity, intralesional IL2 therapies have been developed and are superior to systemic IL2. A systematic review of phase II studies containing 140 pooled patients revealed that intralesional IL2 for in-transit melanoma shows a complete response in 78% of lesions, with 50% of patients achieving complete response [29]. In contrast to systemic IL2, intralesional IL2 has a much

more favorable side effect profile. The most common adverse effects include injection site discomfort, swelling, and erythema. Of the 140 pooled patients, only three experienced a grade 3 adverse event.

Anti CTLA-4

CTLA-4 is an immune checkpoint receptor expressed on activated T cells that, when activated, downregulates T-cell immune responses. Ipilimumab is an anti CTLA-4 monoclonal antibody directed against the inhibitory receptor and serves to counteract the inhibitory effect of CTLA-4 activation, allowing for T-cell activation and tumor lysis [30]. Ipilimumab was then FDA-approved in 2011 for the treatment of unresectable melanoma. First-line ipilimumab compared to dacarbazine demonstrated an enhanced 1-year survival of 45.6 versus 18.9% with dacarbazine for metastatic or unresectable melanoma [31]. Furthermore, ipilimumab can be combined with chemotherapy. In one phase III study, ipilimumab plus dacarbazine, as compared to dacarbazine plus placebo, improves overall survival at one year (47.3% versus 36.3%), two year (28.5% versus 17.9%), and three years (20.8% versus 12.2%), ($P < 0.001$), [12].

Ipilimumab with gp100, a vaccine containing a modified glycoprotein 100 melanoma antigen, has a longer median OS compared to gp100 alone in a phase III trial of metastatic melanoma patients (10.0 months versus 6.4 months, $P < 0.001$), [32]. Vaccine formulation is an important consideration. Gp100 peptide in incomplete Freund's adjuvant formulation showed a surprising dominant-negative effect on efficacy of CTLA-4 checkpoint blockade, whereas nonpersistent vaccine formulations, such as water-based, cellular, viral, and nucleic acid-based, overcome resistance to checkpoint blockade therapy and improve complete cure rates [33].

The long-term survival of patients with advanced melanoma, defined as those with unresectable stage III or IV melanoma, treated with ipilimumab is encouraging. In a pooled analysis of 1,861 patients from 10 prospective and two retrospective trials of ipilimumab, the median OS was 11.4 months [34]. However, the survival improvement plateaus after three years. The three-year survival rates for all patients, treatment-naïve patients, and previously

treated patients were 22%, 26%, and 20%, respectively.

Ipilimumab is currently first-line therapy for BRAF-negative unresectable stage IV melanoma patients with “poor performance status” and is second-line therapy for patients with “good performance status” irrespective of BRAF mutation status [28]. The major drawback to ipilimumab is its toxicity profile. In various ipilimumab clinical trials, 15-56.3% of patients experienced grade 3 or 4 adverse events. Ipilimumab in combination with anti PD1, anti phosphatidylserine antibodies, BRAF inhibitors, or radiotherapy are currently being studied owing to their theoretical increase in response rate [35].

Tremelimumab, formerly known as ticilimumab, is an anti CTLA-4 monoclonal antibody that is safe as a single IV dose up to 15 mg/kg [36]. Tremelimumab has similar OS (12.6 months) as other standard-of-care chemotherapies (temozolomide or dacarbazine; 10.7 months), ($P=0.127$), but the response duration is significantly longer after tremelimumab (35.8 months) as compared to standard-of-care chemotherapies (13.7 months), ($P=0.0011$), [37]. Tremelimumab in combination with IFN α -2b or an agonist CD40 antibody increases the OS to 21 months and 24 months, respectively [38, 39]. Common adverse effects of tremelimumab include diarrhea, pruritis, and rash. A small percentage of patients experience endocrine abnormalities such as thyroiditis and hypophysitis [37].

BRAF Inhibitors

BRAF is a member of the rapidly accelerated fibrosarcoma (RAF) family of kinase pathways and mutation of BRAF leads to constitutively active mitogen-activated protein kinase (MAPK) pathways and cellular proliferation. Nearly 50% of patients with cutaneous melanoma have a BRAF mutation [40].

Vemurafenib is a highly selective inhibitor of mutated BRAF that was initially promising in the treatment for metastatic melanoma. Early studies of vemurafenib were excellent, with 75% of patients achieving partial response, 6% of patients achieving complete response, and median progression-free survival among all patients greater than seven months [41]. Vemurafenib is more effective than

dacarbazine. Patients who received vemurafenib had a 6-month OS rate of 84% as compared to 64% for patients on dacarbazine [42]. In addition, vemurafenib was associated with a relative reduction of 63% in the risk of death compared to dacarbazine ($P<0.001$). Finally, vemurafenib is promising in treatment for those with active brain lesions. Specifically, vemurafenib achieved >30% intracranial tumor regression in 37% of patients with symptomatic brain metastases [43]. Vemurafenib has the longest OS rate (15.9 months) and a rapid response rate (>50%) in patients with previously treated metastatic melanoma [44].

The side effect profile of vemurafenib is relatively well tolerated. The most common adverse effects are fatigue (30%) and arthralgia (60%), which are primarily grade one or grade 2. The most significant adverse effect is its malignant potential. Cutaneous squamous cell carcinomas develop in nearly 25% of patients treated with vemurafenib, although the majority are keratoacanthomas [45]. If they do occur, they typically occur within the first eight weeks of treatment. Development of squamous cell carcinoma typically requires only excision and does not warrant any changes in vemurafenib treatment.

Despite its clinical efficacy, most patients develop resistance to vemurafenib by 6-7 months of treatment. This phenomenon is believed to relate to reactivation of the MAPK pathway (intrinsic pathway) or activation of the P13K/AKT/mTOR pathway (extrinsic pathway), [46, 47]. To address this resistance, dabrafenib (BRAF inhibitor) can be combined with trametinib (selective MEK inhibitor). This combination therapy generated a median progressive-free survival (11 months), significantly longer than dabrafenib alone (5.8 months), [48]. Objective response rate was also higher in the combination group (76%) as compared to dabrafenib alone (54%). The combination therapy also led to minimal squamous cell carcinoma development (7%).

Radiation

The radiotherapy utilization rate for melanoma in the United States ranges from 1-6% [49]. However, the proportion of patients for whom radiotherapy is indicated at some point in their disease process is

estimated to be nearly 23% of all melanoma patients. It is most widely applied as a stereotactic gamma knife for brain metastases. Despite the decreased use, radiotherapy is effective for palliation of non-CNS metastases and is indicated for symptomatic patients [50]. Median OS is 15.6 months for radiotherapy [51]. Prognostic factors conferring improved OS include age (<55 years old), oligometastatic disease, use of stereotactic body radiotherapy, and the ability to treat all lesions. The first in-human phase I study of the DNA-repair inhibitor DT01 in combination with radiotherapy in patients with skin metastases demonstrated excellent safety, with 30% of patients observing complete response [52].

One aspect of radiotherapy that has recently been observed is its ability to reduce tumor growth outside the direct field of radiation, a phenomenon described as the abscopal effect. The ionizing radiation activates inflammatory pathways that lead to dendritic cell activation of tumor-specific T cells [53]. A 2012 phase I study using stereotactic body radiotherapy followed by high dose IL2 lead to a 71.4% response rate for patients with metastatic melanoma [54]. This positive effect was mediated by a greater frequency of proliferating CD4+ T cells and supports the further investigation of CD4+ effector memory T cells as a predictor of response in treating metastatic melanoma. Multisite radiotherapy with checkpoint inhibitors yields 6-month and 1-year OS rates of 77.9% and 58.4%, respectively [55].

Experimental Options

Anti PD1

The programmed death 1 receptor (PD1) is expressed by CD8+ T cells. The PD1 ligand (PDL1) is expressed by tumor cells. When PD1 ligand binds PD1, inhibitory pathways are stimulated to allow cancer cells to protect themselves from immune-mediated cell death. This process is termed adaptive immune resistance [56]. Melanoma cells express high levels of PDL1 to avoid detection and cell death. Anti PD1 therapy serves to disrupt this PD1-PDL1 interaction to preserve the anti-tumor immune response [57].

There are currently two PD1 receptor antagonists used for melanoma, pembrolizumab and nivolumab.

Pembrolizumab achieved overall response rates of 26% at high dose (10mg/kg) and low dose (2mg/kg), with median OS of 7 months [58]. Nivolumab has a similar efficacy profile with an overall response rate of 32% [59]. Furthermore, the safety profile is excellent, with only 3% of patients reporting grade 3 or 4 adverse events that were all associated with fatigue.

Anti PD1 treatments appear to exert a synergistic effect with other melanoma therapies. Nivolumab in combination with ipilimumab have a confirmed objective response rate of 53-61% [60, 61]. In addition, the median progressive-free survival in patients with combination nivolumab and ipilimumab was 11.5 months as compared to 2.9 months for ipilimumab monotherapy and 6.9 months for nivolumab monotherapy. The synergistic effect is likely from their differential action on CTLA-4 and PD1 pathways. Even in patients with PDL1-negative tumors, the combination of PD1 and CTLA-4 blockade is more effective than monotherapy [62]. Combination therapies utilizing both anti CTLA-4 and anti PD1 are promising and will likely play a role in the future algorithmic treatment of metastatic melanoma. The primary adverse events include increased lipase, increased alanine aminotransferase, anemia, and fatigue.

Interferon

Interferons (IFN) exert their mechanism of action through activation of macrophages and upregulation of T cell antigen presentation [63]. However, the efficacy of IFN monotherapy for metastatic melanoma is unclear. One clinical trial of 24 patients utilizing intermediate-dose IFN α as a second-line treatment for recurrent cutaneous melanoma who were pretreated with low-dose IFN α produced poor results, wherein 70.8% of patients experienced progression of disease [64]. However, the authors noted that the patient population were likely unresponsive to IFN regardless of dosage level because they were unsuccessfully treated with low-dose IFN α . Additionally, nearly 30% of patients discontinued IFN because of intolerable toxicity.

The addition of IFN α to chemotherapeutic agents has been largely ineffective. Several phase III

studies have shown no OS benefit when combining IFN to dacarbazine, cisplatin, vinblastine, or temozolomide [65, 66]. Only one phase III clinical trial showed some benefit of adding IFN α to chemotherapeutic agents. Compared to chemotherapy agents alone, the combination of IFN α with cisplatin, vinblastine, and dacarbazine led to higher response rates (19.5% versus 13.8%) and longer median progression-free survival (4.8 versus 2.9 months), but did not extend OS (9.0 versus 8.7 months), [67].

One clinical trial showed benefit of adding IFN α to a polychemotherapy regimen for metastatic melanoma. Response rates were 48% for the combination therapy versus 25% for chemotherapy alone ($P < 0.001$), [68]. A combined meta-analysis of the 18 trials and 2,621 patients assessing the effect of adding IFN α with or without IL2 to a polychemotherapy regimen resulted in improved overall response rates, but this does not translate into improved survival [69]. In 2019, a large cohort study of 464 metastatic melanoma patients treated with interferon combined with high-dose IL2 showed an objective response rate of 25% with a median progression-free survival of 3.4 months and a median overall survival of 14.2 months with 5-year survival rate of 16.6% [70]. In a phase Ib/II study, pegylated-IFN α combined with pembrolizumab in patients with stage IV melanoma demonstrated an objective response rate of 60.5% and a median progression-free survival of 11.0 months [71]. All 43 patients in this study experienced an adverse event and 48.8% experienced a grade 3/4 treatment-related adverse event [71].

Imiquimod

Imiquimod is a toll-like receptor 7 agonist with potent antitumor effects. Through activation of the toll-like receptor 7 pathway, imiquimod induces the production of several important cytokines such as IFN α , tumor necrosis factor, and IL12 [72, 73]. The downstream effects result in mobilization of plasmacytoid dendritic cells and activation of their cytotoxic function. Additionally, imiquimod induces the downregulation of various angiogenic cytokines such as vascular endothelial growth factor, IL8, and

fibroblast growth factor to block tumor vascularization [74].

The evidence supporting imiquimod as monotherapy for cutaneous metastases is sparse. There are only case reports and case series describing imiquimod's effect as monotherapy for cutaneous melanoma metastases. Of the 18 total patients described in the literature, 83.3% of patients achieved a complete response [75, 76]. However, this result is likely influenced by reporting bias and larger-scale, randomized trials are necessary. Furthermore, subcutaneous and dermal melanomas are often resistant to imiquimod [77]. With the available literature, there is insufficient evidence to support the use of imiquimod monotherapy for cutaneous melanoma metastasis.

However, studies are emerging that describe imiquimod's use as adjunct therapy. Imiquimod as an adjuvant to a melanoma peptide-based vaccine in a small cohort ($N = 12$) increases T cell infiltration and immune activation compared to cancer vaccination alone in three of the four patients treated with both imiquimod and the vaccine [78]. IL2, when combined with imiquimod and tretinoin cream, increases local T cell responses, but the therapeutic mechanism still requires elucidation [79]. Imiquimod as an adjunct to local cryotherapy in locoregional cutaneous metastases of melanoma has a response rate of 65% [80]. Common adverse effects of imiquimod include localized dermatologic erythema and xeroderma as well as increased risk of local fungal infection and upper respiratory infection [75].

Adoptive T cell therapy

Adoptive T cell therapy involves injecting tumors with tumor-infiltrating T cells that have been selected in vitro to recognize melanoma antigens. Initially, this therapy showed promise and achieved objective response rates of 29-49% [81, 82]. However, its utility is limited by several factors. The challenge of generating enough tumor-specific lymphocytes in vitro that retain their cytotoxic activity in vivo has not been overcome [83]. Additionally, not all tumor-infiltrating T cells are tumor-specific and the preferential proliferation of tumor-specific lymphocytes without selecting for bystander T cells has proven too expensive and time-

consuming. Signs of toxicity include fever, tumor lysis syndrome, transient hypotension, and transient renal and hepatic insufficiency.

Vaccines

Vaccines play a role in melanoma treatment owing to their ability to activate systemic host immune responses against cancer cells. Melanoma vaccines can be categorized based on their composition: whole-cell, dendritic-cell, ganglioside, DNA, and peptide vaccines [84]. Traditionally, two of the most successful vaccines have been gp100 and MAGE-3 peptide vaccines because of their 11-16% response rate when combined with immunotherapy [85, 86]. Recently, oncolytic vaccines, which are modified herpes simplex viruses known as T-VEC, have shown promise with their ability to enhance tumor antigen release and presentation. Oncolytic vaccines also exhibit the abscopal effect, wherein treatment responses are seen in sites outside of the injection site. In a 2016 phase III study including 436 patients with stage III or IV melanoma, complete resolution of lesions occurred in 47% of injected lesions and 22% of uninjected lesions [87].

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Conclusion

Stage IV metastatic melanoma is a cancer that has spread beyond the skin and regional lymph nodes to distant organs or skin. Treatments for metastatic melanoma remained relatively poor and static until the early 2000s. Over the last 20 years, several new treatments and combination therapies have emerged for metastatic melanoma. The treatments with the greatest survival benefit include BRAF inhibitors (vemurafenib, dabrafenib), alone and in combination with MEK inhibitors, pembrolizumab, nivolumab, IL2, and ipilimumab. Radiation therapy and vaccines have shown promising results in clinical trials and will likely play a role in the algorithmic approach to metastatic melanoma treatment in the future.

Potential conflicts of interest

The authors declare no conflicts of interests.

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