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REVIEW

Current Trends of Immunotherapy in the Treatment of Cutaneous Melanoma: A Review

Piyu Parth Naik

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ABSTRACT

Cutaneous melanoma remains a severe public health threat, with annual incidence increasing slowly but steadily over 4 decades. While early-stage melanomas can typically be treated with complete surgical excision with favorable results, the development of metastatic cancer, which is related to a lower survival rate, is linked to the primary tumor's rising stage and other high-risk features. Even though the first discoveries of an immunological anti-tumor response were published about a century ago, immunotherapy has only been a feasible therapeutic option for cutaneous melanoma in the last 30 years. Nonetheless, for the treatment of various cancers, including metastatic melanoma, the area of cancer immunotherapy has made significant progress in the last decade. As a result, melanoma continues to be the subject of several preclinical and clinical investigations to further understand cancer immunobiology and test different tumor immunotherapies. Immunotherapy's resistance to radiation and cytotoxic chemotherapy is one of its most distinguishing features. Furthermore, the discovery of biomarkers will aid in patient stratification and management during immunotherapy treatment. In this article, we discuss current knowledge and recent developments in immune-mediated therapy of melanoma.

Keywords: Immunotherapy; Melanoma; Ipilimumab

Key Summary Points

Cutaneous melanoma remains a severe public health threat, with annual incidence increasing slowly but steadily over 4 decades. Immunotherapy has only been a feasible therapeutic option for cutaneous melanoma in the last 30 years

The pembrolizumab, nivolumab and ipilimumab have been approved by the FDA for melanoma treatment. The first FDA-approved immune checkpoint inhibitor in metastatic melanoma is ipilimumab, a human monoclonal IgG1 antibody against CTLA-4

High dosages of IL-2 and interferons are the most commonly utilized drugs in biological immunotherapy

The first class of immunomodulatory drugs to be used in the treatment of melanoma is cytokines. Indeed, the FDA has approved both IL-2 and IFN-α as adjuvant treatments for melanoma

P. P. Naik (✉)
Department of Dermatology, Saudi German Hospitals and Clinics, Dubai, United Arab Emirates
e-mail: drpiyu85@gmail.com

INTRODUCTION

Cancer is the world's second greatest cause of death, and it is a major public health concern. In 2021, 608,570 cancer deaths and 1,898,160 new cancer cases are predicted in the US [1, 2]. Cutaneous melanoma is a more severe form of the disease that develops when melanocytes change and become malignant. Melanoma is the most serious skin cancer. It is less prevalent than basal cell and squamous cell carcinomas [3]. In recent decades, the cutaneous melanoma incidence has risen dramatically. Melanoma is the ninth most common type of cancer and the second leading cause of death. Every year, > 100,000 new instances of melanoma are detected in the US, with around 9000 deaths occurring from the disease [4]. When melanoma is detected early, surgical excision of the tumor is linked to a better prognosis. On the other hand, surgery is no longer sufficient for people who have advanced or metastatic disease locally. Localized melanoma has a 99% 5-year survival rate, but distant metastases have a 20% 5-year survival rate [5].

- Melanoma is one of the most susceptible cancers to immune suppression. High tumor mutational burden due to production of cancer-testis antigens, ultraviolet (UV) light exposure and pathogen-associated antigens mimicking melanocyte lineage proteins are all possible explanations for the sensitivity of melanoma cells to immune system activation [6, 7]. In this case, the T cell response appears to be crucial in preventing melanoma. The tumor infiltrated lymphocytes (TILs) play a crucial role in the anti-tumor immune response formation, and a fraction of TILs in melanoma patients shows cytolytic activity against autologous tumors. They are also linked to a better chance of survival and a decreased risk of metastasis [8]. Immunotherapy, molecularly targeted therapy and cytotoxic chemotherapy are current systemic treatment options for individuals with metastatic melanoma. The therapeutic landscape for melanoma patients has evolved dramatically since 2011, with the approval of 11 new medicines and combination regimens. Immunotherapy drugs, in particular, have been linked to long-term survival in responding individuals and have become the standard of care in most melanoma patients [9]. Melanoma has high immunogenicity due to its high immunogenicity; therefore, immunotherapy is one of the most effective therapeutic options. The mechanisms of action of immunotherapy are targeted at specific targets in the immune response's counter-regulatory processes [10]. Several therapeutic trials aimed at generating a T-cell response with local or systemic immunomodulatory medications have been conducted in recent decades, such as interleukin (IL)-2 [11], interferon (IFN)-α [12], cancer vaccines [13] and adoptive cell transfer [14]. In this review, we discussed recent developments in the field of immune-mediated therapy of melanoma. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EPIDEMIOLOGY

Melanoma occurs in a moderately significant number of patients, with a global incidence rate of about 3 per 100,000 [15]. Globally, 352,000 new cases of melanoma were estimated to be diagnosed in 2015, with a 5 case per 100,000 age-standardized incidence rate. Melanoma led to the deaths of > 60,000 people worldwide [16]. Males have a higher incidence rate than females, and it is linked to a lower median age at diagnosis (57 years) than other solid tumors (65 years) [15, 17]. Australasia (54%), North America (21%) and Western Europe (16%) were found to have the highest incidence of melanoma [16]. Furthermore, the fact that global melanoma incidence rates are continuing to rise is highly alarming. There were about 225,000 new cases of melanoma in 2005, but by 2015, that number had risen to nearly 352,000, a 56% increase [18]. While incidence rates of melanoma in Australia and North America are beginning to settle down, in Eastern and

Southern Europe, they are still increasing [19]. As a result, melanoma is a significant cause of death and disease worldwide, necessitating new therapies and prevention strategies.

PATHOPHYSIOLOGY AND CLINICAL SUBTYPES

Melanoma's exact etiology is unknown [20]. However, the molecular and histological characteristics of the many melanoma subtypes have been extensively studied [21, 22]. Melanomas that develop from chronically sun-damaged skin (CSD) have been found to occur in anatomical sites such as the neck and head. Non-CSD melanomas, on the other hand, are located in anatomical regions with little sun exposure, including the extremities and trunk [20]. In general, non-CSD melanomas have less mutation than CSD melanomas [20, 22]. Melanomas are closely attributed to benign melanocyte neoplasms. Naevi (commonly known as moles) are these lesions, and elevated levels of naevi are thought to be a melanoma risk factor [20, 23]. Non-invasive melanoma, benign naevi and abnormal cellular characteristics in dysplastic naevi in situ are among these lesions [20, 24]. Melanoma in situ is a type of melanoma limited to the epidermis and has a 100% survival rate if wholly removed [24]. The American Joint Committee on Cancer's (AJCC) current melanoma staging system is based on an examination of the tumor (T), the presence of distant metastases (M) and the number of metastatic nodes (N) [25, 26]. The clinical stages of cancer are subsequently grouped, ranging from 0 to stage IV [25]. Because distant metastases are present, stage IV melanoma is characterized as metastatic melanoma, whereas metastases exclusively distinguish stage III melanoma in regional lymph nodes (LN) [27].

Malignant melanoma has traditionally been divided into four histopathological subtypes, but certain melanomas cannot be categorized totally into either group [28]. Furthermore, this classification is based on morphological and clinical factors; it has minimal predictive significance, although it helps identify the disease's many histological presentations [28]. The four main melanoma subtypes are as follows: nodular melanoma (NM), lentigo maligna melanoma (LMM), superficial spreading melanoma (SSM) and acral lentiginous melanoma (ALM) [29]. However, several new clinical subgroups have been identified in recent years. Melanoma from a blue naevus, desmoplastic melanoma (DM) and persistent melanoma are examples of these [28].

RISK FACTORS AND DRIVER MUTATIONS

Melanoma develops as a result of a complicated interaction between environmental and genetic risk factors. UV rays from tanning beds and UV solar radiations are the critical environmental risk factors to be concerned about [30, 31]. Individual risk factors include a family history of melanoma, elevated levels of melanocytic naevi and skin complexion [31, 32]. Melanomas have one of the highest mutation rates of all solid malignancies [33]. As a result, current research is focusing on the molecular profiles linked with specific subtypes of melanoma. It is crucial to distinguish between "driving" mutations, which offer a survival advantage, and mutations that have little or no influence on tumor growth are known as "passenger" mutations [34]. The ability to create targeted therapies based on cancer's mutational landscapes allows for significant improvements in clinical outcomes. In 2015, researchers from The Cancer Genome Atlas Network published an extensive study revealing that the first complete genetic classification system for cutaneous melanomas was developed [35]. The significantly mutated genes' patterns, namely triple wild-type (WT), neurofibromin 1 (NF1), RAS and BRAF, which is related to greater copy numbers and structural rearrangement abnormalities but lacks mutations in the three genes mentioned above, were used to create these four distinct subtypes. These subtypes do not predict the outcome, but they may aid in identifying the genetic abnormalities linked to melanoma, hence identifying possible molecular targets [35]. It was also surprising to learn that immune cellular infiltrates and immune gene expression were associated

with patient survival [35]. Although studies of the significant genetic anomalies in melanoma have been well covered elsewhere, this section will focus on a few of the most common driver mutations seen in cutaneous melanoma [20, 33, 36].

IMMUNOTHERAPY FOR CUTANEOUS MELANOMA

Tumor immunotherapy is the use of pharmacological medicines to induce or replace host anti-tumor immunity in cancer patients. Immunotherapy's cytotoxic chemotherapy and resistance to radiation are one of its most distinguishing features. Dacarbazine was previously the most effective treatment for melanoma, with an overall response rate (ORR) of 10–20%; however, there were no differences between dacarbazine monotherapy and combination treatment. For radiotherapy, no improved results have been documented. Despite the dismal clinical results, these approaches have been the main drivers in melanoma treatment for decades [37, 38]. Most immunotherapeutic drugs' mechanisms of action are unknown, but these treatments are significant for their capacity to provide a long-term benefit in a subset of patients [39]. In the metastatic situation, ipilimumab has been linked to a considerable increase in overall survival [40]. Several caveats must be considered while using immunotherapy. Even though therapy advantages might last for years, only a tiny percentage of patients respond.

Furthermore, immunotherapy's distinctive side effects, which are related to the induction of autoimmunity and pro-inflammatory-like states, may limit eligibility or provide clinical management issues [41]. In this case, the T-cell response appears to be crucial in preventing melanoma. Establishing an anti-tumor immune response requires TILs, and a fraction of TILs in melanoma patients show cytolytic activity against autologous tumors [8]. The various steps involved in the immunity cycle of cancer were represented in Fig. 1. Recently, the treatment of both metastatic and unresectable melanoma have dramatically changed by the programmed death-1 (PD-1) and immune checkpoint inhibitors (ICIs) against cytotoxic T lymphocyte antigen-4 (CTLA-4) as well as those at high risk for recurrence following resection (Table 1) [42, 43]. Unfortunately, ICI therapy is beset by issues such as the lack of predictive response indicators and primary and secondary resistance [44]. Combining immunotherapy approaches helps to enhance response and decrease resistance, while biomarker identification is crucial for better patient selection.

IMMUNE CHECKPOINT BLOCKADE (ICB)

Drugs that target the inhibitory receptors CTLA-4 and PD-1 to mediate ICB have been demonstrated to produce long-term responses in subsets of patients with cancers such as melanoma and renal cell cancer (RCC) [52, 53]. Antibodies targeting the PD-1 ligand, PD-L1, are also tested in clinical studies and have objective responses in various cancer types [54, 55]. To date, the Food and Drug Administration (FDA) has approved four mAbs for ICB therapy: (1) atezolizumab (αPD-L1), (2) pembrolizumab (αPD-1); (3) nivolumab (αPD-1); (4) ipilimumab (αCTLA-4) [56]. They have been approved treating a wide range of advanced and metastatic malignancies, including melanoma, which can range from resectable to metastatic and urothelial carcinoma (atezolizumab) [56, 57]. Pembrolizumab, nivolumab and ipilimumab have been approved by the FDA for melanoma treatment [58]. Because checkpoint receptors are critical in regulating autoimmunity, the most serious side effects linked with ICB medications including immune-related adverse events (IRAEs) are a group of autoimmune symptoms [59]. IRAEs are prevalent, with rates ranging from 90% in those receiving CTLA-4 antibodies to 70% in patients receiving PD-1/PD-L1 antibodies, and immunosuppressive medications must be used with caution in the clinic [59]. Biomarkers that can predict the efficacy of a specific ICB treatment are needed because ICB elicits objective responses in only a fraction of patients, or it is crucial to identify a

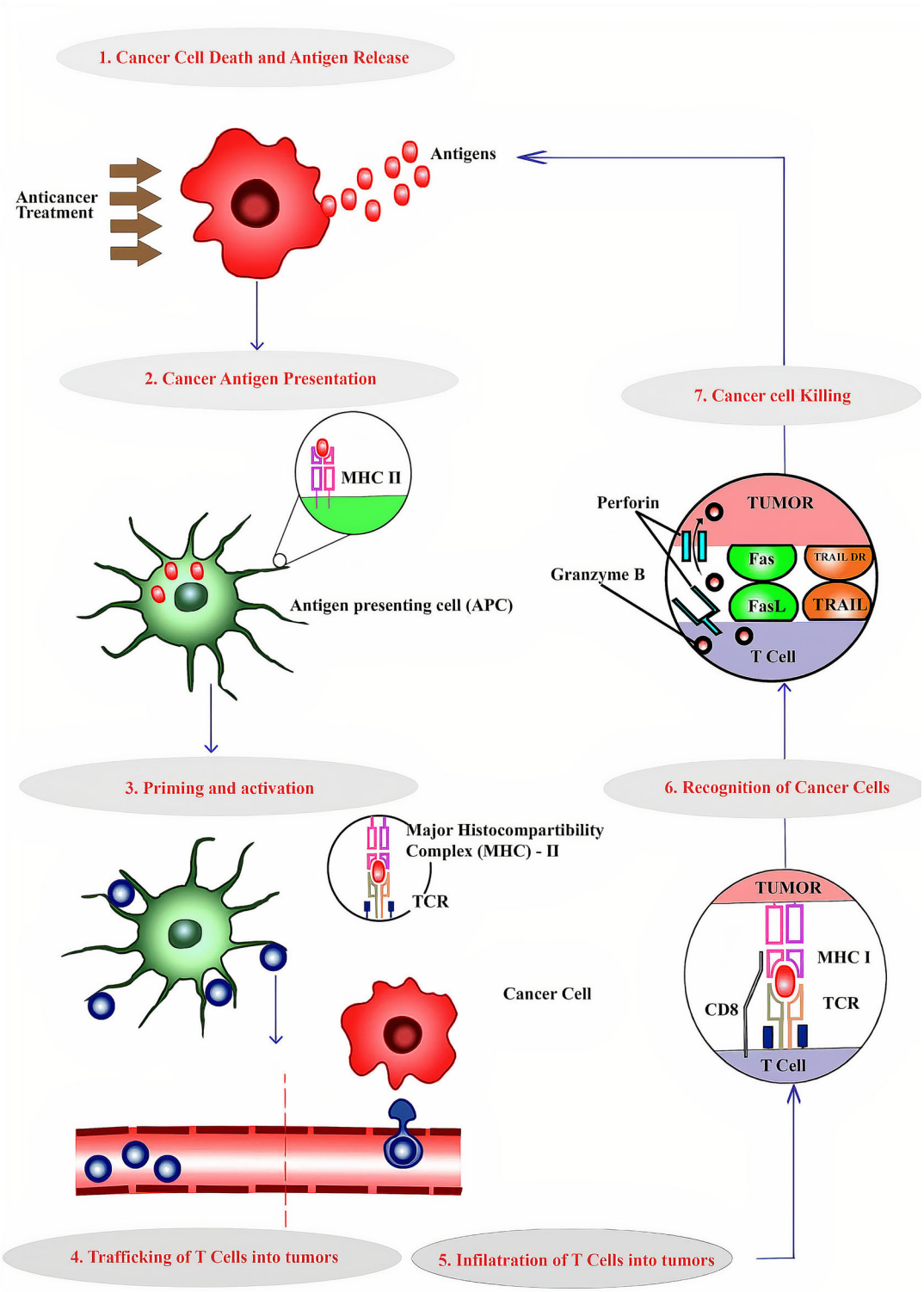

Fig. 1 Steps involved in the immunity cycle of cancer

subset of patients who could benefit from ICB therapy [60].

CTLA-4 BLOCKADE

After CD28 binding and activation, CTLA-4, a member of the CD28 superfamily, is activated. CTLA-4's specific ligands are B7-1 and B7-2. When CTLA-4 interacts with activated T cells, a downregulator signal is produced, which inhibits transcription of IL-2 and hence cell cycle progression [61, 62]. Ipilimumab is the most critical drug that inhibits CTLA-4 [47]; studies have indicated that this molecule has promising results and that the response is long-lasting, even after the treatment is stopped [63]. The first FDA-approved immune checkpoint

Table 1 Immunotherapy clinical trials in locally advanced and metastatic melanoma

Trial name	Primary outcome	Treatment arms	Median OS (months)	Median PFS (months)	ORR (%)	1 year-RFS (%)
KEYNOTE-006 [45, 46]	PFS, OS	Pembrolizumab q3w		4.1	32.9	–
		Pembrolizumab q2w	32.7a	5.6	33.7	–
		Ipilimumab	16	3.4	11.9	–
CheckMate 238 [47]	RFS	Ipilimumab	–	–	–	60.8
		Nivolumab	–	–	–	70.5
CA184-024	OS	Dacarbazine + ipilimumab	11.2	3	15.2	–
		Dacarbazine	9.1	3	10.3	–
EORTC1325/ KEYNOTE-054 [48]	RFS	Placebo	–	–	–	61
		Pembrolizumab	–	–	–	75.4
CheckMate 067 [49]	PFS, OS	Nivolumab + ipilimumab	NR	11.5	58	–
		Nivolumab	36.9	6.9	45	–
		Ipilimumab	19.9	2.9	19	–
CheckMate 066 [50]	OS	Dacarbazine	11.2	2.2	14.4	–
		Nivolumab	37.5	5.1	42.9	–
OPTiM [51]	Durable response lasting ≥ 6 months	T-VEC	23.3	Not reported	Not reported	–
		GM-CSF	18.9	Not reported	Not reported	–
CA184-002 [52]	OS	Ipilimumab	10.1	2.9	11	–
		gp100 vaccine	6.4	2.8	1.5	–
		gp100 Vaccine + ipilimumab	10	2.8	5.7	–

q2w every 2 weeks, *q3w* every 3 weeks, *NR* not reached, *RFS* relapse-free survival, *PFS* progression-free survival, *OS* overall survival, *ORR* overall response rate

inhibitor in metastatic melanoma is ipilimumab, a human monoclonal IgG1 antibody against CTLA-4. It was given four times at a 3 mg/kg dose every 3 weeks [47].

PD-1 BLOCKADE

PD-1 is an inhibitory cell surface molecule that reduces effector function and is expressed by activated T and B cells and natural killer lymphocytes [64, 65]. Studies have shown that PD-1 levels are higher in melanoma, implying a significant downregulation of activated T lymphocytes, which aids tumor cell survival [66, 67]. The presence of interferon-gamma-secreting cells from the microenvironment raises PDL-1 expression in melanoma. Pembrolizumab and Nivolumab target the interaction between PD-1 and its ligands PDL-1 and PDL-2. In melanoma, many trials comparing pembrolizumab and nivolumab to ipilimumab have found significant clinical effectiveness [68, 69]. The importance of measuring circulating PD-1 + regulatory T cells to predict treatment response to PD-1 blockers such as pembrolizumab and nivolumab was recently recognized by Gambichler and his co-workers. After starting treatment with PD-1 blocking antibodies, the researchers discovered that circulating PD-1 + Tregs rapidly fall, resulting in a lower probability of disease progression and metastatic illness [70].

COMBINATORIAL CHECKPOINT BLOCKADE

Despite the enormous effectiveness of ICB, only a tiny percentage of patients have long-term therapeutic responses [58, 71]. Immune checkpoint therapies' potency, on the other hand, has ushered in a new era of cancer treatment by allowing them to be combined with traditional cancer treatments like targeted molecular therapy, radiation and chemotherapy (e.g., BRAF/MEK inhibitors) [72, 73]. This section will primarily focus on the efficacy of combined checkpoint blockade therapy for melanoma. Despite this, no clinical data exist to distinguish between ICB and BRAFi/MEKi targeted therapy as first-line melanoma treatment, and a clinical trial (NCT02224781) is being done to compare clinical outcomes in patients who get checkpoint blockade drugs after targeted therapies vs. individuals who get targeted therapies after checkpoint blockade drugs [72].

TALIMOGENE LAHERPAREPVEC (T-VEC)

T-VEC is a genetically modified herpes simplex type 1 virus that selectively replicates in tumor cells, expresses granulocyte–macrophage colony-stimulating factor (GM-CSF) and increases MHC class I antigen loading to promote tumor antigen presentation by dendritic cells (DCs) [74]. In 2015, the FDA approved T-VEC for advanced melanoma. T-VEC was found to improve the response rate in unresected stage IIIB-IV melanoma patients in a phase 3 trial compared to GM-CSF (26 vs. 6%). Most of the reactions occurred only at the injection site and nearby non-injected lesions (primarily lung and visceral sites), while few reactions were recorded in distant non-injected lesions [75]. T-VEC and ICIs in combination have yielded promising outcomes. The ORR was improved in the phase II study of T-VEC + ipilimumab vs. ipilimumab alone in individuals with advanced melanoma (39 vs. 18%, respectively) [76]. In a phase Ib trial combining T-VEC with pembrolizumab, the verified objective response rate was 62%, with a complete response rate of 33% immune-related response criteria [77]. MASTER KEY-265/KEYNOTE-034, a phase III trial (NCT02263508) comparing T-VEC with pembrolizumab to pembrolizumab alone, is expected to publish its findings soon.

OTHER IMMUNOTHERAPY STRATEGIES

Biological Immunotherapy

The biological immunotherapy was the first used in the treatment of metastatic melanoma to replace or complete the action of

chemotherapy. High dosages of IL-2 and interferons are the most commonly utilized drugs in biological immunotherapy [78, 79]. Biological immunotherapy and stereotactic radiation are frequently combined [80, 81], although such combination techniques have yet to be validated, and except in clinical studies, only single-agent use is permitted; such combined techniques have yet to be proven.

Cytokines

The first class of immunomodulatory drugs to be used in the treatment of melanoma is cytokines. Indeed, the FDA has approved both IL-2 and IFN-α as adjuvant treatments for melanoma [82, 83]. In preclinical and clinical settings, cytokines such as GM-CSF and IL-12, 15, 18 and 21 have shown promising outcomes. Because of their pleiotropic action and high toxicity, especially at high doses, a single-agent cytokine method does not appear to be practicable [82]. In light of this, NTRK-214 is a human recombinant IL-2 conjugated prodrug with the same amino acid sequence. The core of IL-2 is attached to six releasable polyethylene glycol (PEG) chains in vivo, which progressively release in the presence of oxygen, resulting in active IL-2 conjugates [84]. The tolerance and efficacy of ipilimumab with nivolumab and NTRK-214 with nivolumab are analyzed in a phase I/II clinical trial (NCT02983045).

Adoptive Cell Therapy

To promote anticancer immunity, ex vivo modified cells are supplied directly to patients is known as adoptive cell therapy (ACT) [85, 86]. To date, most ACT clinical trials have used autologous TIL collected and grown from excised melanoma tissue [87, 88]. Other cell types, such as natural killer cells, have been explored for use in adoptive transfer therapy since the 1980s, but not as extensively as T cells [89]. As a result, the primary focus of this section will be on T cell ACT research. This approach has the advantage of allowing tumor-specific cells to develop ex vivo without being impacted by the immunosuppressive tumor microenvironment (TME), and they may be given in large enough doses to cause tumor regression [86]. As previously indicated, Rosenberg and colleagues pioneered this field by utilizing autologous TIL from metastatic melanoma patients, which generated long-term anticancer responses [90]. Since then, advances in molecular biology have enabled the identification of a variety of tumor antigens as well as the production of genetically altered T cell products with chimeric antigen receptors (CARs) or tumor-specific T cell receptor (TCR) [86, 91].

IDO Inhibitors

Indoleamine 2,3-dioxygenase 1 (IDO1) is an enzyme involved in tryptophan degradation that has a significant immunosuppressive effect within the TME. Several IDO inhibitors (BMS-986205, indiximod and epacadostat) are now being studied in combination with pembrolizumab, nivolumab or ipilimumab clinical trials [5]. Unfortunately, in phase III clinical trial ECHO-301/KEYNOTE-252, which compared epcadostat to pembrolizumab alone with pembrolizumab in advanced melanoma, the pembrolizumab with epcadostat group failed to show a PFS benefit [92].

Cancer Vaccines

Infectious disease vaccination is a pivotal point in human medicine. Cancer vaccines aim to activate the immune system, particularly the T cells, to attack the tumor by combining the tumor antigen with an adjuvant [93]. The vaccines might be a single-target antigen or polyvalent, with autologous tumor lysates or whole allogeneic cells [94]. To date, no vaccination combination has exhibited the same effectiveness in established malignancies as checkpoint blockade or ACT [93, 95]. Metastatic melanoma patients who received IL-2 and a gp100 peptide vaccine fared better than those who received only IL-2, according to research by Schwartzentruber et al. published in 2011 [94, 96]. However, cancer vaccination for solid tumors is particularly problematic because of

Table 2 Key immunotherapeutics and their primary mechanisms of action

Treatment	Mechanism(s) of action	Clinically tested agents	References
Cytokines			
Interferon alpha	Activate multiple facets of immunity and has direct effects on tumor cells	Interferon alfa 2b (Intron A, Sylatron™)	[97, 98]
Interleukin-2	Activates and expands T cell	Aldeslesukin (proleukin)	[99, 100]
Vaccines			
Oncolytic viral vaccines	Viral induction of tumor cell lysis and adjuvant medical host immune activation	Talimogene laherparepvec (T-VEC/Imlygic™)	[51, 101]
Peptide vaccines	Induction of tumor-specific adaptive immunity	Various tumor antigen peptides/ lysates + adjuvant)	[93, 95]
Cell-based vaccines	Induction of tumor-specific adaptive immunity	Tumor cells or activated DC/ APC	[102, 103]
Adoptive T cell therapy			
Engineered T cells	Infusion of engineered T cells specific for tumor antigens	Transgenic TCR or CAR bearing T lymphocytes	[86, 87]
TIL	Infusion of pool anti-tumor T cells	Ex vivo expanded TIL	[85, 86]
Immune activating mAbs			
αLAG-3	Blockade of T cell surface inhibitory molecule	BMS986016	[58]
αKIR	Blockade of NK cell inhibitory receptor	Lirilumab	[104, 105]
αCD137 (4-1BB)	Against of T cell costimulatory receptor	Urelumab	[106]
αPD-L1	Blockade of inhibitory checkpoint ligand expressed on immune cells and tumor cells	Atezolizumab, durvalumab, avelumab	[58, 66],
αPD-1	Blockade of inhibitory checkpoint receptor	Nivolumab (Opdivo), pembrolozumab (Keytruda),	[57, 58]
αCTLA-4	Blockade of T cell checkpoint receptor Depletion of intratumoral Treg	Ipilimumab (Yervoy)	[58, 71]

the immunosuppressive TME and a constantly expanding tumor-targeted immune escape [95]. Several key immunotherapeutics and their primary mechanisms of action are presented in Table 2.

Immunotherapy Biomarkers

The success of targeted therapy is based on the presence of a specific tumor feature, such as the BRAF V600 mutation, that drives tumor growth and serves as a specific biomarker of response to treatment that targets the aberrant pathway. Primary and secondary resistance to targeted therapy in melanoma is challenging to solve, and various researchers have attempted to improve BRAF V600 detection of prognostic and predictive indicators [107, 108]. Despite extensive attempts, biomarker response to melanoma immunotherapy, notably ICIs, approved for

clinical use, is lacking. This is especially crucial because of the relatively low response rate of immunotherapy. In clinical trials, including inhibitors of the PD-1/PD-L1 axis, immunohistochemistry (IHC) labeling of PD-L1 expression has been employed as a biomarker. The role of PD-L1 in patient stratification has yielded conflicting results across trials using PD-L1 IHC antibodies with non-homogeneous cut-off values [68, 109]. Although PD-L1 is not currently considered a good stratification marker, it needs additional investigation because it could reveal biological insights [72]. To better characterize the TME and establish predictive immunotherapy biomarkers, more comprehensive models are being investigated.

In this respect, Tumeh et al. [72] observed that near the invasive tumor margin, CD8 + T lymphocytes are present that trigger elevation of expression of PD-L1 on melanoma cells, which may better explain responsiveness to anti-PD-1 mAbs or primary resistance. As a response marker, a gene-expression profile has been proposed [110]. The primary mediator of anti-tumor inflammation is IFNγ, which is secreted by CD8+ T cells. A gene expression profile known as 'T-cell-inflamed tumor' has been linked to responsiveness to various immunotherapies, including cancer vaccines, ICIs and IL-2 [111, 112]. Moreover, primary and secondary resistance to PD-1/PD-L1 pathway inhibitors is associated with a low IFNγ gene expression signature that can be mediated by activation of PTEN and WNT/β-catenin pathway, impairment of JAK2 signaling or alteration of antigen presentation through structural or functional impairment of MHC class I mediated antigen presentation [113, 114]. The most considerable complete exome and transcriptome sequencing research of tumor samples from metastatic melanoma patients using ICI has been published [115]. The findings back up the correlations between treatment response and baseline immune infiltrate. However, they also show that tumor mutational burden has inconsistent associations and that transcriptomic features and multiple novels genomic, including features associated with MHC-I and MHC-II antigen presentation, can predict selective response. In addition, the researchers developed predictive models that included transcriptomic, genomic and clinical data to identify melanoma patients who were intrinsically resistant to anti-PD1 mAb [115]. A growing number of researchers seek to connect ICI efficacy to circulating tumor DNA PD-L1 expression levels [116, 117]. Several studies have suggested that measuring matrix metalloproteinases (MMPs), which are known to play a vital role in melanoma progression, could be a reliable predictor of immunotherapy response [118, 119]. Adjuvant immunotherapy was used to treat primary melanoma tumors; Moogk et al. [120] discovered that the MMP-23 expression and anti-tumor T-cell response have an inverse association. According to the authors, MMP-23 expression is correlated with shorter PFS, so it could be a viable therapeutic target in melanoma and a biomarker for monitoring melanoma patients' immunotherapy response.

CONCLUSION

Over the last decade, significant advancements in melanoma treatment have been made. Immunotherapy is a well-established treatment option for melanoma patients, with some individuals experiencing long-term benefits. Researchers' tireless efforts have given information on key pathways in melanoma biology, paving the way for targeted treatment and immunotherapy. These drugs have distinct modes of action and toxicity profiles, necessitating careful patient selection and management. Tumor immunotherapy, when used correctly, can provide significant benefits to melanoma patients.

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