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Immunotherapy in skin cancers – A narrative review

V. T. Anjali[1], Feroze Kaliyadan[1]

[1]Department of Dermatology, Sree Narayana Institute of Medical Sciences, Kunnukara, Kerala, India.

***Corresponding author:**
Feroze Kaliyadan,
Department of Dermatology,
Sree Narayana Institute of Medical Sciences, Kunnukara, Kerala, India.

ferozkal@gmail.com

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ABSTRACT

Immunotherapy, in the context of cancers, involves the use of various drugs to stimulate the immune system to target cancer cells. Immunotherapy is being increasingly used for cutaneous malignancies, especially melanoma. Immunity plays an important part in protection against cancer. One of the factors limiting the effectiveness of host immunity is improper recognition of cancer cells. Sometimes, despite recognizing the cancer cells as abnormal, the immune response, for various reasons might not be strong enough to deal effectively with the cancer cells. Immunotherapy basically tries to address the two points mentioned above by improving the capacity of the immune system to recognize and effectively destroy cancer cells. In skin cancers, immunotherapy is best established for melanomas, but is increasingly being used for non-melanoma skin cancers too. This article reviews some of the general concepts about immunotherapy in cancer and discusses in detail, the available options and future possibilities in the applications of immunotherapy in skin cancer.

Keywords: Immunotherapy, Melanoma, Non-melanoma skin cancers, Squamous cell carcinoma, Basal cell carcinoma

INTRODUCTION

The body's natural immunity plays an important part in protection against cancer. However, there are limitations in the effectiveness of immune responses against cancer cells. This could be due to various reasons:

- Problem in recognition of cancer cells: Especially in initial stages, our immune response may not recognize the cancer cells as abnormal. Cancer cells can also subvert immune checkpoints to prevent recognition.
- The immune response might recognize cancer cells, but may not be strong enough to deal effectively with them.

Immunotherapy addresses the two points mentioned above, enabling our immunity to work more effectively against cancer cells.

TYPES OF IMMUNOTHERAPY

Passive immunotherapy

The following therapeutic options come under passive immunotherapy.

- Clonally expanded tumor specific T cells
- Immunomodulators - drugs that help in boosting the immune response against specific types of cancer cells

- Specific cytokines to target cancer cells
- Monoclonal antibodies that target specific components of cancer cells.

Active immunotherapy

Active immunotherapy induces better, long term immunity against the tumor. The active immunotherapy options include:

- Cancer vaccines (like traditional vaccines, trigger an immune response against specific types of cancer cells)
- Oncolytic viruses (viruses modified to infect and destroy specific tumor cells)
- Checkpoint inhibitors
- Chimeric antigen receptor T cell therapy (CART).

The immune system has inbuilt checkpoints to prevent destruction of "self" antigens. Cancer cells sometimes make use of these checkpoints to protect themselves from the immune response. Checkpoint inhibitors, as the name suggests, target the checkpoint proteins and enable the immune system to more effectively recognize and act on the cancer cells.

CART: T cells are taken from the patient, and genes for receptors related to the cancer (chimeric antigen receptor) are added to these cells. When reinfused into the patient's blood, these modified T cells bind to the cancer cells and kill them.

Immunotherapy has been used in virtually all types of skin cancers, both melanoma, and non-melanoma.[1-12]

Usually, immunotherapy starts showing response within a few weeks. Candidate selection for immunotherapy depends on various factors like type of cancer, stage of cancer, biomarkers expressed by cancer cells, and evolving treatment guidelines. Programmed cell death receptor ligand 1 (PD-L1) expression, high microsatellite instability or high tumor mutational burden and advanced cancers unfit for other treatment options are all regarded as candidates for immunotherapy. Though immunotherapy is mainly indicated for the treatment of advanced cancers, many trials have been conducted in the treatment of non-metastatic, early-stage cancers for the achievement of prolonged outcome without the long-term side effects associated with chemotherapy. There is no exact cut-off point for stoppage of these drugs. Duration depends on the response to each drug and the development of side effects that require temporary cessation. Besides this, the high cost (running into lakhs) is a major limiting factor for continuing treatment.[13]

IMMUNOTHERAPY IN MELANOMA

Immunotherapy plays a major role in the treatment of melanoma.[13] The different types of immunotherapy used in melanoma are described below in detail.

IMMUNE CHECKPOINT INHIBITORS (ICI'S)

These drugs help to prime anti-tumor immune response via checkpoint receptor inhibition on melanoma cells and immune cells. They include anti cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) inhibitors, anti-programmed cell death protein 1 (PD-1) inhibitors and anti-PD-L1 inhibitors.[13]

Anti cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) inhibitors

Ipilimumab, a fully humanized monoclonal IgG1 antibody that targets and blocks CTLA4 was the first treatment modality approved by Food and Drug Administration (FDA) in 2011 for advanced melanoma and showed overall response rates <20%, but a significant long term survival in a few cases.[14-16] Ipilimumab when used as an adjuvant therapy increased relapse-free interval and overall survival rates. It is administered intravenously in unresectable or metastatic melanoma in adults and children aged ≥12 years in a dose of 3 mg/kg every 3 weeks for a maximum of 4 doses. Side effects were mainly due to immune-mediated T-cell activation and consisted of hepatitis, colitis, skin rashes, and rarely hypophysitis.[17,18]

Anti-PD-1 inhibitors

Nivolumab and pembrolizumab were approved by FDA in 2014 for the treatment of metastatic malignant melanoma and showed overall response rates of 30–40%.[19-23] Pembrolizumab therapy showed better progression free survival and overall survival compared to ipilimumab.[22,24] Adjuvant monotherapy using pembrolizumab or nivolumab is the preferred treatment in resected, stage IIIB to IIID disease. This treatment has less side effects and increased relapse free interval. Nivolumab is administered in a dose of 240 mg intravenously (I/V) every 2 weeks, until stoppage of disease progression or development of intolerable toxicity. Immune-mediated side effects included thyroid disorders (hypothyroidism or hyperthyroidism), Stevens-Johnson syndrome, pneumonitis, and hepatitis. Combination of nivolumab (1 mg/kg I/V) followed by ipilimumab on the same day, every 3 weeks for 4 doses and 240 mg nivolumab every 2 weeks, until disease progression or intolerable toxicity, was approved by FDA, based on high overall response rates.[25] Anti-PD-1 inhibitor resistance noticed in a few cases was overcome by anti-CTLA4 monotherapy or combination treatments. Combination treatment, though having higher response rates, has the disadvantage of higher immune-related side effects.[19-21,26-28] Many cutaneous melanoma patients with intracranial metastasis also benefited from combination therapy.[29]

Anti-PD-L1 inhibitor

Atezolizumab is a fully humanized anti-PD-L1 antibody approved by FDA in 2020 in combination with cobimetinib and vemurafenib for the treatment of patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma. Most common side effects of this combination therapy include pyrexia, rash, edema, itching, stomatitis, musculoskeletal pain, nausea, fatigue, hepatotoxicity, hypothyroidism, and photosensitivity. The recommended dosage is a 28-day cycle of vemurafenib and cobimetinib followed by atezolizumab 840 mg intravenous infusion every 2 weeks with cobimetinib 60 mg orally once daily (21 days on/7 days off) and vemurafenib 720 mg orally twice daily.[30]

TARGETED THERAPIES

BRAF inhibitors and MEK inhibitors

The BRAF inhibitors such as dabrafenib, encorafenib, and vemurafenib and MEK inhibitors such as trametinib, binimetinib, and cobimetinib act by inhibition of mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) overactivation in BRAF V600E-mutant melanoma.[31,32] Patients with mutations in MAPK/ERK pathway respond well to treatment with BRAF and MEK inhibitors, but many cases tend to become treatment resistant in a year.[33-35] Most common side effects of BRAF and MEK inhibitor combination therapy are fever, widespread acneiform rash, alopecia, palmar-plantar hyperkeratosis, arthralgia, diarrhea, hepatic toxicities, cardiovascular toxicities (hypertension, QT-prolongation), and ocular side effects (uveitis and retinal detachment). Rarely pneumonitis, and cutaneous squamous cell carcinoma (SCC) may occur.[36]

Intra-tumoral immunotherapy and various combination therapies

Oncolytic viruses

ONCOS-102, an engineered oncolytic adenovirus expressing granulocyte-macrophage colony-stimulating factor (GM-CSF) acts by causing oncolysis and immune activation by GM-CSF. Talimogene laherparepvec (T-VEC), a modified herpes simplex virus Type 1 (HSV-1) is the first genetically approved virus for treating cutaneous melanomas. It acts by inducing oncolysis and via activation of anti-tumor immune response through interferon (IFN) signaling. Combination treatments of T-VEC with ICI's or BRAF/MEK inhibitors in cutaneous melanoma have shown higher overall response rates compared to monotherapy.[37-39]

Intra-tumoral interleukin-2 (IL-2) is a well-tolerated treatment for cutaneous melanoma with less systemic side effects due to its higher local action compared to systemic IL-2 therapy. It acts via stimulation of tumor immune response. Tavokinogene telseplasmid, a synthetic plasmid that encodes IL-12, acts via stimulating differentiation and causing activation of the adaptive immune system. It was used as an orphan drug in the treatment of unresectable metastatic melanoma.[40-43]

Various studies have evaluated intra-tumoral approaches such as pattern recognition receptor agonists, Toll-like receptor (TLR) agonists, and stimulator of IFN genes (STING) agonists. SD-101, IMO-2125, and CMP-001, are TLR9 agonists under investigation in combination treatments. TLR9 agonist acts by induction of CD8+ T cell response enhancing destruction of cancer cells. STING agonists such as ADU-S100 and MK-1454 formulated cancer vaccines can cure established tumors resistant to PD-1 blockade, via activation of type I IFN signaling.[44,45]

Anti-angiogenic immunotherapy for the treatment of cutaneous melanomas

Abnormal angiogenesis and increase in vascular endothelial growth factor (VEGF) are important mechanisms in melanoma growth and metastasis. Anti-VEGF inhibitors like bevacizumab are used in combination with other drugs for treatment of advanced melanoma. VEGF decreases in old age, thus decreasing the efficacy of treatment with anti-VGEF inhibitors.[46,47]

Adoptive cell therapy

Dendritic cell-based vaccine (Sipuleucel T) has the ability to harness natural killer cell dependent and cytotoxic T lymphocyte dependent immune response and showed an objective response rate of 8–15% and overall survival of 20% in melanoma patients.[48-50]

Tumor infiltrating lymphocytes (TIL's)

TIL is another modality of immunotherapy developed to treat melanoma and showed an overall objective response rate of 49–72% and more than 5 years remission.[51-54] Combination therapy with radiotherapy or conventional chemotherapy was found to be more effective. Major hurdles faced in TIL treatment included the availability of highly trained medical staff to perform surgery to expand tumor cells, restricted availability of patient's own tumor cells, and high cost of the procedure.[55-58]

Recombinant antibody-drug conjugates

Recombinant antibody-drug conjugates specifically detect and destroy melanoma cells overexpressing epidermal growth factor receptors. They are developed in the form of single-chain fragment variable-SNAP-tag fusion proteins conjugated to chemicals like auristatin F.[59-60]

Photoimmunotherapy

It is a light-dependent targeted therapy for the treatment of primary and metastatic tumors using antibody photoconjugates.[61,62] Main mechanism is excitation of near-infrared rays at approximately 690 nm causing penetration into cancer tissues.[63,64] It could activate systemic anti-tumor immune response which is helpful in the management of metastatic malignant melanoma. There are no off-target side effects, but monotherapy has even resulted in resistance to checkpoint inhibitors.[65]

IMMUNOTHERAPY IN NON-MELANOMA SKIN CANCERS

About 30% of skin cancers are non-melanoma skin cancers like SCC, basal cell carcinoma (BCC), Merkel cell carcinoma (MCC), and adnexal tumors. MCC, though rare, is the most aggressive non-melanoma skin cancer whereas BCC and cutaneous SCC respond well to surgery and radiotherapy.

SCC

A summary of available immunotherapy options for non-melanoma skin cancers is given in Table 1.[1] Cutaneous SCCs are most amenable to programmed cell death blockade.[66,67] ICI's like anti-PD-1 and anti-PD-LI inhibitors reactivate the pre-existing anti-tumor response and cutaneous T lymphocyte mediated tumoricidal responses. Pembrolizumab, a PD-1 targeted antibody used in the treatment of recurrent or metastatic cutaneous SCC has shown nearly complete tumor regression after 4 cycles of treatment in patients with treatment-refractory metastatic cutaneous SCC.[68,69] Nivolumab showed 6–19.5 months progression-free survival in seven patients with cutaneous SCC and complete remission in poorly differentiated, advanced, cutaneous SCC treated with nivolumab and cetuximab. Cemiplimab, an anti-PD-1 antibody showed an overall response rate of 44% and 34.3–47% in locally advanced and metastatic SCC respectively.[70,71]

BCC

Hedgehog pathway dysregulation via mutation in PTCH1/SMO gene is the most important mechanism in BCC. In phase II ERIVANCE Trial, vismodegib showed an overall response rate of 47.6% in locally advanced BCC and 33.3% in metastatic BCC after 12 months of treatment.[72,73]

Other immunotherapy modalities used in the treatment of superficial BCC include 5- fluorouracil (an antimetabolite) and imiquimod (a TLR agonist). Locally advanced and metastatic BCC are treated with hedgehog inhibitors such as vismodegib and smoothened inhibitors such as sonidegib phosphate.[1] Besides this, vismodegib also plays an important role in the treatment of Gorlin syndrome characterized by multiple BCC, in which radiotherapy is contraindicated.[74] Cemipilimab, a PD-1 targeted antibody, is used in locally advanced or metastatic BCC refractory to other treatments.[1]

MCC

Efficacy of chemotherapy in MCC is short lived and immunotherapy is considered as the first-line systemic therapy for advanced MCC. Nivolumab, though not approved in advanced MCC, has shown promising results in Phase I/II trials. Anti-PD-L1 agents such as avelumab and pembrolizumab are used in the treatment of metastatic MCC. Avelumab is FDA approved in 2017 for metastatic MCC in patients ≥12 years, irrespective of cryotherapy.[75,76] Pembrolizumab, a PD-1 targeted antibody is used in recurrent, locally advanced or metastatic MCC.[77]

Other immunotherapy methods in non-melanoma skin cancer

Cytokines

IFNα2a and IFNα2b inhibit malignant cell growth and initiate apoptosis by CD95 ligand and CD95R interactions. Intralesional IFN is recommended for patients who cannot be treated by surgery.[78] IFNα directly induces apoptosis in some cases of SCC. Major disadvantages are the need of frequent injections, systemic side effects, and cost of therapy.

Adoptive T cell therapies against various tumor-associated antigens (TAA's)

Tumor-specific T cells, derived from the blood of the patient or the tumor is infused. Cancer testis antigens (CTA) is a tumor-specific antigen without systemic toxicity. At least 1 CTA was expressed in 40% SCC and 81% BCC.[79] The tumor cells that do not express the antigen show lack of response to treatment.

Peptide vaccines

MAGE–A3/human papilloma virus 16 vaccine for SCC of head and neck is under phase I clinical trial and its ability to stimulate antigen-specific CD4+ and CD8+ T cell responses is being studied. Major difficulty is finding suitable antigen peptides to produce these vaccines.[80]

Therapeutic cancer vaccines

Therapeutic cancer vaccines act by boosting the immune response against non-melanoma skin cancer. Antigens in these vaccines are present on tumor cell surface and are recognized by T cells.[81,82]

Table 1: FDA-approved agents for non-melanoma skin cancers.

Drug	Mechanism	Dose and Frequency	FDA approval
5-Fluorouracil	Anti-metabolite	5% cream twice daily for 3-6 weeks	1975–06–30 for superficial BCC
Imiquimod	TLR agonist	5% cream, 5 times/week for 6 weeks	2004–07–14 for superficial BCC
Vismodegib	Hedgehog inhibitor	150 mg daily orally	2012–01–30 for locally advanced/metastatic BCC
Sonidegib phosphate	Smoothened inhibitor	200 mg orally	2015–07–24 for locally advanced BCC
Cemiplimab	PD-1 targeted antibody	350 mg infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity	1.2021–02–09 for refractory locally advanced/metastatic BCC 2.2018–09–28 for locally advanced/metastatic cSCC
Pembrolizumab	PD-1 targeted antibody	200 mg intravenously every 3 weeks or 400 mg intravenously every 6 weeks for cSCC 200 mg, intravenous infusion over 30 minutes every 3 weeks for MCC	1.2020–06–24 for recurrent/metastatic cSCC, not curable by surgery or radiation 2.2018–12–19 locally advanced/metastatic MCC
Avelumab	PD-L1 targeted antibody	10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks	2017–03–23 metastatic MCC

FDA: Food and Drug Administration, TLR: Toll like receptor, PD-1: Programmed cell death protein-1, PD-L: Programmed cell death receptor ligand, BCC: Basal cell carcinoma, cSCC: Cutaneous squamous cell carcinoma, MCC: Merkel cell carcinoma

DNA vaccines

Multiple antigenic targets or multiple cytokines are inserted into a single DNA vector and induce cell-mediated and humoral immune response. A phase II clinical trial assessing the effectiveness of a combination of intra-tumoral interleukin-12 gene and *in vivo* electroporation-mediated plasmid deoxyribonucleic acid vaccine therapy in the treatment of MCC is ongoing.[83] Difficulty in maintaining adequate level of tissue expression of plasmid-encoded protein is a major disadvantage.

Dendritic cell (DC) based strategies

DC based therapies are recently employed in the treatment of cutaneous T cell lymphoma.[84] DCs are incubated with tumor antigens such as peptides or undergo genetic modification to produce mature DCs that have the ability for increased antitumor immune response. TLRs are expressed on DCs for initiating adaptive immunity. Epicutaneous immunization is application of DCs to larger area of skin resulting in increased entry of immunogenic DC's into the regional lymph nodes and has increased immunogenic potential.[85]

Agents targeting immune system pathways

Imiquimod is the first synthetic immune response modifier used for topical treatment of small nodular BCC and SCC in situ. Imiquimod acts by binding to DC receptors TLR7 and TLR8 and via promotion of secretion of cytokines, proliferation of B lymphocytes, activation of Langerhans cells and migration to lymph nodes, stimulation of natural killer cells, and activation of caspases. Side effects are mainly local skin site reactions like flaking, scaling, induration, edema, erythema, scabbing, crusting, erosion, itching and burning, all of which generally decrease in intensity or resolve, once the therapy is stopped.[86]

Synthetic oligonucleotides

Intralesional injection of PF-3512676, a CpG oligodeoxynucleotide showed tumor regression and increase in IL-6 and IFN-Y.[87]

Cancer virotherapy

ONYX-015, a conditionally replicative adenoviral E1B deletion mutant and HF-10 (oncolytic HSV type I) mutant used in the treatment of SCC showed tumor regression.[88]

CONCLUSION

To conclude, immunotherapy has opened new and exciting frontiers in the treatment of both melanoma and non-melanoma skin cancers. While the number of options and available evidence are higher in the case of melanomas, immunotherapy might gradually become more pervasive and effective in the treatment of non-melanoma skin cancers too.

Declaration of patient consent

Not required as there are no patients in this article.

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Conflicts of interest

Dr. Feroze Kaliyadan is on the editorial board of the Journal.

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