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Anti-PD-L1/PD-1 Immunotherapy for Treatment of Non-Melanoma Skin Cancer Basal Cell Carcinoma

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Abstract

Background: Non-melanoma skin cancer is a type of cancer that usually affects white people, has genetic susceptibility, and has a high impact of UV exposure. Basal cell carcinoma is the most common non-melanoma cancer. There are various risk factors for skin cancer, which impact genetic changes in the skin. This cancer treatment can be supported through immunotherapy with anti-PD-L1/PD-1 therapy to increase the effectiveness of long-term healing. This immunotherapy has the potential to block the interaction of PD-1 with PD-L1 in inactivating anticancer cells. This study aims to determine the role of anti-PD-L1/PD-1 immunotherapy as a treatment solution for non-melanoma skin cancer, basal cell carcinoma type. **Methods:** The research method used is Literature review, through search and library research to understand the topic. This article focuses on the integumentary system, non-melanoma skin cancer, and basal cell carcinoma. And anti-PD-L/PD-1 immunotherapy. **Results:** Skin cancer Basal cell carcinoma attacks the basal cells of the epidermis slowly, but when neglected, it spreads more widely and severely. Immunotherapy aims to inhibit the binding of PD-L1 with the PD-1 receptor so that the immune response of T lymphocytes and other anticancer cells is active. **Conclusions:** active anti-PD-L1/PD-1 immunotherapy inhibits the binding interaction between PD-L1 and the PD-1 receptor to influence anticancer activity. Anti-PD-L1/PD-1 immunotherapy plays a role in suppressing the growth, destroying, shrinking cancer cells, and increasing the body's immunity against cancer.

Keywords: Anti-PD-L1; KSB; non-melanoma; skin cancer

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Introduction

Skin is a vital organ that reflects human health. The skin is a complex, elastic, and sensitive organ (Tan, Ghaznawie, & Reginata, 2016). Human skin has various essential functions for the body, primarily to protect the body from external elements (Sagoyo, Widodo, & Dachlan, 2017). One of the diseases that can attack the skin is cancer skin. Skin cancer is a skin disease that ranks third in the highest number of sufferers after breast cancer and uterine cancer (Dewi, 2017). Cancer non-melanoma skin is a type of cancer fierce as usual, attacks skinned people with white, vulnerability genetics, and covers the area with exposure to high UV intensity (Griffin, Ali, & Lear, 2016).

Skin cancer is not only experienced by women but also men. Skin cancer is considered dangerous, although the percentage of death cases in skin cancer patients is relatively low (Wilvestra, Lestari, & Asri, 2018). Skin cancer occurs when the skin loses its ability to regenerate and protect itself (Raflizar & Nainggolan, 2010). In the case of non-melanoma skin, there are various risk factors for this type of cancer, leading to something changing genetics in the skin (Paolino, Bottani, & Cantisani, 2018). Carcinoma basal cells are cancer,

the most common non-melanoma type suffered and aggressive at one lesson by histology followed cancer carcinoma cell squama (Ciazynska, et al., 2021). Risks and symptoms of basal cell carcinoma of the skin ignored consequence of lack of knowledge to condition beginning cancer skin. Patients do not realize the urgency of their situation and do not act on medical and immediate treatment. Skin cancer treatment requires extraordinary measures, primarily through chemotherapy or radiotherapy (Fitriatuzzakiyyah, Sinuraya, & Puspitasari, 2017). Handling others can also be supported through immunotherapy with the application of therapy - PD -L1 /PD-1 to increase the long-term healing effectiveness. According to Lipson, et al., (2017), using antibody monoclonal as targeted immunotherapy _ for controlling tumor growth shows full potential and benefits _ in blocking protein interactions inspection immunity (PD-1 and PD-L1) to hinder anticancer work cells.

The research aims to know the effectiveness of anti-PD-L1/PD-1 immunotherapy as a solution for treating non-melanoma skin type carcinoma basal cells by looking at the previous treatment.

Methods

The type of research method used is a *literature review*. *A literature review* is one activity search and studying literature through the activity read various sourcebooks, journals study, and related publications, with topics or issues ever studied by a particular person (Marzali, 2016). An article will discuss four focus studies: 1) integumentary system, 2) skin cancer, 3) non-melanoma skin cancer, and basal cell carcinoma. And 4) effects of anti-PD-L /PD-1 Immunotherapy.

Results

Integument system

Skin plays an essential role in the body. The skin protects the body from mechanical, chemical, or microbial disturbances, protects the body from harmful ultraviolet radiation, and helps guard the immune system. Melanocytes will send melanosomes to keratinocytes through dendrites. It forms a melanin cap that prevents exposure to epidermal DNA damage due to ultraviolet radiation (Suryani, 2020). The integument system can also lose its functional design. A lost function could be triggered by various possible factors affecting existing cells, such as existing response allergies, viral and bacterial infections, and cancer melanoma and non-melanoma skin. The skin consists of the epidermis, dermis, and subcutis (Hasliani, 2021). The skin consists of millions of skin cells that can die, peel off, and replace new skin cells that grow (Setiawan, Wijono, & Sunaryo, 2013).

The epidermis layer is the outermost layer consisting of stratified squamous epithelium with a horny layer. The epidermis has no blood or lymph vessels, so all nutrients and oxygen are obtained from the capillaries in the dermis layer. The epidermis consists of five layers, namely the stratum basale, stratum spinosum, stratum granulosum, stratum corneum, and stratum lucidum. Epidermal cells can be divided into four types: melanocytes, Merkel cells, keratinocytes, and Langerhans cells (Kalangi, 2013).

Skin cells are continuously renewed through cellular mitosis, which occurs in the basal layer before being transferred to the epithelial surface. The stratum basale, also known as the stratum germinativum, separates the epidermis from the dermis. These cells consist of basal keratinocytes and two types of neural crest-derived cells, namely Merkel cells and melanocytes (Suryani, 2020). Stratum basale is located in the deepest part, which plays a role in epithelial regeneration (Kalangi, 2013).

The stratum spinosum is composed of irregular polyhedral keratinocytes containing Langerhans cells. Stratum granulosum contains keratohyalin, which will increase in number and size if the nucleus condition worsens and cells die. The stratum corneum

consists of corneocytes which will differentiate into cornified cells to fortify the body from physical and chemical hazards (Suryani, 2020).

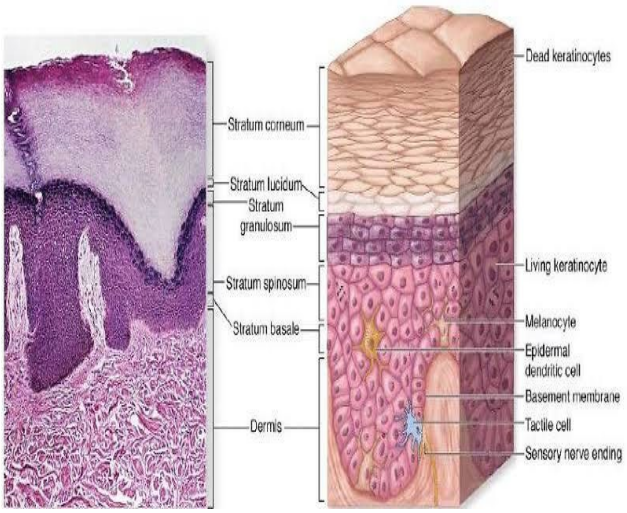

Figure 1. The skin layer consists dermis, stratum basale, stratum pinosum, granulosum, stratum lucidum, and stratum comeum (Kalangi, 2013).

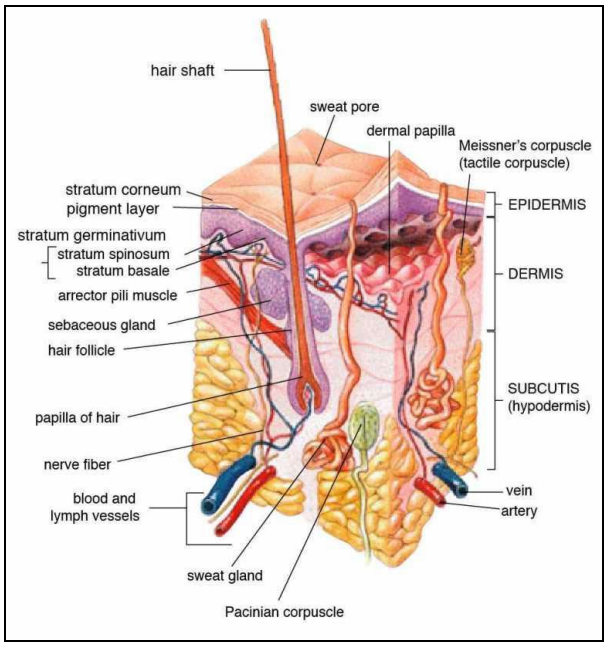

Figure 2. The skin structure (Youseft, Alhajj, & Sharma, 2021).

The papillary and reticular layers form the dermis. The dermis consists of immune cells to prevent possible infections from entering the skin. Another function of the dermis is to supply blood, nutrients, and oxygen for itself and the epidermis (Sagoyo, Widodo, & Dachlan, 2017). The dermis layer is about 2-4 mm thick. This layer contains the nervous system, blood vessels, lymphatics, skin secretory organs, and immune cells such as macrophages and mast cells. The dermis consists of (1) excretory and secretory glands consisting of sebaceous, eccrine, and apocrine glands, (2) hair and nail follicles, and (3) sensory nerve receptors, namely Pacinian blood cells, Merkel, and Meissner blood cells, and Ruffini cells (Suryani, 2020). Subcutis tissue, or hypodermis tissue, is a layer of fat and connective tissue that plays an essential role in regulating body temperature (Sagoyo, Widodo, & Dachlan, 2017).

Skin cancer

As the integumentary system, the skin consists of cells that will replace dead cells by forming new cells to repair damaged tissue. Damage to cell regeneration function causes cell abnormalities and damage to cell DNA, thereby causing cancer. Cancer cells will grow and continue to divide into abnormal cells, affecting normal tissue cells and developing into melanoma or non-melanoma skin cancer, depending on the cell or tissue background (Setiabudi, Wardhana, Indira, & Puspawati, 2021).

Skin cancer has various characteristics but is generally characterized by small lumps that enlarge over time. Another characteristic is the growth of excess skin tissue on some or all skin tissue. Skin cancer causes the skin structure to look irregular due to the differentiation of infiltrative cells in the nucleus, chromatin, and cytoplasm. That damages the surrounding tissue and metastasizes through blood vessels or lymph vessels (Wilvestra, Lestari, & Asri, 2018). There are two main types of skin cancer: melanoma skin cancer and non-melanoma skin cancer.

Melanoma skin cancer

Melanoma skin cancer is a type of skin cancer that occurs due to abnormal growth of melanocytes or cell abnormalities that produce melanin or skin pigment that can spread to the brain and lungs of sufferers. An example of this skin cancer is malignant melanoma, characterized by skin color changes with irregular and prominent edges due to exposure to ultraviolet light (Mohartono & Hanriko, 2017). Malignant melanoma skin cancer is a type of malignant skin cancer.

Non-melanoma skin cancer

More than a third of cancer cases in the world are non-melanoma skin cancers, and this number continues to grow. The development factors for non-melanoma skin cancer are environmental exposure, phenotypic characteristics, genetic factors, lifestyle, medical history, and family susceptibility (Hanriko & Hayati, 2019).

In general, non-melanoma skin cancer is divided into two types, namely non-melanoma basal cell carcinoma and non-melanoma squamous cell. Basal cell carcinoma (BCC) is one of the most common types of skin cancer (75% patient donation) and is a malignant neoplasm originating from non-keratinized cells in the basal skin layer of the epidermis (Pramuningtyas & Mawardi, 2012). Basal cell carcinoma is a common tumor in the white population. Patients with basal cell carcinoma in Indonesia are still relatively few compared to America, Australia, and England. However, it should be further understood that skin cancer needs to be quickly handled. Non-melanoma causes physical defects that spoil the appearance and become more dangerous when it reaches an advanced stage (Raflizar & Nainggolan, 2010).

Non-Melanoma Skin Cancer Basal Cell Carcinoma

Basal cell carcinoma (BCC) was first reported in 1824. Although considered a type of cancer with a low mortality rate, basal cell carcinoma can reach a hazardous stage. This type of cancer can damage tissue or cause tissue damage around the area of spread cell cancer. Influence negative of condition this not only change the patient's physical but also psychological health. Basal cell carcinoma is a malignant tumor that is locally invasive but rarely metastasizes, so this disease's mortality rate is relatively low (Miryana, Reza, Sarwono, & Cholis, 2013). Based on studies, Basal cell carcinoma (BCC) is estimated to appear on the head or neck (52%), arms (13%), trunk (27%), and lower limbs (8%). Most carcinomas are found in the face, especially in the eyelids, nasolabial folds, and lips, followed by the ears, nose, and cheeks (Lestari, et al., 2018).

Basal cell carcinoma is destructive because it can damage the patient's skin tissue, and impact cartilage and bone around the distribution area (Tan, Ghaznawie, & Reginata, 2016). The most significant complication of basal cell carcinoma is the effect of local

invasion. Generally, this cancer grows in 6 months to 1 year. Although it grows slowly and rarely metastasizes, it can spread widely and cause disability if not treated immediately (Lestari, et al., 2018). Non-melanoma Basal cell carcinoma can be categorized into several subtypes, namely pigmented, nodular, superficial, morphea form, and fibroepithelioma of Pinkus (FOP) types (Fakrosa, Sutedja, Agusni, Feriza, & Saraswati, 2018).

Common symptoms that appear in non-melanoma basal cell carcinoma patients are itchy or painful patches on the face that bleed easily and are difficult to heal naturally, such as enlarged moles (Tan, Ghaznawie, & Reginata, 2016). Moles larger than twenty millimeters carry a high risk of developing into cancer. The initial symptoms caused by basal cell carcinoma are not severe and are only considered minor skin problems. However, it is essential to note that basal cell carcinoma cancer has the potential to develop into more malignant types of cancer, such as malignant melanoma (Wilvestra, Lestari, & Asri, 2018).

Clinical symptoms of basal carcinoma cells are marked by the appearance of small papules or nodules (Braun, Scope, Marghoob, & Kerl, 2012). The nodular subtype is the most common subtype of basal cell carcinoma. Early lesions of this subtype are complicated to identify because they look like normal skin in general. Meanwhile, enlarged lesions with necrosis in the middle are the basis for *rodent ulcers* which are often referred to as the nodulo-ulcerative subtype (Longo, Lallas, & Kyrgidis, 2014).

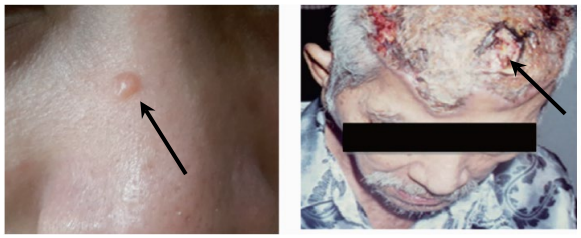

Figure 3. Arrows indicate abnormal tissue growth in the skin area as evidenced by (1) BCC nodules on the nose, (2) Extensive BCC lesions on the scalp (Tan, Ghaznawie, & Reginata, 2016).

Early symptoms of the superficial subtype include erythematous plaques on the body that appear multicentric. It is usually associated with chronic arsenic consumption. Symptoms resemble Bowen's disease, lupus erythematosus, psoriasis, or dermatomycosis. On the other hand, early signs of the pigmented basal cell carcinoma subtype include the presence of translucent papules, hyperpigmentation, and erosions (Moraskar, Shirodkar, & Lambor, 2015). The morphea subtype appears as sunken sclerotic plaques white or yellow, shiny like scars or morphea lesions, and grows aggressively. Pink *fibroepithelioma* is usually found on the lower back as pink papules without stems or short stems on the surface (Fakrosa, Sutedja, Agusni, Feriza, & Saraswati, 2018).

Nom-melanoma basal cell carcinoma (BCC) is caused by two main factors, namely environmental factors and genetic factors. The etiopathogenesis of basal cell carcinoma is related to genetic factors associated with the inability to protect chromosomes 1 and 5, 7, 9, and 12 against sun exposure. Environmental factors that can cause basal cell carcinoma include hydrocarbons, arsenic, coal, tar, topical drug methoxy psoralen, and UV light (Tan, Ghaznawie, & Reginata, 2016). The main factor is exposure to sunlight on the skin with a wavelength of 290-320 nm. It is also caused by heterozygous sun exposure. Exposure to UVB sunlight, UV radiation is known to cause mutations in tumor suppressor genes, exposure to hydrocarbons, chronic wounds, arsenic, and the topical drug methoxy psoralen, and acute trauma can result in the growth of keratinocytes into basal cell carcinomas (Fatmasari & Djakaria, 2017). Sun exposure between 11.00 and 15.00 is also risky because the intensity of UV radiation is highest during this period (Pramudianti, Sidharta, & Sinambela, 2017).

Damaged skin tissue structure will damage the surrounding tissue. Basal cells are equipped with functions to produce new skin cells and push or lift dead skin cells to the skin surface (Wilvestra, Lestari, & Asri, 2018). When basal cells undergo abnormality (abnormal) then could affect function, causing the development of abnormal cells to become cancerous skin. Basal cell carcinoma will attack the cells in the deepest part of the skin's epidermal tissue. This causes cells to undergo excessive division beyond normal limits (Tan, Ghaznawie, & Reginata, 2016).

Cancer non-melanoma skin type carcinoma basal cells will also the more exacerbated, with level expression cell fast cancer consequence affected anticancer cells. System immune is a factor defense body to infection and molecules incoming foreigner _ to the body. When a stimulus is identified as infection, particularly transformation cell cancer, the system immune system will respond by activating CD8 cytotoxic T lymphocytes, which are presented by APCs (Antigen Presenting Cells) as in dendrites (Pramono et al., 2019). However, a consequence of the existence of PD-1 (*programmed death receptor.)* interactions 1) with PD-L1 (*programmed death-ligand* 1) causes a decline in response immune, hindering the growth of tumor cells (Janah, Rujito, & Wahyono, 2020). The existence bond between PD-L1 and PD- 1 receptor too much on cells immunity, causes T lymphocytes to undergo inactivation, so the tumor grows active and proliferates (Pramono, et al., 2019). The more causing lesson cancer the more spread out, so need proper handling. In particular, it inhibits the interaction of PD-L1 bonds with PD-1 receptors via therapy or immunotherapy.

The value of the quality of the patient's history will depend on the physician's ability to review the relevant information. Basal cell carcinoma non-melanoma lesions can also resemble other non-malignant skin lesions such as dermatitis, psoriasis, or *skin tags* thus explaining why the lesions are malignant (Wilvestra, Lestari, & Asri, 2018). Therefore, in addition to clinical manifestations, it is necessary to carry out supporting examinations such as histopathological examination before deciding on the final diagnosis (Fakrosa, Sutedja, Agusni, Feriza, & Saraswati, 2018).

Histopathological examination in the form of an anatomical pathology examination or a biopsy is an examination process carried out by taking samples of body tissue suspected of being a tumor or cancer and checking the level of malignancy (Fakrosa, Sutedja, Agusni, Feriza, & Saraswati, 2018). In addition, preventive examinations can be carried out independently through the skin self-examination method (SAKURI). Steps SAKURI examination includes: First, examine the back of the body with a mirror, then to the right and left with the hands raised. Second, bend your elbows and arms, armpits, and palms. Third, pay attention to the back, palms, and between the toes. Fourth, check the back of the neck and scalp using a mirror. Fifth, check the buttocks area using a hand mirror (Tan, Ghaznawie, & Reginata, 2016). This examination aims to identify skin changes early to prevent carcinoma development.

Discussion

Effects of Anti-PD-L1 /PD1 Immunotherapy on Basal Cell Carcinoma

Non-melanoma skin cancer is often treated using immunotherapy (Lawrenti, 2018). Immunotherapy or vaccine therapy is therapy against cancer through an immune reaction that can eliminate all cancer cells. Even though these cells have metastasized or reappeared several years later (Sugiharto, 2006). Immunotherapy is a systemic therapy or drug entry into the patient's body system that is developed using active tumor-specific T cells that can lyse tumor cells and eradicate cancer in the body (Lawrenti, 2018; Hudson, Cross, Jordan-Mahy, & Leyland, 2020).

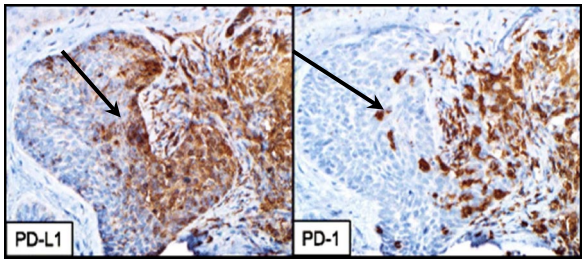

Figure 4. Arrows show the expression of PD-L1 tumor cells interacting with PD-1+ infiltrative cell-associated immune cells in basal cell carcinoma *(*Lipson, et al., 2017*).*

PD-L1 tumor cells can inactivate anticancer immune cells, which contributes to the faster spread of basal cell carcinoma. The binding of PD-L1 to the PD-1 immune receptor will result in the deactivation of T lymphocytes, thereby causing tumor cells to be protected from the body's immune cells. One of the skin cancer treatments is through the application of immunotherapy using anti -PD-1/anti-PD-1 therapy in non-melanoma skin cancer patients with carcinoma type—basal cells. Handling non-melanoma skin through anti-PD-L1/PD-1 immunotherapy will push the bond between both so that the antitumor T-cell immune system will reactivate, and the spread of basal cell carcinoma cells can be inhibited (Ikeda, et al., 2016). In tumor microscopy, PD-L1 and WW-1 will bind to each other to form a ligand-receptor system. PD-L1 present in tumor or cancer stromal cells will interact with PD-1 found in immune cells such as monocytes, T lymphocytes, and B lymphocytes, increasing immunosuppressive T lymphocytes (Pramono, Saraswati, & Zuraidah, 2019).

This immunosuppressive property suppresses the ability of T lymphocyte cells to fight cancer cells that enter the skin, thus requiring the reactivation of T lymphocyte cells in the treatment of cancer and tumors. The use of immunotherapy aims to inhibit or suppress the binding of PD-L1/PD-1 until the immune response is triggered by activating T lymphocytes and other anticancer cells to fight and inhibit and destroy basal cell carcinoma skin cancer.

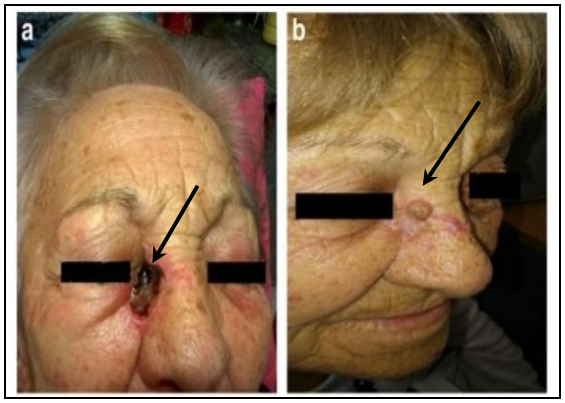

Figure 5. Arrows show comparison of nasal basal cell carcinoma (BCC) before and after Anti-PD-L1 use, A) Before cancer drug use [continuous recurrence]. B) After the use of the cancer drug Anti-PD-L1 in BCC (Sabbatino, et al., 2018).

Several studies related to cancer and tumor cell carcinoma involving several patients explained that anti-PD-L1/PD-1 immunotherapy gave a higher patient survival rate, and anti-PD-1 was able to inhibit the interaction between PD-L1 and PD-1 in effects antitumor cells (Yu, et al., 2016). Another study conducted by Lipson, et al., (2017), related the exploration of PD-L1 expression in basal cell carcinoma as a consideration for the clinical application of anti-PD-L1/PD -L1, that the patients before and after anti-PD-1 therapy for 6.5 months showed positive metastatic regression. The clinical evidence suggests that long-term administration of anti-PD-1 leads to decreased expression of MHC-1 and increased T cells in the tumor microenvironment as antitumor immune factors. This

clinical evidence also considers that anti-PD-1/PD-L1 therapy can be breakthrough immunotherapy in treating non-melanoma skin cancer and basal cell carcinoma type.

Anti-PD-l/anti -PD-L1 immunotherapy can increase the number of antitumor or anticancer immune cells in the body. This specific immunotherapy method decreases the rate of progression (regression) of basal cell carcinoma. It reduces the likelihood of skin cancer recurrence in patients by acting as an active controller that prevents the spread and shrinks cancer cells (Lipson, et al., 2017). Anti- PD- L 1/PD-1 helps patients feel the benefits of healing skin cancer both short and long term (Sabbatino, et al., 2018). Thus, handling cancer non-melanoma skin type carcinoma basal cells using anti-PD-L1/PD-1 immunotherapy is a good solution for better skin cancer treatment.

Conclusions

Skin plays an essential role in sustaining life because it protects the body from harmful elements in the surrounding environment, including UV radiation from sunlight. Human skin cells can regenerate themselves based on each cell and tissue's systems, functions, and mechanisms. One of the most common skin diseases is the non-melanoma skin cancer basal cell carcinoma type. This specific type of cancer attacks the basal cells located in the skin's epidermis, contributing to damage from negative physical changes. An effective treatment method for this cancer is immunotherapy Programmed Death Ligand 1/Programmed Death receptor 1 (anti-PD-L1/PD-1). Anti-PD-L1/PD-1 immunotherapy hinders the interaction between PD-L1 and PD-1 receptors, affecting anticancer activity like T lymphocytes. Effect the will increase factor T cells, suppress the growth of cancer cells by shrinking and destroying and increase immunity against cancer cells and prevent recurrence of skin cancer.

Declaration statement

The authors reported no potential conflict of interest.

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