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Immunotherapy in Cutaneous Oncology: Revolutionizing Treatment Approaches

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Abstract

Background: Cutaneous oncology encompasses a broad range of skin malignancies, including melanoma, cutaneous squamous cell carcinoma (SCC), and basal cell carcinoma (BCC), all of which pose significant global health challenges. The World Health Organization (WHO) estimates that melanoma incidence has increased by approximately 50% over the past three decades. While SCC and BCC are generally less aggressive than melanoma, they contribute significantly to the overall burden of skin cancer due to their high prevalence. Traditional treatment modalities for these malignancies, such as surgery, radiation, and chemotherapy, have shown limitations in achieving durable responses and minimizing systemic toxicity. As a result, there is an increasing need for more effective and less toxic treatment options. Immunotherapeutic strategies have emerged as a promising avenue in oncology, with the potential to revolutionize treatment approaches for cutaneous malignancies. **Objectives:** This literature review aims to undertake an in-depth examination of immunotherapeutic strategies for melanoma, SCC, and BCC. Specifically, the review focuses on the role of immune checkpoint inhibitors, adoptive cell therapies, and emerging immunotherapies, assessing their impact on treatment outcomes, survival rates, and patient quality of life. **Methods:** A literature search was conducted using databases such as PubMed, Google Scholar, and Scopus. The search terms included "cutaneous oncology", "immunotherapy", "immune checkpoint inhibitors", "adoptive cell therapy", "melanoma", "cutaneous squamous cell carcinoma", and "basal cell carcinoma". Peer-

reviewed articles published in the last 10 years that reported clinical outcomes from immunotherapy-based treatments for cutaneous malignancies were included. The studies were reviewed and analyzed based on their reported clinical outcomes, including survival rates, adverse events, and quality of life metrics. **Results:** Our review identified significant advancements in immunotherapeutic strategies for cutaneous oncology. Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, demonstrated improved overall survival rates, particularly in melanoma patients. In addition, adoptive cell therapies, including tumor-infiltrating lymphocyte (TIL) therapies, showed promise in managing both cutaneous SCC and BCC, with reported reductions in tumor burden and durable responses. Emerging immunotherapies, such as cancer vaccines and oncolytic viruses, are in early clinical trials but exhibit potential in enhancing antitumor immunity and expanding treatment options. **Conclusions:** Immunotherapeutic strategies represent a critical advancement in the management of cutaneous malignancies, offering improved outcomes compared to traditional therapies. Immune checkpoint inhibitors and adoptive cell therapies are already reshaping clinical practice, while emerging immunotherapies provide exciting avenues for future research. These therapies not only enhance survival rates but also reduce systemic toxicities, representing a transformative approach to treating skin cancer. Further research and clinical trials are needed to refine these strategies and expand their applicability to a broader patient population.

Keywords

Cutaneous Oncology, Advanced Melanoma, Immunotherapy, Treatment, Novel Treatment Approaches

1. Introduction

Traditional treatment modalities for cutaneous oncology, such as melanoma, squamous cell carcinoma, and basal cell carcinoma, have shown limitations in achieving durable responses and minimizing systemic toxicity. Over the past decade, there has been a paradigm shift in the field, with a growing emphasis on immunotherapeutic strategies that harness the body's immune system to combat these cancers. Our review evaluates the intricate landscape of immunotherapy within the realm of cutaneous oncology, exploring the transformative potential of immune checkpoint inhibitors, adoptive cell therapies, and emerging immunotherapies, such as oncolytic viruses and vaccines, in reshaping treatment approaches.

Numerous studies in academic literature have highlighted the promising outcomes of immune checkpoint inhibitors, such as anti-PD-1 and anti-CTLA-4 antibodies, in the treatment of advanced melanoma. The blockade of these immune checkpoints unleashes the immune system's ability to recognize and eliminate cancer cells. Additionally, adoptive cell therapies, particularly chimeric antigen

receptor (CAR) T-cell therapies, have demonstrated remarkable success in hematological malignancies, prompting investigations into their efficacy in the treatment of cutaneous cancers. Existing literature provides a foundation for understanding the molecular mechanisms and clinical outcomes associated with these immunotherapeutic interventions.

Our analysis critically evaluates the mechanisms underlying immune checkpoint inhibitors and adoptive cell therapies, shedding light on their efficacy and limitations. We aim to provide a comprehensive understanding of the potential synergies between these modalities and their applications in different cutaneous malignancies. By highlighting both the successes and challenges, we contribute to the ongoing discourse on refining and optimizing immunotherapeutic approaches in the context of skin cancer.

As we navigate the evolving landscape of immunotherapy in cutaneous oncology, this review identifies crucial areas for future research. Optimization of combination therapies, exploration of novel immunotherapeutic agents, and a deeper understanding of patient-specific responses emerge as key avenues for advancing the field. These insights lay the groundwork for future investigations aimed at refining and personalizing immunotherapeutic interventions, ultimately contributing to the continued revolution in the treatment of cutaneous malignancies.

2. Methods

This literature review was conducted through a comprehensive search of multiple databases, including PubMed, Google Scholar, and Scopus. The search strategy focused on immunotherapeutic strategies within the context of cutaneous oncology, specifically targeting immune checkpoint inhibitors, adoptive cell therapies, and emerging immunotherapies. Search terms included combinations of "cutaneous oncology", "immunotherapy", "immune checkpoint inhibitors", "adoptive cell therapy", "melanoma", "cutaneous squamous cell carcinoma", and "basal cell carcinoma".

Inclusion criteria were peer-reviewed articles published in English over the last 10 years, studies that involved human subjects, and those that specifically addressed immunotherapeutic interventions in skin malignancies. Articles that provided data on clinical outcomes, patient survival rates, adverse effects, and quality of life were prioritized. Exclusion criteria included non-peer-reviewed articles, studies focusing solely on animal models, and those not providing oncology.

3. Results & Discussion

This review highlights some important findings among existing and developing immunotherapy options. Regarding the efficacy of immune checkpoint inhibitors, there was found to be significantly improved survival outcomes in advanced melanoma and cutaneous SCC, particularly when used in combination therapies. Combination treatments like nivolumab and ipilimumab show higher survival rates, especially in BRAF-mutant melanoma cases. Toxicity considerations were

looked at as well. While effective, immune checkpoint inhibitors, particularly in combination, present substantial toxicity risks. Managing these side effects is crucial for patient care, necessitating individualized treatment plans. When looking at tumor mutation burden (TMB) and treatment response, high TMB in cutaneous SCC due to UV-induced mutations supports the efficacy of checkpoint inhibitors. The immunogenic nature of cutaneous SCC makes it a suitable candidate for immunotherapy, though recurrence and resistance remain challenges. Adoptive cell therapies offer a promising avenue for melanoma treatment by expanding and modifying adult t-cell lymphomas/leukemia ex vivo. This approach allows for tailored and robust immune responses, enhancing therapeutic outcomes. Emerging therapies such as genetic engineering of T-cells and the use of oncolytic viruses present new, synergistic treatment options. Oncolytic viruses like TVEC have shown potential in increasing tumor-specific immune responses and improving outcomes in cutaneous SCC.

3.1. Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are a foundation in the treatment of advanced melanoma; of the available treatments for advanced melanoma, immune checkpoint inhibitors, when used in combination, have the highest five-year overall survival rate in advanced melanoma and have shown promising results in patients with brain metastases [1]. The mechanism of immune checkpoint inhibitors primarily surrounds anti-CTLA4 and anti-PD-1 antibodies, which induce cell death via CD8+ T cells. Immune checkpoint evasion is central to cancer propagation and provides researchers with a direct therapeutic target. Ipilimumab, a CTLA-4 checkpoint inhibitor, was the first immune checkpoint inhibitor therapy available for melanoma treatment and aimed to improve survival in those with advanced melanoma. Subsequently, PD-1 checkpoint inhibitors, such as nivolumab and pembrolizumab, were introduced to the clinical market and showed improved survival in patients who were treatment-naïve when compared to treatment with the anti-CTLA-4 antibody. Cutaneous SCC exhibits heightened expression of Programmed Death Ligand (PDL)-1 that interacts with Programmed Death (PD)-1 on T-cells, thereby suppressing the antitumor immune response [2] [3]. This immune checkpoint mechanism, exploited by cancer cells for immune evasion, serves as the fundamental rationale for employing PD-1 inhibitors in cutaneous SCC therapy.

While individual use of immune checkpoint inhibitors is considerably effective, when used in combination, increased dose response rates have been shown with a statistically larger reduction in overall tumor size. A study by Larkin *et al.* revealed a sustained five-year survival rate and no reduction in the quality of life among patients who received combination therapy of nivolumab and ipilimumab, when compared to patients who received ipilimumab alone [4]. In addition, overall improved survival has been shown in patients with BRAF-mutant melanoma treated with combination therapy of nivolumab and ipilimumab, when compared

to targeted BRAF immunotherapy alone (73% vs. 65%) [5]. Synergy of these treatments may have enhanced tumor response; however, combination treatments have increased toxic response rates in patients.

Toxicity is most common in the first weeks of treatment and may appear in many organs such as the skin, colon, endocrine system, and liver. Toxicities appear at different rates based on the immunotherapy combination utilized; toxicity is seen at higher rates in those treated with the ipilimumab/nivolumab combination when compared to a combination of ipilimumab and relatlimab, a LAG-3 immune checkpoint inhibitor [6]. Researchers have found that the Grade 3 and Grade 4 treatment related adverse events were reported in 54% of patients receiving combined treatment of ipilimumab/nivolumab, compared to the 16% and 27% seen in the nivolumab and ipilimumab single therapy groups, respectively [7]. However, patients most commonly experienced the side effects of diarrhea, fatigue, and pruritus. These treatments are statistically efficacious in tumor response, but a risk-benefit analysis must be done as part of the standard of care for treatment of advanced melanoma. The choice of immune checkpoint inhibitors must consider each patient's unique tumor factors in addition to the patient's ability to tolerate toxicities associated with the specific immunotherapy utilized.

Mounting evidence suggests that compromised immune surveillance plays a critical role in cutaneous SCC development. Compared to immunocompetent patients, sun-exposed individuals receiving immunosuppressive therapy after organ transplant exhibit a 65 to 250-fold increase in cutaneous SCC risk [8]. Conversely, ceasing immunosuppression leads to a dramatic decline in new cutaneous SCC cases, and milder immunosuppression correlates with lower malignancy rates [9] [10]. Across various cancers, response to checkpoint inhibitor therapy often correlates with tumor mutation burden (TMB), as assessed by tumor genome sequencing; notably, cutaneous SCC exhibits a remarkably high average TMB that presumably stems from the extensive, cumulative mutational load induced by ultraviolet (UV) exposure in keratinocytes, driving malignant transformation [11] [12]. This extensive mutational landscape fuels the creation of a vast repertoire of neoantigens, readily recognized by the immune system's adaptive arm. This inherent immunogenicity, coupled with the well-established link between immunosuppression and increased cutaneous SCC risk, highlights the critical role of natural immunosurveillance in controlling tumor progression [13]. Collectively, these findings strongly suggest that cutaneous SCC possesses unique characteristics rendering it highly susceptible to checkpoint inhibitor therapy. This rationale has guided the development of successful therapeutic strategies targeting immune checkpoints in cutaneous SCC, offering promising options for patients with this prevalent skin cancer.

The advent of immunotherapy has significantly transformed the landscape of advanced cutaneous SCC, demonstrably improving ORRs, survival outcomes, and patient quality of life. However, a crucial caveat emerges: patients with advanced cutaneous SCC who have undergone multiple recurrences after surgery exhibit

significantly lower response rates to immunotherapy [14]. This observation suggests the potential presence of intrinsic or acquired resistance mechanisms that impede therapy effectiveness [15]. Immunotherapy with checkpoint inhibitor therapy presents a unique treatment dynamic in cutaneous SCC. Some patients experience a swift response within weeks, suggesting a direct immunological attack on tumor cells; however, a phenomenon known as pseudo-progression, a temporary enlargement of existing lesions or the appearance of new lesions that often precede actual tumor shrinkage attributed to immune cell infiltration at the tumor site, can complicate response assessment [16]. This underscores the importance of interpreting responses beyond size change of the tumor and utilizing tools such as fludeoxyglucose-18 positron emission tomography (FDG-PET), which can inform therapeutic decisions and ensure optimal patient outcomes [17].

For patients with advanced cutaneous SCC who fall into high-risk categories due to pre-existing conditions, administering checkpoint inhibitor therapy necessitates a meticulous and individualized approach. Immunosuppression associated with transplants, especially solid organ transplant recipients, significantly increases the risk of cutaneous SCC, often leading to aggressive and multiple tumors. While checkpoint inhibitor therapy offers potential benefits, it carries the theoretical risk of graft rejection due to targeting PD-1 signaling, a crucial component in organ rejection prevention [8]. The complex interplay between checkpoint inhibitor therapy and underlying hematological malignancies necessitates thorough consideration of potential interactions and adverse effects. Cutaneous SCC presents a unique challenge for patients with specific underlying conditions.

The potential for checkpoint inhibitor therapy to exacerbate existing autoimmune conditions demands careful evaluation and risk-benefit analysis before proceeding with this therapy. Observational data suggests that some patients with autoimmune diseases can tolerate off-trial checkpoint inhibitor therapy with careful monitoring. However, the risk of disease flare-ups and other high-grade autoimmune toxicities becomes two to three times greater compared to the general population [18]. This necessitates a meticulous risk-benefit analysis, carefully weighing the potential exacerbation of existing autoimmune conditions against the severity of cutaneous SCC and available alternative treatment options. Individualized decision-making is paramount, considering factors such as disease severity and potential risks associated with different autoimmune flares.

3.2. Adoptive Cell Therapies

Melanoma retains the ability to naturally generate a substantial number of antitumor lymphocytes (ATLs), which sets it apart from other human cancers [19]. The efficacy of cancer immunotherapy hinges upon the presence of a substantial population of ATLs that possess robust homing and effector capabilities, empowering ATLs to effectively localize and eradicate cancer cells *in vivo* [20]. The successful isolation and characterization of ATLs derived from patients with melanoma has facilitated the identification and comprehensive analysis of a diverse

repertoire of melanoma-associated antigens, paving the way for their subsequent exploitation as targets in immunotherapeutic interventions [21]-[23].

Adoptive cell transfer (ACT) therapy constitutes a potent immunotherapeutic strategy by harnessing the power of *ex vivo* expanded ATLs. This approach involves the meticulous identification and isolation of lymphocytes with high avidity for tumor antigens, followed by their cultivation *ex vivo* to achieve significant numerical amplification, permitting the infusion of significantly larger populations of these lymphocytes into patients, compared to their naturally occurring amounts. Upon infusion, the ATLs are often accompanied by adjuvants such as vaccines or growth factors to further bolster their *in vivo* efficacy. ACT therapy facilitates the meticulous assessment of cell activity prior to infusion; a crucial step allowing for the selection of highly potent lymphocytes exhibiting exceptional avidity for recognizing and binding to tumor antigens. It is noteworthy that in their natural state within the body, ATLs are often rendered functionally compromised due to anergy or tolerance mechanisms; *ex vivo* culture offers a unique advantage by isolating these cells from such suppressive influences. These can include lymphocytes and myeloid cells, ultimately dampening the effectiveness of traditional immunotherapies such as interleukin (IL)-2 or cancer vaccines. This cultivation process fosters the development of highly activated lymphocytes capable of exerting diverse anti-tumor effector functions upon infusion into the patient, ultimately enhancing their therapeutic efficacy [24]. Perhaps the most remarkable aspect of the efficacy of ACT therapy lies in its ability to precondition the host, creating a more favorable microenvironment for infused cells.

Tumor-infiltrating lymphocytes (TILs) and peripheral blood lymphocytes repeatedly stimulated with autologous melanoma cells demonstrably exhibit an *in vitro* recognition of melanoma cells, as evidenced by assays measuring lytic activity and cytokine secretion [21]. Rosenberg *et al.* (2009) reported objective response rates (ORRs) ranging from 49% to 72% in three separate melanoma trials, with complete response (CR) rates of 28%. These findings collectively underscore the therapeutic potential of TIL-based ACT and pave the way for further exploration in different cancer types.

ACT represents a significant advancement in immunomodulation for cancer treatment [25]. This strategy differs from other methods by circumventing immune regulation through *ex vivo* expansion in which *ex vivo*-grown, tumor-specific immune cells are harnessed. ACT therapy sidesteps the natural regulatory mechanisms of the patient that might otherwise limit their potency; this expansion outside the body allows for the infusion of much larger, unsuppressed cell populations, maximizing their potential impact. The second way is through tailoring recognition specificity via genetic engineering in which during the *ex vivo* cultivation phase, ACT offers the unique advantage of potentially modifying the properties of these cells, particularly their tumor-recognition capabilities, through genetic engineering, allowing for the creation of highly targeted immune "soldiers" specifically designed to recognize and eliminate cancer cells with enhanced

precision. The ability to overcome immune regulation and manipulate cell recognition through *ex vivo* expansion and genetic engineering sets ACT apart, highlighting its potential for more robust and personalized cancer treatment strategies. Early efforts in adoptive T-cell therapy employed the strategy of cloning individual reactive clones to achieve high specificity; however, this approach resulted in decreased in vivo T-cell survival and limited clinical response rates [26]. A shift towards using partially selected cells, combined with more intensive preconditioning regimens, revealed a significant improvement in T-cell survival and in many cases, this enabled substantial *in vivo* expansion, translating to enhanced response rates and longer response durations [27]. The cumulative body of evidence from clinical trials and supporting preclinical data has shaped the current paradigm for utilizing ACT in cancer therapy. This approach now routinely incorporates preconditioning chemotherapy alongside the infusion of T-cells. These trials confirmed the critical influence of T-cell characteristics and solidified the benefit of using rapidly growing cells, a finding established in the early stages of research.

3.3. Emerging Immunotherapies

The management of cutaneous SCC has undergone a transformative evolution with the advent of immunotherapy, representing a fundamental departure from established therapeutic paradigms, offering novel mechanisms for combating this prevalent skin cancer [13]. As our understanding of the intricate immunological landscape of cutaneous SCC deepens, a diverse array of novel therapeutic targets emerge. These promising approaches aim to unleash the full potential of the immune system to combat cutaneous SCC malignancy.

Two primary approaches have emerged for genetically engineering T cells to amplify their anti-tumor potential, Natural T Cell Receptor (TCR) and Chimeric Antigen Receptor (CAR) gene transfer therapies [24]. TCR gene transfer involves introducing genes encoding naturally occurring TCRs isolated from tumor-reactive T-cells that allows for the re-arming of T-cells with highly specific recognition capabilities against tumor antigens [28]. CAR gene transfer introduces genes encoding artificially designed CARs [29]. These chimeric receptors typically comprise an antigen-binding domain derived from an antibody fused to a T-cell signaling domain [29]. Combining CAR-T-cell therapy with dendritic cell vaccination shows promise in animal models, potentially boosting T-cell priming and response [30]. Clinical trials utilizing genetically modified Epstein-Barr virus (EBV)-specific T-cells demonstrate improved survival and clinical outcomes without additional toxicity, suggesting this approach merits further investigation [31]. Utilizing tumor-derived cytokines to stimulate T-cell expansion *in vivo* presents an intriguing concept, but concerns arose regarding potential uncontrolled antigen-dependent and -independent proliferation and required careful evaluation in further research [32]. These diverse strategies highlight the ongoing exploration beyond gene editing to identify and implement complementary methods for optimizing T-cell

function and survival, ultimately aiming to maximize the success and safety of adoptive T-cell therapy.

Oncolytic viruses, genetically modified for direct tumor injection, represent a novel strategy in immunotherapy by inducing both direct tumor necrosis and antigen release and triggering a potent immune response, making oncolytic viruses a promising candidate for synergistic therapy with immunotherapy [33]. Studies suggest that oncolytic viruses can enhance the activity of checkpoint inhibitor therapy by attracting and activating CD8+ T-cells, boosting interferon gamma signaling, and even upregulating PDL-1 expression in the tumor microenvironment [34].

Oncolytic herpes simplex viruses (HSV) have promise in cutaneous oncology treatment. Clinical trials have demonstrated tolerable safety and encouraging tumor regression when the oncolytic HSV virus RP1 is used alone or in combination with nivolumab, an immune checkpoint inhibitor, in various cancer types, including cutaneous SCC [34]. Talimogene laherparepvec (TVEC), another promising oncolytic HSV, is modified to be non-neurovirulent and express granulocyte-macrophage colony-stimulating factor (GM-CSF) in order to specifically replicate within tumor cells, lyse tumor cells, and release virally-derived GM-CSF and tumor antigens subsequently triggering a broader systemic immune response that can target distant, non-injected tumor lesions [35]. Direct intratumoral injection of oncolytic viruses leverages their unique ability to infect and lyse tumor cells, while simultaneously promoting the release of tumor-associated antigens (TAAs) that triggers the host's immune system to mount a potent antitumor immune response [36]. Further research is needed to fully optimize the use of oncolytic viruses in cutaneous SCC therapy. However, these initial findings paint a promising picture for their potential to improve patient outcomes [37].

3.4. Future Research Considerations

Given the ongoing disease progression, drug resistance, and severe toxicities that remain with the current treatments utilized for cutaneous oncologic disease, further research is necessary within the field. While immune checkpoint inhibitors have been instrumental in advancing treatment options, the multi-faceted individualized progression of a cutaneous oncology diagnosis renders it necessary to continue to explore the long-term effectiveness of these treatments and embellish upon ways to reduce adverse effects of the medications. Currently, this involves optimization of combination therapies and associated dosing in order to standardize treatment regimens. For both cutaneous SCC and melanoma, neoadjuvant, adjuvant, combined novel therapies, combined neoadjuvant and adjuvant immune checkpoint inhibitor therapies with surgery, and radiation therapy are all being explored as ways to expand treatment options. A recent study combining immune checkpoint inhibitor therapies and BRAF-MEK inhibitors in the treatment of $BRAF^{V600}$ mutation positive advanced or metastatic melanoma has elicited decreased toxicity and increased progression free survival (PFS) paving the way

for further exploration of combination treatment involving these two classes in the future [38]. While PD-1 inhibitors have shown success in certain populations with melanoma, innate resistance and later acquired resistance remains challenging [39]. Despite the limitations with immune checkpoint inhibitor monotherapy, combined PD-1 and CTLA-4 blockade has proven to be effective; however, the adverse toxicities remain concerning. Studies that strategically adjusted immune checkpoint inhibitor therapy-combined dosing suggested decreased toxicity without significant decrease in overall response rate.

Patient outcomes have been greatly affected by timing the administration of immune checkpoint inhibitors, rendering the necessity of further investigation of adjuvant versus neoadjuvant immunotherapy. Data suggests that neoadjuvant treatment enables the inhibition of immune checkpoints prior to antitumor T-cell resection [40]. The use of neoadjuvant pembrolizumab exemplified this by resulting in longer event free survival in patients with resectable stage III and IV melanoma. Additionally, adjuvant treatment has been shown to have favorable overall survival and disease-free survival when compared to lymph node dissection for certain grades of melanoma [41]. Given that immune-related events in neoadjuvant treatment may delay surgery and adjuvant treatment may cause unexpected immune-related adverse events as well, use of these therapies must be thoughtfully executed. Further research is supported in this field given that neoadjuvant treatment may decrease surgical requirements.

The potential use of immune checkpoint inhibitor therapy as monotherapy or as combination therapy for non-melanoma skin cancer (NMSC) remains encouraging. PD-1 inhibitors are becoming first line therapeutic options for patients with advanced staged cutaneous SCC for patients who are not able to undergo surgery, chemotherapy, or radiation therapy [42]. The PD-1 blockade is also being further investigated as a monotherapy or combination therapy with sonic hedgehog inhibitors in treating advanced BCC [43]. Continued evaluation of these therapies and alternative dosing strategies are required to evaluate the risk versus benefit of these treatments.

Other personalized treatments include oncolytic viruses and messenger (m)RNA vaccines. mRNA vaccines provide the potential to enhance expression of tumor-specific antigens, deliver antitumor antibodies, alter the microenvironment, and program cell self-destruction [44]. In addition, oncolytic virus therapy in the treatment of metastatic and unresectable melanoma has been associated with decreased toxicity and higher durable response rate, ORR, and overall survival [38]. The promising nature of these results prove the role of continued research in future virus therapy and their place in combined treatment regimens both in melanoma and other cutaneous oncologic diseases. More broadly, there is a call to further explore the role the microbiome has on immune checkpoint inhibitor therapy response. Dzutsev *et al.* report that previous lack of response to immune checkpoint inhibitor therapy was reversed by administration of a fecal microbiota transplant in patients with advanced melanoma [45]. Future research involves honing

in on the specific microorganisms that are involved in a tumor's resistance to immunotherapy treatment. Ultimately, the future within cutaneous BCC, SCC, and melanoma treatment involves highly personalized combination therapy that focuses on perfecting timing of treatment, target specification, genetics of the tumor and consideration of a tumor's microenvironment.

4. Conclusion

This in-depth review of 45 manuscripts serves as a comprehensive examination of the currently available immunotherapeutic strategies in cutaneous oncology. From the gold standard of immune checkpoint inhibitors to adoptive cell therapies and new emerging immunotherapies, the treatment of advanced cutaneous malignancies is undoubtedly evolving each day. Current literature has provided unique insights on the individual therapies, their efficacies, and their risks, but future research is warranted to determine optimal treatment plans that prioritize patient-centered needs. Future research should investigate personalized combination therapy considering timing, target, genetics, and the microenvironment of cutaneous oncology, whether it be BCC, SCC, or melanoma. Because a few manuscripts in our review mentioned the use of oncolytic viruses and mRNA vaccines to shrink tumor size and increase the immune response, future projects should evaluate the potential of these modalities for further innovative treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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