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Review Article

A review of photodynamic therapy as a prevention modality for actinic keratoses and non-melanoma skin cancers in immunocompetent patients and immunosuppressed organ transplant recipients

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Abstract

Patients who have undergone solid organ transplant surgeries and are on immunosuppressive therapy have a significantly higher risk of developing actinic keratoses and non-melanoma skin cancers. Various treatment options including cryotherapy or surgical excision via Mohs procedures have traditionally been used as treatment methods for these types of skin lesions. In recent decades, photodynamic therapy (PDT) has been shown to be a well-tolerated, non-invasive skin cancer treatment that provides cosmetic outcomes that are comparable to the standard treatment modalities with a relatively mild side effect profile. Photodynamic therapy uses light, oxygen, and photosensitizing agents to target and kill cells with malignant potential. PDT has been used as an effective outpatient treatment method for precancerous and cancerous skin lesions that is supported in the literature. However, the use of PDT as a preventative measure has not been outlined as clearly. There is a need for further research surrounding this topic to help improve quality of life and health outcomes in solid organ transplant recipients and others who are susceptible to developing skin cancers. The purpose of this review is to describe the novel role of PDT as prophylaxis against the development of actinic keratoses and non-melanoma skin cancers in both immunocompetent and immunosuppressed patients who have undergone solid organ transplants.

Keywords: Photodynamic therapy; actinic keratosis; non-melanoma skin cancer; basal cell carcinoma; squamous cell carcinoma; solid organ transplant; immunosuppression.

Introduction

The incidence of precancerous actinic keratoses and non-melanoma skin cancers has been increasing worldwide because of several factors such as skin tone, age, and primarily, exposure to ultraviolet radiation [1]. Actinic keratoses constitute a spectrum of skin lesions that form as rough, scaly macules or patches on the skin that have the potential to develop into a squamous cell carcinoma if left without intervention [2]. Non-melanoma skin cancers comprise a group of anaplastic cutaneous diseases namely basal and squamous cell carcinomas as well as rarer cancers such as Kaposi sarcoma and Merkel cell carcinoma [3]. The association between the risk factors for developing actinic keratoses and non-melanoma skin cancers in immunocompetent patients has previously been elucidated and is well known [4, 5, 6].

Patients who have undergone an organ transplant surgery and are on long-term immunosuppressive therapy face a more than fifty times increased risk of developing widespread actinic keratoses and non-melanoma skin cancers than immunocompetent individuals [7]. Current treatment modalities for immunocompetent and immunocompromised patients with cutaneous cancers include outpatient procedures such as cryotherapy for precancerous lesions, simple excision surgery, or Mohs micrographic surgery for basal and squamous cell carcinomas in functionally and cosmetically important areas such as around the face, scalp, and genitals. In recent decades, photodynamic therapy has been shown to be another viable treatment option for cutaneous precancers and cancers that can be done in a similar outpatient fashion [8, 9]. The main aims of this review are to discuss the clinical use of photodynamic therapy as a prevention modality for actinic keratoses and non-melanoma skin cancers in both immunocompetent and organ transplant recipients.

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Background

Photodynamic therapy (PDT) is a treatment method that utilizes light, oxygen, and photosensitizing agents such as aminolevulinic acid or methylaminolevulinate to kill cancer cells. The process capitalizes on the heme synthesis pathway. PDT necessitates the exogenous administration of one of the photosensitizing agents either intravenously or epidermally in order to form protophorphyrin IX, which is a photosensitive agent. The accumulated protophorphyrin IX in tumor cells is then subjected to an LED light source. The interaction of light with the affected area of skin initiates the formation of reactive oxygen species that ultimately cause tumor cell death by attacking the cancer cells in the areas with accumulated protophorphyrin [10, 11].

Over the years, there has been much research into various light sources that can be used for PDT. Cutaneous photodynamic therapy most commonly uses LED light sources in either the red or blue range. Red light (635 nm) has been used as the predominant source of PDT in Europe. However, blue light (400 nm) is more widely available in the United States. Some research has been published that compares blue-light and red-light photodynamic therapy. Helander et al. studied the effects of red versus blue light illumination in PDT using aminolevulinic acid in vitro and found that the efficacy of treatment was several folds higher with blue light than with red light [12]. However, they also noted that red light seemed to induce more apoptosis than blue light. In another study in 2018, Maytin et al. concluded that both blue and red-light therapy were equally safe and effective in patients with basal cell nevus syndrome [13]. PDT destroys any surrounding blood vessels that may have been nourishing the tumor cells, but is limited to only areas that the light source can reach; typically, this localizes to the superficial layers of the skin and mucosa and thus, is not a feasible cancer treatment method for visceral or deeper cancers.

Side effect profile of PDT

The major reported adverse event in PDT treatment is pain. The pain, at times, can be so intolerable to patients that it leads to incomplete treatment regimens. There is some research on pain-reducing interventions that can accompany PDT including inhaled oxygen/nitrous oxide during treatment that has been shown to significantly reduce pain and therapy interruptions. Other common side effects include a burning, tingling, erythema, or edema at the target site immediately after treatment is stopped. Rare side effects of photodynamic therapy include allergic contact dermatitis reported with methylaminolevulinate use, suppression of the innate and adaptive immune responses, and the potential to stimulate future skin carcinogenesis. Though rare, adverse events can be even more dangerous in organ transplant recipients who are already in an immunocompromised state and should not be ignored in patients presenting with side effects caused by PDT [14, 15, 16].

Risk factors in organ transplant recipients

Studies show that 40% of malignancies that develop in organ transplant recipients are cutaneous cancers. Within this patient population, Caucasians have up to a 50% chance of being diagnosed with skin cancer and non-whites have around a 6% chance. There are several factors that increase the risk further in organ transplant recipients. In addition to increased ultraviolet radiation exposure, prior skin cancer history, type of transplant, and intensity of immunosuppressive therapy following transplant surgery play a role in the development of non-melanoma skin cancers in organ transplant patients [17, 18, 19]. Patients with a history of pretransplant skin cancer are at nearly a three times higher risk of post-transplant malignancies including non-melanoma skin cancers [20]. Several studies have also shown an association between both the degree and duration of immunosuppressive therapies using cyclosporine, azathioprine, and high-dose corticosteroids and an increased incidence of both non-melanoma and melanoma skin cancers. Particularly, a 2016 meta-analysis of 27 research studies found that azathioprine increases the risk of developing squamous cell carcinoma more than other post-transplant immunosuppressive agents [21].

There have been numerous cases showing that heart and lung transplant recipients account for the greatest number of post-transplant non-melanoma skin cancers [22, 23]. In a cohort study conducted in Norway of 2,561 heart and renal transplant patients, those who underwent a heart transplant were 2.9 times more likely to develop squamous cell carcinomas than the renal transplant recipients [24]. Yearly full-body skin exams are recommended for all patients; however, there are no formal guidelines currently in place regarding skin checks for organ transplant recipients. In 2019, a widespread study was conducted to develop a standardized approach to skin cancer screening in solid organ transplant recipients. The research showed that high-risk transplant patients who are Caucasian should be screened within two years after surgery, while all other high-risk patients should be screened within five years after transplant. They identified 'high-risk' patients as those who had thoracic organ transplants, are above the age of 50, and are male [25]. Due to their increased susceptibility to skin cancer because of their immunocompromised state, dermatologic follow-up of organ transplant recipients should be included in post-transplant disease management plans.

Prevention of actinic keratoses with PDT

Actinic keratoses are the most common precancerous skin lesions that present primarily on heavily sun-exposed areas typically involving the head and neck. They are characterized by a proliferation of neoplastic keratinocytes of variable sizes and shapes with abnormal nuclei and are found in the epidermis. They are more prevalent in light-skinned immunocompetent individuals as well as many immunocompromised patients such as those who have undergone an organ transplant. Actinic keratoses have the ability to either spontaneously enter remission, remain stable without further progression, or develop into invasive squamous cell carcinoma with a rare chance of metastasis [26]. The development of actinic keratoses into squamous cell carcinoma has been analyzed. Studies show that it is very difficult to predict whether an actinic keratosis will progress into a squamous cell carcinoma; however, it is significant to note that most squamous cell carcinomas arise from actinic keratoses. They can present either as singular lesions or as multiple within a localized field of skin [27, 28, 29].

To prevent the progression of actinic keratoses current treatment modalities include cryotherapy, chemical peels, and PDT. Of these procedures, PDT is known for its high efficacy in preventing the development of squamous cell carcinoma from actinic keratoses especially when there are multiple lesions located in areas of skin with poor wound healing. Additionally, PDT has been shown to have excellent cosmetic outcomes and higher satisfaction with relatively few adverse events in comparison to other available modalities for both immunocompetent and immunocompromised patient populations [30, 31]. Early intervention is essential for preventing the development of more actinic keratoses lesions and possibly squamous cell carcinomas. In 2004, a group of researchers compared the use of photodynamic therapy for actinic keratoses in immunocompetent and immunocompromised patients. The results of their study showed that four weeks after therapy had begun, the complete clearance rate between the two groups of patients was 94% for immunocompetent patients and 86% for immunocompromised patients [32]. Additionally, for organ transplant recipients, it is recommended that at least two PDT sessions are performed at baseline followed by further sessions throughout the year to ensure adequate clearance and prevention of actinic keratosis [33].

Prevention of non-melanoma skin cancers with PDT

PDT has also been studied as a prevention modality for non-melanoma skin cancers. The prophylactic effects of photodynamic therapy have been of great interest to researchers for decades and there is still a lot of work to be done in this area. One of the major risk factors for non-melanoma skin cancer is a previous history of skin cancer, especially for organ transplant recipients undergoing long-term immunosuppression. The idea that recurrent non-melanoma skin cancers can occur around the site of primary tumors defines the idea of the field cancerization theory. This theory suggests that the entire epithelial surface of skin in a particular area has an increased risk for developing malignant lesions in both immunocompetent and immunocompromised patients [34].

In one study, Apalla et al. conducted a randomized control trial in which they sought to investigate whether PDT on photodamaged skin could help prevent new non-melanoma skin cancers in immunocompetent individuals compared to placebo-photodynamic therapy. The results of the study showed that 20% aminolevulinic acid field photodynamic therapy that was given on one half of patients' faces had a significant delay in the average time for the appearance of new lesions compared to the other half of patients' faces that had the control treatment. Additionally, the treatment group had a greater total reduction in the number of new lesions on the half of the face treated with aminolevulinic acid PDT than with the placebo treatment [35]. Another study also looked into photodynamic therapy as a prevention strategy for those with field damage where they compared the effects of conventional photodynamic therapy and daylight PDT. The results of the study showed that both forms of therapy had an equal preventative effect on non-melanoma skin cancers though patients who received daylight PDT treatment experienced less pain overall [36].

Organ transplant patients face an even greater risk of developing non-melanoma skin cancers with or without previous skin cancer history due most likely to the use of long-term immunosuppressive drugs. Most of these drugs impair immune surveillance in the body and allow the unopposed proliferation of malignant cells most commonly affecting the skin. Particularly, calcineurin inhibitors such as cyclosporine and tacrolimus have been shown to markedly decrease DNA nucleotide excision repair leading to an increased the risk of developing skin malignancies. Additionally, in an immunosuppressed state, oncogenic viruses have the ability to invade and cause further destruction. Much is the case for human herpes virus-8 that has been known to cause a non-melanoma skin cancer known as Kaposi sarcoma, a type of cancer that develops from the cells that line blood vessels or lymph channels in severely immunocompromised patients. Studies show that CD4 T-cell counts below 500/mm3 put patients at an increased risk for developing non-melanoma skin cancer [37, 38]. PDT is greatly dependent upon the human immune system to exert its anti-cancer effect when used for the treatment of various skin malignancies. It is now widely accepted that photodynamic therapy has a multifactorial approach to cancer therapy which includes directly killing tumor cells, obliteration of cancer cell vasculature, and activation of the innate and adaptive immune system by triggering numerous cell-signaling cascades that release cytokines and inflammatory molecules. These chemical mediators help alter the microenvironment of the tumor and lead to its eventual destruction [39, 40]. Long-term immunosuppressive therapy, however, dampens the body's ability to activate these immune responses and sparks discussion about the effectiveness of photodynamic therapy in organ transplant recipients.

There is strong support within the medical community that photodynamic therapy is highly effective in the treatment of non-melanoma skin cancers in both immunocompromised and immunocompetent patients, but now the new area of interest surrounds the use of photodynamic therapy as a prophylactic method to help prevent the development of cutaneous cancers in organ transplant patients. It has been noted that the risk of developing a non-melanoma skin cancer is 60 to 250-fold times higher in organ transplant recipients and the risk of subsequent non-melanoma skin cancers was not only increased, but also accelerated with shrinking intervals of time between the presentation of cancerous lesions on the skin [41]. Additionally, there are over 150,000 organ transplant recipients living in the United States and because of the advances in medicine, the five year survival rate post-transplantation are much higher now than in the past. This means that dermatologists are increasingly caring for these patients who can present with non-melanoma skin cancers during the post-transplantation period. This further highlights the need for effective prophylactic therapy for these patients and others [42].

Recent studies are discussing the use of cyclic PDT as a prevention modality for non-melanoma skin cancers in organ transplant patients. In 2010, a group of researchers used cyclic 5-aminolevulinic acid photodynamic therapy on twelve high-risk organ transplant patients. They delivered the treatments in four to eight-week intervals for two years post-transplant. The number of new squamous cell carcinoma lesions were counted prior to beginning therapy and at 12- and 24-months post-therapy. The results of the study showed 79% median reduction at 12 months and 95% median reduction at 24 months for squamous

cell carcinomas compared to the counts before therapy was initiated [43]. Another research team conducted a randomized controlled trial in which they studied cyclic PDT as a primary prevention method for skin dysplasia in twenty-five kidney transplant recipients. 63% of patients developing some form of skin dysplasia on untreated skin compared to only 28% in the PDT-treated skin. This study concluded that cyclic PDT treatments can delay the development of skin dysplasia that has the potential to develop into actinic keratoses and further into non-melanoma skin cancers in organ transplant recipients [44]. A recent systematic review and meta-analysis concluded that PDT is effective for both the prevention and treatment of pre-cancerous lesions and non-melanoma skin cancers in solid organ transplant recipients [45]. Despite the promising results by these types of studies, it is important to acknowledge the need for more research on this topic to determine the efficacy of PDT as prophylaxis for non-melanoma skin cancer in not only immunocompromised patients, but also for those who are immunocompetent.

Conclusion

PDT is a well-tolerated, non-invasive skin cancer treatment that has very few long-term side effects and provides excellent cosmetic outcomes for patients. It has been shown to be an effective treatment modality for actinic keratoses and non-melanoma skin cancers in healthy patients as well as immunocompromised organ transplant recipients. The role of PDT as a prevention modality has been studied to a lesser degree and there is still a great need for further research on this topic. However, there is promising data from early studies on photodynamic therapy prophylaxis suggesting that the use of cyclic photodynamic therapy given in short intervals in the immediate years following transplant surgery can significantly help prevent the development and progression of both actinic keratoses and non-melanoma skin cancers in organ transplant recipients. Prophylactic PDT is entering the field of skin cancer management as a novel and innovative approach to decreasing morbidity from cutaneous cancers and thereby, increasing quality of life for patients.

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