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Photodynamic therapy in the treatment of non-melanoma skin cancer: A literature review

Terapia fotodinâmica no tratamento do câncer de pele não-melanoma: Uma revisão de literature

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ABSTRACT

Objective: The following study aims to analyze the mechanism of action, efficacy, safety, and recent trends in the use of photodynamic therapy (PDT) as a therapeutic approach in the treatment of non-melanoma skin cancer. In addition, it seeks to offer a comprehensive view of the current state of knowledge on the subject, highlighting its use and availability in the Brazilian scenario. Methods: The research was carried out based on a literature review with a database published in CAPES Journals, Virtual Health Library (VHL) and UpToDate. Results: PDT is a globally consolidated technique and has several advantages in the treatment of non-melanoma skin cancer, as well as actinic keratoses, even in comprehensive cases. PDT is considered a non-invasive, fast, safe method with few side effects, providing quick recovery and being well tolerated by patients. It has a significant cure rate and excellent aesthetic results, differing from other treatments frequently cited by its disadvantages, such as undesirable scars. Conclusion: It is crucial to further explore the benefits of PDT by considering its application in different subtypes of non-melanoma skin cancer and optimizing protocols to broaden its clinical application. As a promising innovation, the technology has prospects of contributing to the improvement of the quality of life of patients affected by this specific type of skin cancer.

Keywords: Photodynamic therapy, Basal cell carcinoma, Squamous cell carcinoma, Cutaneous neoplasms, Dermatology.

INTRODUCTION

According to the Global Cancer Observatory, non-melanoma skin cancer (NMSC) has an annual incidence of 5.8% of the world's population and in recent years there has been an increase in its prevalence (between 3% and 7%), estimating that this growth will continue in the future. In Brazil, non-melanoma skin cancer corresponds to about 30% of all malignant tumors registered in the country, with the most common types being: basal cell carcinoma (BCC) and squamous

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cell carcinoma (SCC) (BUSSOLOTTI, R., 2022; WELLS, G., 2022; FELIPPE, R. M. S. et al., 2023).

BCC is characterized by a lesion (wound or nodule) and originates from keratinocytes located near the basal cells of the epidermis, being the most common neoplasm in the world. It is related to prolonged exposure to UV rays, with a higher incidence in people with lighter skin tone (Fitzpatrick's phototype I and II), especially in the most exposed areas of the body such as:ears, neck, scalp, shoulders and back, presenting evolution slowly. The most commonly found type is nodular-ulcerative BCC, which translates as a red, shiny papule with a central crust that can bleed easily. Histologically, we can divide painless growth subtypes into: superficial and nodular (BUSSOLOTTI, R., 2022; WELLS, G., 2022; FELIPPE, R. M. S. et al., 2023).

Superficial BCC is characterized as a well-circumscribed, scaly, erythema-ridden plaque commonly present on the trunk. The histological subtypes of aggressive growth are divided into four classifications: morpheform, characterized as an infiltrative plaque, with ill-defined margins and a shining surface, found on the head and neck; and the infiltrative, presenting as a poorly defined plaque, with a hard, flat or cavitated consistency, white, yellow or pale pink in color, with the possibility of crusts, erosions, ulcers or papules. Nodular BCC, on the other hand, can be described as a refulgent papular or nodular lesion with a smooth surface, with upright telangiectasias and tropism in the head and neck regions (BUSSOLOTTI, R., 2022; WELLS, G., 2022; FELIPPE, R. M. S. et al., 2023).

However, SCC can arise from old scars or chronic wounds of the skin, especially those injured by burns, thus originating in the outermost layer of the epidermis (Marjolin's ulcers). In general, it affects areas of the body exposed to the sun, such as the face, ears, neck, lips and back of the hands, and can also develop in the genitals and sometimes can start in actinic keratoses. The risk factors can be designated in order of relevance, the most common being chronic exposure to UV rays (mainly UV-B), triggering damage to the genome, older age groups, with an average age of involvement at 60 years, lighter skin tones, and different degrees of immunosuppression. In addition, it has a higher prevalence in males, with a ratio of 3:1. Human papillomavirus subtypes 16 and 18 correlate with the manifestation of cutaneous squamous cell carcinoma in the periungual and anogenital regions (BUSSOLOTTI, R., 2022; WELLS, G., 2022; FELIPPE, R. M. S. et al., 2023).

SCC in situ (restricted to the site where it originated), also known as Bowen's disease, is characterized by the appearance of a reddish area covered with crusts, with well-defined lesions with irregular borders. It mostly affects elderly patients with multiple lesions. It can occur on the

skin of the anal and genital areas due to human papillomavirus (HPV) infections. The disease can progress to invasive cancer and should be treated quickly (BUSSOLOTTI, R., 2022; WELLS, G., 2022; FELIPPE, R. M. S. et al., 2023).

In this sense, photodynamic therapy (PDT) is a therapeutic modality that has been widely used in the treatment of malignant tumors and, primarily, in non-melanoma skin cancer, since it has advantages over other treatments, such as a minimally invasive, selective and repeatable approach for the treatment and prevention of skin cancer. Also known as PDT, Photodynamic Therapy, is a treatment consisting of two stages: initially a drug, which acts as a photosensitizer, is administered to the patient to specifically target a diseased tissue of interest, followed by illumination with visible light, to activate the drug and destroy the target tissue (MAYTIN, E., WARREN, C., 2022; TOREZAN, L. et al., 2009; CERRO P., et al., 2022).

In the case of cancer treatment, a dye fulfills the function of the photosensitizer administered to the patient, being able to sensitize target cells and/or tissues to light rays to which, in general, they are not sensitive. Subsequently, an optical fiber is used to irradiate with light, with specific wavelengths, in the tumor region. The photosensitizer applied to that area will absorb the light energy and transfer it to oxygen molecules present in the tissue, forming *singlet* oxygen, toxic to the cell. As singlet oxygen has a very short lifetime, it will react in the tumor region itself, selectively oxidizing and killing tumor cells (PEREIRA, R., 2022 & LIN, J.; WAN, M. T., 2014).

METHODS

This review was carried out through scientific texts that addressed the theme, where criteria were established for their selection, with subsequent processing of the data, through a literature review, analysis of the material found to provide the synthesis of knowledge of what has already been published and interpretation of the data.

Data collection took place from September to November 2023. The articles were searched in the following databases: CAPES Journals; Virtual Health Library (VHL); and UpToDate. The articles were found from the descriptors of the Descriptors in Health Sciences (DeCS) platform: *"Photodynamic therapy", "Basal Cell", "Squamous Cell", "Skin Neoplasms"* and *"Dermatology"*. Inclusion criteria were peer-reviewed articles, written only in English and published in the years 2018 to 2023. Case reports, literature reviews, theses, and monographs were excluded as exclusion criteria. A total of 39 articles were found.

The period of publication of the articles would initially be those published in the last five years, however, after an initial search of works, where it was observed that there was a scarcity of publications on the subject and data for the collection and construction of this work, it was decided to extend the period of publication to fifteen years. A total of 66 articles were found, of which 13 were used in the review.

DISCUSSION

PHOTODYNAMIC THERAPY

The basis of the PDT technique consists of the application of a substance known as a photosensitizing agent, which can be applied systemically, locally, or topically to the site of the lesion, and a light of specific wavelength to activate it. The association of a photosensitizer with light provides a photorelocation, which produces cytotoxic agents generated from the presence of molecular oxygen, resulting in the death of cells in this part of the biological tissue. It is important to emphasize that photodynamic reactions do not occur when photosensitizing agent and light are administered alone (S. BAGNATO, V.; B. REQUENA, M., 2023).

Photosensitizing agents

Photodynamic therapy (PDT) involves the application of a photosensitizing substance and its activation, together with light and oxygen, generates the induction of cytotoxicity of proliferative cells. There are several types of photosensitizers available for this treatment, and three alternative routes for this: intravenous, topical or oral; however, two specific drugs are primarily used for the treatment of non-melanoma cancer: MAL (Methyl Aminolevulinate) and ALA (Amino Levulinic Acid). The first step of the process occurs after the topical application of the photosensitizer, which will be absorbed by the neoplastic cells and converted into heme (porphyrins), tetrapyrrole molecules produced in the mitochondria of the cells, so that, after an "occlusion time", the drug is metabolized and accumulates porphyrins in the tumor cells, before light activation (MAYTIN, E, WARREN, C, 2022; AASI, S., 2022; ORENGO, L., 2022).

The second step of treatment involves illuminating the photosensitizer with a prescribed amount of light (provided by an approved broadband lamp or laser) to activate protoporphyrin IX (PPIX), a form that absorbs light more efficiently.

Porphyrins are conjugated organic compounds (containing multiple double bonds) capable of absorbing visible wavelengths of light very efficiently and converting the energy into chemical reactions. However, MAL (Methyl Aminolevulinate) and ALA (Amino Levulinic

Acid) are prodrugs that characterize the second step in the porphyrin synthesis pathway, so they act in photodynamic therapy, disregarding the first feedback (inhibitory) step in the heme synthesis pathway and allowing PPIX to accumulate at high levels in target tissues. Subsequently, they are exposed to light of wavelengths that coincide with their absorption spectra (HASI, S., 2022; MAYTIN, E, WARREN, C, 2022).

The photosensitizers are activated after capturing the irradiation, in a process called photoactivation of the PPIX and transfer energy directly to the oxygen, forming the singlet oxygen, which generates reactive oxygen species, oxidizing various substrates and generating free radicals in the treated cells. This process triggers failures in the integrity of the tumor cell membrane, causing changes in permeability and transport function between their intra- and extracellular media, in addition to changes in the membranes of the nucleus, mitochondria, lysosomes, and endoplasmic reticulum, which culminate in the induction of cancer cell death (ISSA, M., MANELA-AZULAY, M., 2010; MAYTIN, E, WARREN, C, 2022; ORENGO, L., 2022).

Mechanism of action

Selective destruction of the tumor, without damaging the surrounding healthy tissues, can be achieved with the use of PDT, a treatment that works by inducing the toxicity of proliferative cells through a light source. For this to occur, the technique requires three essential components: a photosensitizer, a source of light and oxygen (TOREZAN, L. et al., 2009; LIN, J.; WAN, M. T., 2014 & AGOSTINIS, P. et al., 2011).

In the case of skin cancer or skin lesions in general, PDT acts in two stages. First, a photosensitizing agent is administered to the lesions, which accumulates in the tumor cells. In general, this application is done by means of a cream containing ALA or one of its derivatives (methyl aminolevulinate, M-ALA), which, when in contact with the lesions, initiates a process of penetration into the cells, producing protoporphyrin IX (PpIX), an endogenous porphyrin, which is in fact the photosensitizing agent. Then, the lesion is illuminated by means of a light source of a specific wavelength to the photosensitizing agent. During illumination, the PpIX molecules absorb energy and go to a higher energy state, called the "excited state", and, when they return to the ground state, they transfer energy to other molecules, mainly molecular oxygen (*singlet oxygen*, ^{1O2}), triggering cellular apoptosis (TOREZAN, L. et al., 2009; LIN, J.; WAN, M. T., 2014; AGOSTINIS, P. et al., 2011 & S. BAGNATO, V.; B. REQUENA, M., 2023).

$^{1}O_2$ acts on tumor cells by destroying membrane integrity, which alters permeability and transport functions in intra- and extracellular environments, especially in nucleus membranes, mitochondria, lysosomes, and endoplasmic reticulum. The loss of cell integrity causes the release of inflammatory factors and the activation of the complement cascade, culminating in cell death. Mitochondrial phototoxicity stands out as the leading cause of PDT-induced cell death (TOREZAN, L. et al., 2009).

In general, PDT-induced cell death is highly dependent on the type and dose of photosensitizer used. These include the time from administration to exposure to light, the amount and dose rate of light, and the concentration of intratumoral oxygen. Therapeutic selectivity is determined by several factors, including the uptake of the photosensitizer into target cells/tissues, metabolism to the active form, and penetration of the light source. Considering these variables, clinical response varies from patient to patient and can be difficult to predict (AGOSTINIS, P. et al., 2011 & LIN, J.; WAN, M. T., 2014).

Light fonts

The variety of light sources in TFD is virtually limitless, encompassing broad-spectrum continuous wave light sources (with blue, red, and green light), incoherent polychromatic sources (such as gas discharge lamps, light-emitting diodes), as well as coherent monochromatic sources (including intense pulsed light [IPL], potassium-titanium-phosphate [KTP] lasers, pulsed dye lasers, and infrared lasers). In addition, studies have been carried out on the application of photopneumatic technology and natural light. The action of these devices depends fundamentally on the emission spectrum, irradiance, spatial distribution of light and power of the device (LIN, J.; WAN, M. T., 2014 & AGOSTINIS, P. et al., 2011).

To generate therapeutic effect, the spectral output of the light source must correspond to the excitation peaks of the photosensitizer. PpIX (formed from the metabolization of ALA) has two important peaks, 404-420 nm in the blue wavelength regions and 635 nm in the red wavelength regions of the visible spectrum. The depth of light penetration into the skin depends on the wavelength, increasing as they get longer. In this sense, blue light penetrates less efficiently through the tissue, being effective for the treatment of fine actinic keratoses, while red and infrared radiation penetrate deeper, being more effective for the treatment of thicker and deeper lesions (LIN, J.; WAN, M. T., 2014 & AGOSTINIS, P. et al., 2011).

It is important to emphasize that no single light source is suitable for all indications of PDT. The choice of light source is determined by the absorption of the photosensitizing agent

(fluorescence excitation and spectrum of action), the disease (location, lesion size, accessibility, and tissue properties), cost, and size. The efficacy of PDT technology depends on the dose, method of administration (single or fractional), and time of exposure to the light source; in addition, of course, to the creep rate (LIN, J.; WAN, M. T., 2014 & AGOSTINIS, P. et al., 2011).

ONCOLOGICAL APPLICATIONS OF PDT IN DERMATOLOGY

The clinical use of PDT in oncology began in the late 1970s with a study of the light effects of hematoporphyrin derivative (HPD) in five patients with bladder cancer. The discovery of the technique culminated, in 1978, in the first large series of patients successfully treated, presenting complete or partial responses in 111 of the 113 malignant lesions. Therefore, since this initial work, more than 200 PDT clinical trials have been conducted. Currently, a systematic review in dermatology has shown that PDT is considered a reasonable option for the treatment of malignant and premalignant non-melanoma skin lesions (AGOSTINIS, P. et al., 2011).

In the latter scenario, PDT is currently approved in the United States (US), Canada, and the European Union (EU) for the treatment of actinic keratosis and in the EU and Canada for the treatment of basal cell carcinoma (BCC). However, PDT has also been shown to be effective in the treatment of localized squamous cell carcinoma (SCC)/Bowen's disease and has been used with some success in Paget's disease (AGOSTINIS, P. et al., 2011).

TFD in actinic ceratoses

Actinic keratoses are rough, scaly lesions that usually appear in areas chronically exposed to ultraviolet (UV) radiation and can progress to SCC. In the treatment of actinic keratosis, the standard in PDT is the use of blue-light ALA. This involves applying ALA for one hour, followed by incubation under occlusion prior to exposure to blue light (10 J/cm²). Although there are several protocols, including the use of red light, randomized controlled trials have indicated that complete elimination of actinic keratoses occurred eight weeks after treatment with 4-hour incubation of ALA self-adhesive patch (86% of actinic keratosis lesions) and red light therapy (LIN, J.; WAN, M. T., 2014).

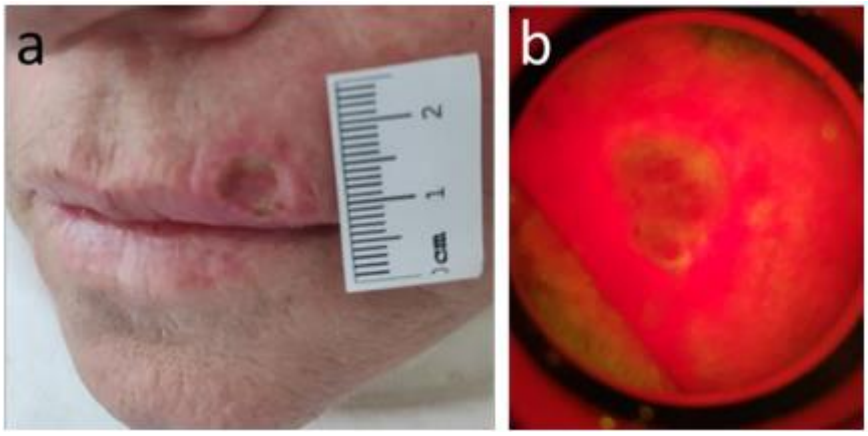
Protocols recommend sessions every 1 to 2 weeks of conventional red-light-excited ALA-PDT for actinic keratosis. The procedure includes: cleaning the lesion (1); application of a formulation containing 10–20% ALA on the surface of the lesion and its surrounding area, within 1 cm, with protection of the lesion from the lumen for 1 to 6 hours by means of occlusion

(2); after removal of ALA from the lesion surface, red light irradiation with an energy density of 100 to 150 J/cm² and a power density of 50 to 120 mW/cm² is recommended (3). The number of sessions can be adjusted according to the response to treatment (S. BAGNATO, V.; B. REQUENA, M., 2023).

PDT in basal cell carcinomas

Photodynamic therapy with delta-aminolevulinic acid (ALA-PDT) is applied for the clinical treatment of superficial and nodular BCC with a depth of less than 2 mm, demonstrating healing efficacy and excellent cosmetic results. For superficial BCC, pretreatment follows the same protocol used for actinic keratosis (Figure 1). It is recommended to evaluate the depth of the nodular BCC, which should be less than 2 mm, before performing ALA-TFD (S. BAGNATO, V.; B. REQUENA, M., 2023).

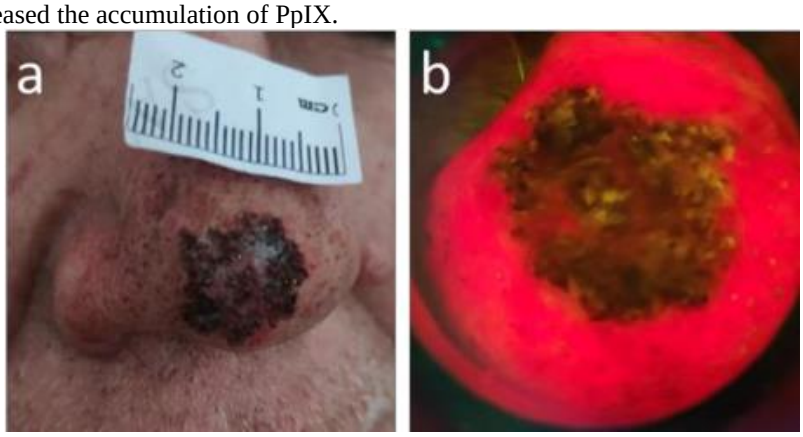
Figure 1. a) PDT of BCC on the left upper lip, without curettage; b) Fluorescence image after 3 hours of cream applications.



Source: S. BAGNATO, V.; B. REQUENA, M., 2023.

In the ALA-PDT procedure for nodular BCC, it is essential to use a surgical blade or curette, or CO_2 laser, to remove the upper tumor (Figure 2). Then, the 10 to 20% ALA solution is applied to the lesion and the surrounding area, up to 1 cm, protecting it from light for 1 to 6 hours. Subsequently, the excess ALA is removed from the surface of the lesion and irradiated with red light, with an energy density of 100 to 200 J/cm² and a power density of 50 to 150 mW/cm². Treatment is performed once every 1 to 3 weeks, and another approach is indicated if there is no improvement in 3 weeks. In cases of positive evolution in the healing of the lesions, a new PDT session may be considered, with a maximum of 6 sessions (S. BAGNATO, V.; B. REQUENA, M., 2023).

Figure 2. a) CBC nasal tip; After curettage of the lesion, cauterization was performed with an electric scalpel; b) Fluorescence image 3 hours after the application of the cream, where the use of the cauterization technique with an electric scalpel decreased the accumulation of PpIX.

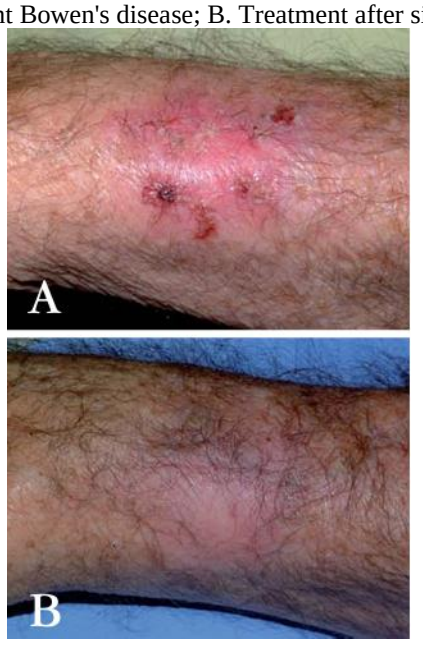


Source: S. BAGNATO, V.; B. REQUENA, M., 2023.

PDT in squamous cell carcinomas (Bowen's disease)

Management of SCC is categorized by metastatic potential, i.e., low-risk cutaneous SCC or high-risk (aggressive) cutaneous SCC, with surgical excision being the gold standard for the latter. PDT is not recommended for the treatment of invasive SCC, being used only in SCC *in situ* (Bowen's disease), especially in the presence of multiple lesions, in areas where multiple surgeries would result in morbidity (such as in the lower extremities), or when lesions are known to be noninvasive (Figure 3). In addition, recent studies indicate that red light is more indicated for treatment and affirm that MAL-TFD achieves better penetration and has been shown to be more effective than ALA-TFD. PDT cannot be recommended for invasive CPB due to its high metastatic potential and reduced efficacy rates (LIN, J.; WAN, M. T., 2014).

Figure 3. A. Pre-treatment Bowen's disease; B. Treatment after six months of MAL-PDT.



Fonte: TOREZAN, L. et al., 2009.

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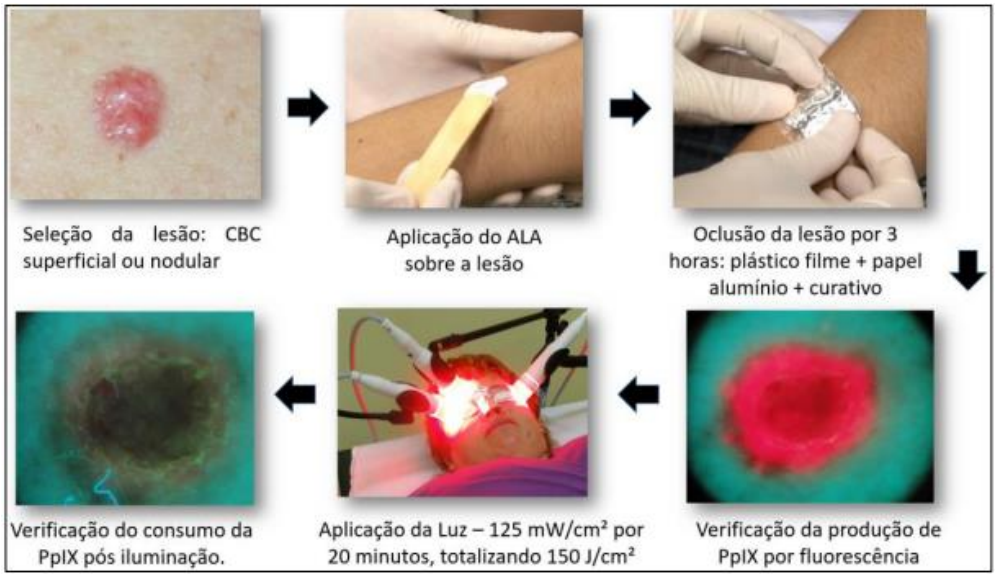
THE USE OF TECHNOLOGY IN BRAZIL

Clinical protocol and results of PDT in the country

In 2012, the Photodynamic Therapy Brazil (TFB) project was created, which was financed by the National Bank for Economic and Social Development (BNDES) and the subsidy program of the Financier of Studies and Projects (FINEP). The idea of the project was to legitimize PDT in Brazil, enabling an alternative form of treatment for non-melanoma skin cancer. In this way, patients who previously waited months for minor surgical procedures could be seen more quickly, reducing queues and prioritizing them for more severe cases. The project also helped to make treatment available to more distant locations, making it possible to treat patients in rural areas (S. BAGNATO, V.; B. REQUENA, M., 2023).

During the project, eligible patients were men and women over 18 years of age with specific lesions of superficial non-melanoma BCC skin cancer, with a maximum of 2 cm in length, or nodular, with up to 2 mm of infiltration. Each team received the national equipment and medications necessary for the treatment of the lesions, accompanied by specific training of the team, with theoretical and practical parts (Figure 4). Thus, 72 centers were trained throughout the national territory and 12 international centers. Regarding response rates, according to Bagnato and Requena (2023), the results were largely positive, reaching 78% efficacy after 30 days of treatment (S. BAGNATO, V.; B. REQUENA, M., 2023).

Figure 4. Summary protocol of the TFD Brazil Program. Prior curettage should always be performed, repeating the same steps after one week for the second session.



Source: S. BAGNATO, V.; B. REQUENA, M., 2023.

Availability in the Unified Health System

In July 2023, the National Commission for the Incorporation of Technologies (CONITEC) recommended the incorporation of GT into the Unified Health System (SUS). The device is part of the TFB project, from 2012, and was designed by the São Carlos Institute of Physics of the University of São Paulo (USP), considered the only one in the world with a double system on the same platform, allowing the diagnosis and treatment of non-melanoma skin cancer, being able to evaluate and treat the disease on the same day. avoiding mutilations and painful procedures (Figure 5). The decision to incorporate the technology in the country now depends on the Secretary of Science, Technology, Innovation and Health Complex of the Ministry of Health (SECTICS/MS), and will later be published in the Official Gazette of the Union (DOU) (BRASIL, 2023).

Figure 5. Equipment used in photodynamic therapy, developed by scientists from IFSC-USP and manufactured by the company MM Optics, in São Carlos, São Paulo

Fonte: FAPESP, 2023.

It should be noted that the availability of GT in the SUS may vary according to different factors, including health policies, local infrastructure, and the specific application of GT for different medical conditions (S. BAGNATO, V.; B. REQUENA, M., 2023).

TFD according to the INCA technique

PDT was introduced in the Dermatology Session of the José de Alencar Gomes da Silva National Cancer Institute (INCA) in 2012 and, since then, hundreds of patients have been treated. At the institute, PDT is used only in the treatment of skin cancer. The main indications are actinic keratosis and low-risk non-melanoma skin cancers such as superficial basal cell

carcinoma and squamous cell carcinoma *in situ* (Bowen's disease). However, the technique can also be used in the treatment of field cancerization and nodular basal cell carcinoma (S. BAGNATO, V.; B. REQUENA, M., 2023).

The management of referred cases consists of photographic documentation (clinical and dermoscopy) and biopsy of the lesion for histopathological diagnosis. At INCA, all patients undergo two PDT sessions separated by seven days apart. In this way, better results and lower recurrence rates are observed. Didactically, the procedure can be divided into three stages: preparation of the lesion, technique for applying the MAL, and exposure to red light (S. BAGNATO, V.; B. REQUENA, M., 2023).

FINAL THOUGHTS

Thus, as research continues to advance, the benefits of Photodynamic Therapy are even more imperative, considering its application in different subtypes of non-melanoma skin cancer and optimizing protocols to broaden its clinical reach. With the prospect of contributing to the improvement of patients' quality of life, Photodynamic Therapy stands out as a promising innovation in the treatment of this specific type of skin cancer.

The occurrence of non-melanoma skin cancer is high both in Brazil and in the rest of the world, demonstrating a continuous increase. Once the malignant nature of the lesion is confirmed, the most common medical approach is surgical intervention. In certain situations, plastic surgery may be necessary for reconstruction and repair, depending on the location and extent. In specific cases, chemotherapy or radiation therapy may also be recommended. Although there are solutions, the lack of adequate infrastructure and specialized doctors distributed throughout the country significantly compromises the response to this demand. The simultaneous lack of these factors in multiple geographic regions results in the neglect of skin cancer, making it a relevant public health problem.

Given this scenario, the adoption of innovative approaches emerges as an alternative to overcome the barriers that hinder the fight against skin cancer in the Brazilian context. Photodynamic therapy (PDT) is a globally consolidated technique and has several advantages in the treatment of non-melanoma skin cancer, as well as actinic keratoses, even in comprehensive cases. The simplicity of the technique, associated with the ease of training of professionals and the possibility of performing it in outpatient clinics, makes PDT an excellent therapeutic option.

According to the analysis of studies, PDT is considered a non-invasive, fast, safe method, with few side effects, providing fast recovery and being well tolerated by patients. It has a

significant cure rate and excellent aesthetic results, differing from other treatments frequently cited by its disadvantages, such as undesirable scars. PDT stands out as the most appropriate therapy for many patients and hospitals.

Given this context, as research progresses, it is crucial to further explore the benefits of Photodynamic Therapy, considering its application in different subtypes of non-melanoma skin cancer and optimizing protocols to broaden its clinical application. As a promising innovation, Photodynamic Therapy presents prospects to contribute to the improvement of the quality of life of patients affected by this specific type of skin cancer.

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