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# ADVANCE OF PHOTODYNAMIC THERAPY IN THE TREATMENT OF NON-MELANOMA SKIN CANCER: LITERATURE REVISION

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## ABSTRACT

Non-melanoma skin cancer is the cancer with the highest incidence in Brazil, corresponding to 30% of all malignancies registered in the country. This type of neoplasm has low lethality, but delayed diagnosis can lead to physical deformities and worsening of quality of life. Photodynamic Therapy (PDT) is a promising therapeutic modality for the treatment of several types of cancer, including that of skin. This literature review aimed to report the progression of PDT in the treatment of non-melanoma skin cancer, summarizing the basic concepts of therapy, knowledge of photosensitizers, and mechanisms involved in the destruction of cancer cells, indications and the limitations of photodynamic treatment in the skin cancers. This review suggests that PDT is constantly advancing and has studies proving its efficacy as a first-line treatment in precancerous lesions, especially in non-melanoma skin cancer, as well as improving the quality of life of the patient.

**KEYWORDS:** Non-melanoma skin cancer, photodynamic therapy and photosensitizers.

## INTRODUCTION

Cancer is characterized by a set of more than 100 diseases, caused by the disordered growth of cells that invades tissues and organs, a genetic disease which develops through the initial mutation in some gene involved in cell replication. [1] Cloned cells have a higher proliferation capacity and escape the cell cycle and the signals that lead to apoptosis.[2]

Skin cancer is the one with the highest incidence in Brazil, corresponding to 30% of all malignant tumors registered in the country. It is estimated that 165,580 new cases of non-melanoma skin cancer will be registered, 85,170 men and 80,410 women.[1]

The incidence of skin cancer has been worrying because it demonstrates a significant increase which, this is explained by the excessive exposure to the sun's rays (UVA and UVB), result of the destruction of the layer of ozone that is the protector against UVB rays, a known powerful carcinogenic for the man.[3] The most common skin cancers are non - melanoma type known as Basal Cell Carcinoma (BCC), Squamous Cell Carcinoma (SCC), Bowen's disease (BD) and Kaposi's Sarcoma (KS). They have high cure rates if detected early and are less aggressive than melanomas.[4]

In the face of the critical side effects and therapeutic limits found in conventional therapies (chemotherapy, radiotherapy), other therapies are being investigated and presented as an alternative in oncological treatment, among which a modality called photodynamic therapy (PDT) stands out.[5]

PDT is defined as a photochemical reaction, involving activation of photosensitive substances, light source, and cytotoxic generation of oxygen and free radicals with the objective of causing selective destruction of a target tissue, resulting in cell death. The application of this therapy proved to have cost-benefit and better quality of life for the patient.[6]

**PHOTODYNAMIC THERAPY**

PDT is a current therapeutic modality for treating various diseases, including cancer, which requires exposure of cells or tissue to a photosensitizing drug, followed by the interaction between visible non-ionizing light of the appropriate length and photosensitizing agent (FS), topical or systemic, with potential effect to eliminate cancer cells.[7]

The PDT has been studied since the nineteenth century and its first application was made by Oscar Raab, in Munich, where the effect of eosin and acridine dyes, both photosensitizers, in a culture of paramecium (*Paramecium Caudatem protozoan*), verified that in the presence of light the microorganisms were inactivated.[8]

In 1960, Lipson and Schwartz at Mayo Clinic produced a new drug from the purification of hematropin which was called hematroporphyrin derivative (HpD). Fluorescence was

observed when it was applied to neoplastic lesions, providing visualization during surgery.[4] Since then, considering the studies that have been discovered, PDT has been a modality of great clinical interest and it is applied as a treatment in several areas such as oncology, cardiology, dermatology, ophthalmology and microbiology.[9]

In Brazil, the clinical experience of PDT began in São Paulo, around 1987, by a group of researchers from the Physics Institute of São Carlos, he University of São Paulo, and the University of São Paulo School of Medicine, in Ribeirão Preto, in partnership with the Amaral Carvalho Hospital, in Jaú, a reference hospital in the treatment of cancer.[10]

**Mechanism of action**

The photodynamic effect depends on two individually non-toxic components that together are capable of inducing lesions in the cancerous tissue through oxygen-dependent reactions, that is, the combination of visible light with a FS in the presence of tissue molecular oxygen, triggers lethal cytotoxic processes.[6]

Treatment begins when a given dose of a photosensitizing substance is administered to the patient, which accumulates in the tumor tissue. It is then irradiated with visible light to cancerous lesion. The applied amounts of FS and the characteristics of the laser (type, power dosage and lighting time) depend on the drug that is being applied and the species and severity of the treated disease. There is a therapeutic window where the light used through the laser should have a range of 400 to 650 nm, providing maximum visible light transmittance, and in the case of wavelengths below 400 nm it can be harmful to the tissue.[11]

FS can be administered intravenously or cutaneously (topically). Light absorption is applied at a specific wavelength; this coincides with the absorption spectrum of FS. This activator transfers energy to molecular oxygen, generating reactive oxygen species, oxidation of lipids, amino acids and proteins that induce cellular apoptosis and necrosis. The process described is explained by two types of reactions: photooxidation by radical (Type I) and photooxidation by singlet oxygen (Type II). (Fig 1).[12]

The type I mechanism involves the participation of FS in the transfer of electrons between FS and its $^{1}$FS or $^{3}$FS excited state, resulting in the formation of radical ions that tend to react instantaneously with molecular oxygen, producing highly reactive oxygen intermediates (superoxide, oxygen peroxide and hydroxyl) capable of oxidizing numerous biomolecules.[4]

In the Type II reaction, there is interaction between FS, $^3$FS and molecular oxygen. Molecular oxygen absorbs energy and originates to singlet oxygen ($^1$O2) which is cytotoxic. The reactions of photooxidation via singlet oxygen are responsible for the elimination of cancer cells. Because it is a highly reactive species with an electrolytic character and with short life in biological systems, and a limited action radius (maximum of 10 mm), the damage of the photodynamic treatment is restricted only to the cancerous cells, adding a great differential in relation other traditional cancer therapies.[13,14]

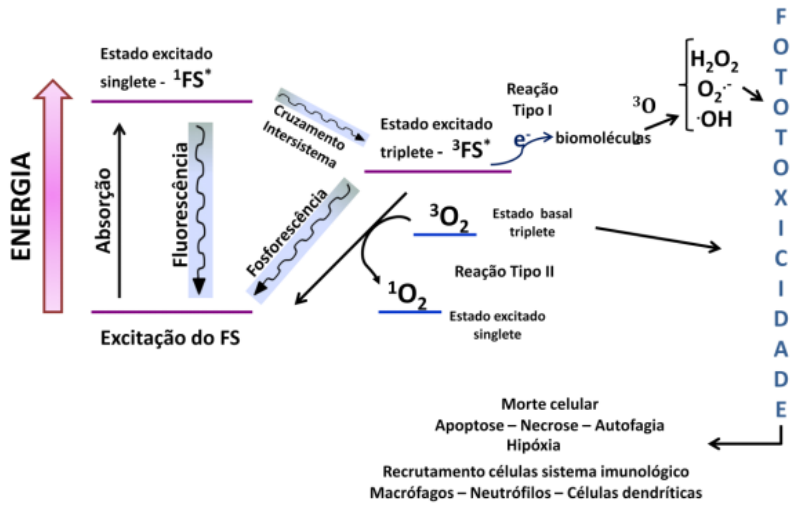


**Figure 1: Schematic representation of the photosensitization mechanism.[14]**

## PHOTOSENSITIZERS

FS stands out for having the ability to accumulate in tumor tissue and for generating cytotoxic substances to induce expected photobiological damage. Some characteristics are important to consider a photosensitizer as ideal as shown in Table 1.[15]

**Table 1: Characteristics of an ideal photosensitizer.[15,16]**

| | |
|---|---|
| **Physical-chemical properties** | Substance highly pure, low molecular weight, low tendency of aggregation in aqueous medium and present composition stable in temperatures to which they will be exposed. |
| **Photophisycals** | Maximum absorption of light (between ~ 700 and 850 nm), where the light has greater penetration in the tissue. High quantum yield, resulting in singlet oxygen, to eliminate cancer cells. |
| **Pharmacologicals** | High selectivity (accumulate only in cancerous tissues), rapid elimination of the organism, non-prolonged photosensitivity. |
| **Pharmacotherapy** | It must not present mutagenic and carcinogenic potential. It should be cytotoxic only in the presence of light and have minimal toxicity in the dark. Marketing and affordable cost. |

The photosensitizers have structures of conjugated aromatic compounds that can be modified and chemically exploited, providing improvement in the chemical processes and greater use

of their activity in the treatment with PDT.[17] Photosensitizers are classified by families, according to their chemical structure (Table 2).

**Table 2: Classification of photosensitizers.[18]**

| Family | Photossensitizers | Commercial Nome of Drug | Clinic Application |
|---|---|---|---|
| **Derivatives of Porphyrin** | Hematoporphyrin Benzoporphyrin | Photoforin® | Cancer of the esophagus, lung, bladder, gastric esophagus, cervical, Barrett's esophagus and cervical dysplasia. |
| | 5-Aminolevulinic acid | Levulan® e kerastick® | Actinic keratosis. |
| | Methyl aminolevulinate | Metvix® | Basal Cell Carcinoma, Squamous Cell Carcinoma. Actinic keratosis, Basal cell carcinoma. |
| **Derivatives of Chlorophyll** | Chlorines and Bacteriochlorins | Foscan® | Cancer of the head, neck and non-melanoma skin. |
| **Dyes** | Phthalocyanines and Naphthalocyanines | Photosens® | Cancer of non-melanoma skin and breast. |

**Photofrin®** - The first photosensitizer approved as a medicine in the treatment of cancer in the application of PDT by the FDA. Its structure is characterized by a complex mixture of hematoporphyrin oligomers, known as porfimer sodium and dihematoporphyrin ether (Fig. 2). The photosensitizer has a low light absorption of 630nm, causing skin photosensitization, benefiting its use in the treatment of skin cancer. The recommended dose is 2mg / kg of the patient. Although it presents a beneficial composition, it has half-life time of approximately 250h, causing the patient to need to be hospitalized for two days before its application, and after the injection it is need to protect from the light of 4 to 12 weeks, characterizing a disadvantage in its pharmacokinetics. These disadvantages are minimal in comparison to the adverse effects found in other conventional methods (chemotherapy, radiotherapy) and even today it is used worldwide as a medicine in the treatment of cancer.[3,18,19]

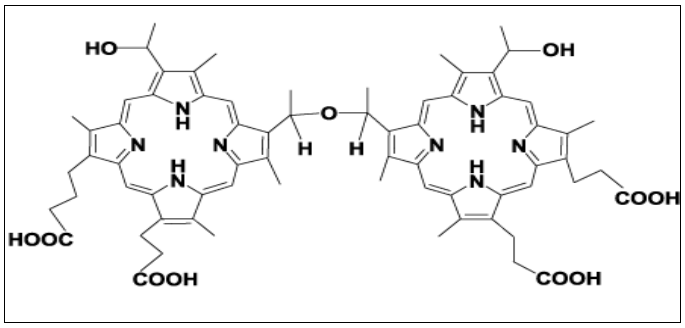


**Figure 2: Chemical structure of the drug Photofrin®.[19]**

**Levulan® e kerastick®** - Classified as second generation, they are derivatives of 5-amino-4-oxopentanoic acid (ALA), one of the most used acids in PDT in the treatment of non-melanoma skin cancer. ALA, is a prodrug, and when administered in the patient, after 3 to 6 hours it is converted in situ by an enzyme in protoporphyrin IX (PIX), endogenous photosensitizer, through the HEME biosynthetic pathway.[21] (Fig. 3). The maximum absorption is similar to other porphyrins, which can reach up to 635nm. When administered intravenously or orally, it can cause systemic photosensitivity, causing the patient to avoid direct sunlight for several days. Studies are being conducted to develop other ALA precursor more effective than DMSO. ALA treatment is preferably topical and has a high cost because it is imported substance.[20,15]

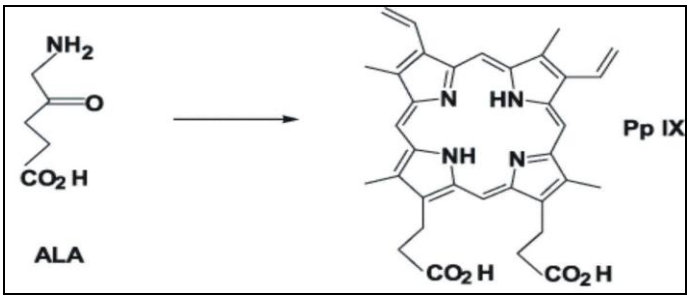


**Figure 3: Conversion of ALA into PpIX.[3]**

**Metvrix®- (MAL- (methyl aminolevulinic acid**) – is a methyl ester precursor of ALA, with greater lipophilic properties and cutaneous penetration (Fig. 4). It is also a pro-drug, with the same mechanism of action of ALA, and after 3 hours of its topical application, conversion to PpIX occurs. It has visible light application of 570-670 nm. Comparative studies of Levitan® and Metvrix® in Basal Cell Carcinoma (BCC) patients have analyzed the depth of fluorescence penetration and have shown that Metvrix® has 2mm while Levitan® has 1mm. This important advantage has been of great value in its application in cancer dermatology. [15]

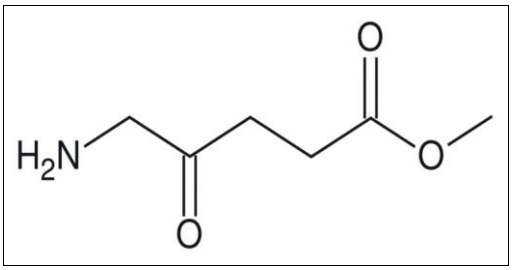


**Figure 4: Structure of methyl aminolevulinic acid (MAL).[18]**

**Photosens®-** It has a mixture of sulphonated aluminum phthalocyanine derivatives. Approved in Russia, belongs to the second generation of photosensitizers, called phthalocyanines (Fig. 5). These compounds have properties of purity, resistance to biochemical changes, efficient generators of reactive oxygen species (ROS) and high light absorption (650nm to 800nm). Because they have a relevant wave spectrum where the maximum transmission of light by cancerous tissues occurs, they are often used in skin cancer treatments.[21]

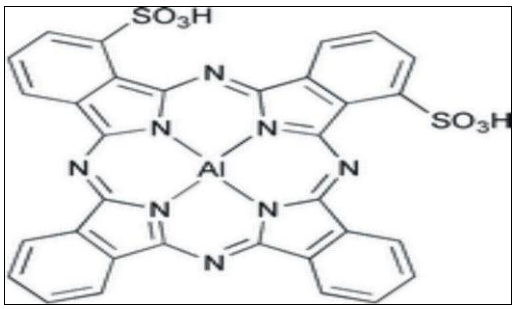


**Figure 5: Structure of sulphonated aluminum phthalocyanine.[21]**

**Foscan®-** Systemic derivative of the chlorin family, produced by meso-tetra-hydroxyphenyl-chlorine (m-THPC) and belongs to the third generation of photosensitizers (Figure 6). It is a drug that has maximum absorption into the skin after 96 hours of its intravenous administration, and can be excited at the wavelength of 652nm. Foscan®, despite the fact that it has greater selectivity and longer life in the singlet oxygen state, presents slightly lower skin photosensitivity than Photofrin®.[18]

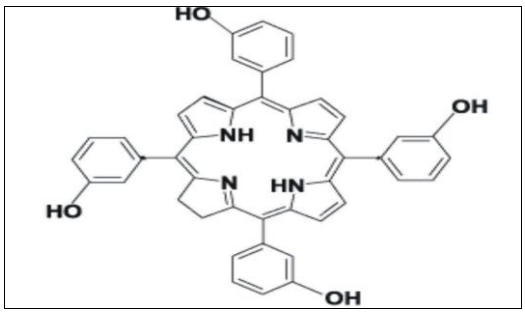


**Figura 6: Chemical structure of Foscan® drug.[18]**

## CLINICAL APPLICATION

Important advances with PDT in the treatment of cutaneous diseases have been achieved, including pre-cancerous and cancerous lesions. Treatment has been applied to non-melanoma skin cancer, usually basal (BCC) or squamous (SCC and BD) cells including actinic keratosis.[16]

Actinic keratosis (AK) is mainly developed by exposure to ultraviolet (UV) rays, and in 8% of cases, can develop into squamous cell cancer of the skin through metastases. The treatment is done with the cutaneous application of ALA cream (Levulan®) or MAL. The 20% ALA solution applied to the skin undergoes $\lambda = 417$ nm, 100-150 J / cm, with maximum absorption of 3 to 6 hours after application. While the MAL solution at 16.8% after 3 hours allows visible light illumination at 630nm, 37 J / $cm^2$.[22]

Basal Cell Cancer (BCC) is the most common cutaneous tumor in adulthood, originating from basal cells of the epidermis. Your treatment should be chosen from criteria such as disease stage, size and location.[16] Studies show that the treatment performed with PDT has great effectiveness when using MAL, resulting in a cure rate of 95% in the superficial BCC, this is applied because it has greater selectivity in comparison to the ALA.[8]

Squamous cell cancer (SCC) originates in the epidermis, specifically in the outer layer, corresponding to 20% of skin cancers. It usually reaches parts of the body that are exposed such as hand, ear, lips, neck and face. The SCC may arise from exposure to ultraviolet rays or from primary scars or chronic skin lesions.[23] The early stage of squamous cell cancer develops a disease called Bown's disease. BD is distinguished by the fact that it presents the erythematous surface of pink spots, scabs and edges of irregular proportion. PDT in the treatment of SCC and BD can be performed by skin administration of ALA (20%) or by intravenous administration of Photofrin®, and in the case of SCC, the drug Foscan®.[8]

## DISCUSSION AND CONCLUSION

Studies demonstrate the efficacy of PDT in the treatment of non-melanoma skin cancer, especially in actinic keratosis and basal cell cancer. The choice of PDT as a treatment for several diseases has been relevant.[16]

The advantages of PDT compared to other conventional therapies are reduced morbidity rate, disease recurrences, and, in addition, the selective capacity of FS minimize the side effects and do not cause mutilation to the patient.[24]

After the present review, it is suggested that the search for photosensitizers with ideal properties and the development of light sources that fit the different surfaces to be illuminated, makes PDT a promising future in the fight against cancer non-melanoma skin,

using it in protocols of cancer centers, and can be used as a method of early diagnosis or administered in combination with other therapies.

**Competing interests**

All the authors declare that do not have any competing interest which can interfere in their judgement of analysis and interpretation of results of this study.

**Authors contributions**

All the authors participated in the design of the study, execution of the research and writing of the article.

Ana Laura Remédio Zeni Beretta - Participated in the conception, design, and implementation of research, writing the article and final approval of the version to be published.

All authors read and approved the final manuscript.

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