Analysis of Photodynamic Therapy applied to skin disorders by a topical photosensitizer

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ABSTRACT

Optical treatment of pathological tissues comprises techniques like Low Intensity Laser Treatment (LILT) or Photodynamic Therapy (PDT). PDT consists on the inoculation of a photosensitizer in the tissue, which tends to be accumulated in cancerous cells, and on the posterior optical radiation of the area. The photosensitizer, that can be topical or systemic, is excited and cell necrosis is provoked. The collateral harmful effects of other destructive techniques, like radiotherapy or chemotherapy, are avoided with PDT. PDT can also be used as a complementary technique of conventional excisional surgical operations. The application of PDT to skin disorders is straightforward due to the fact that it is an external and accessible tissue. In this work, we analyze the application of PDT to several skin pathologies and the results obtained, by means of mainly the usage of Metvix® as a topical photosensitizer and with an optical source in the range of 635 nm. The analysis includes a predictive model of the PDT process, based on an optical propagation equation and a photosensitizer degradation approach that provides an estimation of tissue destruction.

Keywords: Photodynamic Therapy, topical photosensitizer, Metvix®, skin disorders

1. INTRODUCTION

Skin disorders are becoming even more common in the recent years, due to several facts like the increase of solar exposition of the population, the change in clothing habits that let a greater skin area exposed, the increase of the longevity and the lack of ozone in the atmosphere. In particular, the nonmelanoma skin cancer is a big health problem in the western countries. Basocelullar carcinoma or squamous cell carcinoma are included in this group. One third of the diagnosed cancerous processes is of this kind [1]. The conventional treatment of these skin disorders includes surgery, electrocoagulation, cryosurgery, radiotherapy or pharmacological solutions like Imiquimod. Although they are efficient in general, they present several disadvantages. Most of them are invasive methods and even require anaesthesia for their application, so there are patients that could not be treated in this way. Also the cosmetic results are in general non-satisfactory, due to the existence of scars after treatment.

Biomedical optics is a scientific branch that allows the existence of new or improved tools for practitioners, either in the optical characterization or optical treatment of biological tissues [2]. Regarding optical treatment, there are techniques like Thermotherapy [3], in which a slight temperature increase provokes an improvement in the pathological tissue, or Photodynamic Therapy (PDT) [4]. Photodynamic Therapy is an optical technique whose objective is malignant tissue destruction. This tissue, usually cancerous, is destroyed by means of the inoculation of a photosensitizer. This substance is accumulated mainly in the region that is intended to be suppressed. The radiation exposition of the area makes the photosensitizer activate and it starts the destructive effect. Having this mechanism in mind, it is clearly seen that one of the main aspects of the application of this technique is the delimitation of the volume of tissue affected. The effort must

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be concentrated on the protection of adjacent tissues, to avoid these undesired collateral effects. The amount of tissue destroyed will depend on the substance inoculated in the tissue, on its reactive characteristics and its spatial distribution. It will also depend on the specific properties of the optical source used for irradiation, that is, optical irradiation, wavelength and exposition time.

In this work, the application of PDT to several skin disorders is analysed by means of mainly a topical photosensitizer, Metvix®. First of all, a general description of the skin disorders that will be considered is provided. Afterwards PDT technique is described in some detail, in order to better understand the process. Next section shows some results of the application of PDT in these skin disorders. Finally, a PDT model that tries to simulate the therapy application is presented. Optical propagation is modelled by means of the diffusion approach of optical radiation [2]. Optical energy deposition inside the tissue affects the photosensitizer properties, in such a way that its absorption varies due to the degradation provoked by the incident radiation. All these considerations are used to construct a PDT model that estimates necrosis depth in tissue as a function of the treatment parameters, mainly optical source power, wavelength and exposition time.

2. SKIN DISORDERS AND CONVENTIONAL TREATMENTS

2.1 Nonmelanoma skin cancer

Nonmelanoma skin cancer is one of the main health problems in western countries. One third of the diagnosed cancers is of this type, and it is the most frequent malignant neoplasia in humans [1]. The origin of this cancer is epithelial and they include 80% of cutaneous cancers. In this way, they appear 20 times more than the melanoma. Nonmelanoma skin cancer includes basocellular carcinoma or squamous cell carcinoma, among others. The former appears in the basal epidermal cells and it is originated without presenting a previous lesion. Metastasis risk is extremely low, but this kind of cancer is able to provoke great local tissue destruction. An example of basocellular carcinoma can be seen in Figure 1. Squamous cell carcinoma can be basal or spinous, presents a fast growing process and it is more likely to invade other tissues. Previous lesions that degenerate in squamous cell carcinoma are actinic keratosis and Bowen disease [5]. Actinis keratosis is the most frequent premalignant lesion, with an apparition rate ten times over that of the basocellular carcinoma. It is the main lesion that acts as a precursor of squamous cell carcinoma. Squamous cell carcinoma provokes metastasis in 5% of the cases, due to linfatic or vascular infiltration.

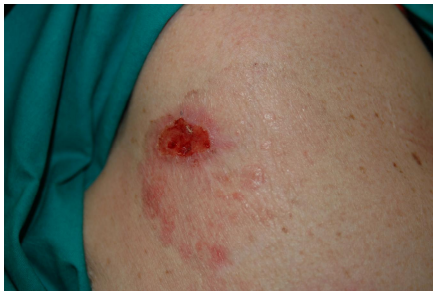

Fig. 1. Superficial basocellular carcinoma.

The origin of nonmelanoma skin cancer is greatly varying, but the main present cause is the chronic exposition to ultraviolet radiation. These cases are daily seen in medical praxis, either in the primary service or by the specialist. The incidence of nonmelanoma skin cancer is increasing by 4% each year. Nowadays a white male has a 33% risk of developing a basocellular carcinoma and more than 9% of suffering from a squamous cell carcinoma. This great increase in the incidence is thought to be related with some habits like the rising amount of solar exposition, the change in clothing habits that let more skin exposed to solar radiation, the increased longevity and the reduction of ozone in the atmosphere. The fact that the most usual areas affected are the exposed body parts like the face, and the low death rate of nonmelanoma skin cancer make cure and cosmetic the principal objectives of the treatment. In this way, the treatment must be oriented to tumour elimination, relapse avoidance, recovery of the cosmetic and functional appearance of skin and maximization of the rate cost-effectiveness.

2.2 Nonmelanoma skin cancer conventional treatments

There is no consensus about the most appropriate treatment for skin cancer. In case of basocellular carcinoma or actinis keratosis some techniques are frequently used, like excision surgery, electrocoagulation, cryosurgery, micrographic

Mohs surgery, radiotherapy, CO_2 laser or pharmacological treatments like Imiquimod or 5-fluoracil. The choice of one of these techniques is motivated by the localization and size of the lesions, the previous treatments employed, the age and preferences of the patient, the skills of the practitioner and the rate cost-effectiveness.

Excision surgery is considered by many practitioners as the first choice treatment due to its high exit rate in most of the cases. Furthermore, it allows a histological analysis of the tumour in order to confirm the elimination of cancerous tissue. However, it is a total invasive method, so it implies a lot of inconvenience for the patient and even anaesthesia. The application of this technique is limited when the tumour is located in critic functional or cosmetic areas (like for instance in ears, nose or lips), and it is able to provoke scars in most cases. In the same line, electrocoagulation is usually employed in superficial low-risk lesions. This is due to the fact that it is a cheap, quick and easy process. As excision surgery, it is an invasive procedure and requires local anaesthesia. Healthy tissue could also be affected and scars could appear. There is a risk of infection coming from the operation as in the previous case. The relapse rate is about 7.7%.

Cryosurgery consists on the application of cold to the skin so as to provoke controlled tissue destruction. The most usual cryogenic is liquid nitrogen. Cryosurgery is a quick and simple technique, which can be applied out of the operating room. However, the procedure is invasive and painful for the patient. Practitioner skills are fundamental in this case due to the fact that the process is non-normalized. Again this technique destroys also healthy tissue and the cosmetic result is not good, resulting in scar formation. There is also a risk of infection of the wound.

Mohs surgery is the technique that offers the best cure rates for basocellular carcinoma, with a 99% in primary treatments and 95% in relapse diseases [6]. The use of this technique is indicated in tumours located in complicated parts, bad defined, with an aggressive appearance or coming from a relapse process. As in the case of conventional surgery, it is an invasive procedure and requires the use of even general anaesthesia.

Radiotherapy is employed in big tumours and usually in old patients, whose tolerance to surgery could be difficult or even impossible. The cure rate is high under trained practitioners. On the other hand, it requires special radiological areas, the treatment is applied is various long sessions and the cost is high. Furthermore, the relapse tumours are much more aggressive and invasive than the previous ones.

CO_2 laser is a technique that is not used in the usual praxis. The method allows precise treatments, but the cost is high and the practitioner must carry out a learning process before the application.

Imiquimod is a drug that allows a non-invasive treatment of basocellular carcinoma and Bowen´s disease at home. It can be employed in big areas, but the main disadvantage is the appearance of collateral effects like pain, irritation, inflammation, ulceration or even necrosis. As a consequence, some patients leave the treatment and others suffer from complications due to infections. Furthermore, the relapse rate is greater than in other techniques.

In conclusion, conventional treatments are efficient, but they present limitations in big or numerous lesions. Furthermore, they are painful in many cases and the cosmetic results are in general non-satisfactory. In this way, there are patients that cannot or do not want to be treated by surgery (multipathology patients, those who carry a pacemaker, allergic to the anaesthesia, etc.). New approaches are required in order to provide a non-invasive, efficient, safe and good cosmetic treatment.

3. PHOTODYNAMIC THERAPY

Photodynamic Therapy consists on the administration of a photosensitizer that is located and remains longer in malignant cells rather than in healthy ones. After this substance disappears almost completely from healthy cells, it is excited by optical irradiation at an appropriate wavelength, depending on the specific photosensitizer absorption response [4]. The amount of photosensitizer inoculated is not dangerous by itself, but when optically excited it encourages photochemical and photobiological processes that lead to a lethal effect in tumoral tissues.

When the photosensitizer is irradiated with an appropriate optical source, it is excited. As it goes back to the ground state, the decays activate the molecular oxygen to create reactive oxygen species (ROS). These species are greatly cytotoxic, and as a consequence they provoke an irreversible oxidation of the essential cellular structures. In other words, the PDT is based on the use of a chromophore that catalyzes the reaction known as photosensitized oxidation. Oxygen is absolutely necessary for these photochemical reactions, and so cellular necrosis could not appear in anoxic conditions [7].

There is an effect that has a great influence on the amount of photosensitizer and, as a consequence, on its distribution in cells. This is called photobleaching, and most of the photosensitizers used in Photodynamic Therapy show this behavior. This fact makes the selectivity of the therapy increase. Photobleaching is a permanent photochemical degradation of the chromophore due to the action of the products formed during the photochemical reactions. Having this in mind, the contribution of the photobleaching effect to PDT efficiency, in the sense of selectivity, is clear. The reason is related with the photosensitizer reduction in healthy adjacent tissues. If this concentration is reduced until it goes below the photochemical reactions threshold, no cytotoxic products are generated and no damage is provoked. Of course photobleaching implies also that the photosensitizer in malignant tissues could be extincted. If this takes place, all the subsequent irradiation would be useless, because no destruction would appear in tissue.

Although the main application of PDT is the destruction of cancerous tissue, it can also be employed in other medical procedures. For instance, PDT could also be used in the fields of dermatology, ophthalmology (Age-related Macular Degeneration), molecular biology or even esthetics [7].

4. PHOTODYNAMIC THERAPY IN DERMATOLOGY

As it was stated in previous paragraphs, PDT is an interesting therapeutic technique, non-invasive and with a great selectivity. Here we will center the application of PDT by means of Metvix® photosensitizer. The clinical procedure of PDT in dermatology consists of the following steps. First, flakes in actinic keratosis or tumour material in basocellular carcinoma are removed. For this task, anaesthesia could be required. The wound is cleaned with saline solution, and afterwards a 1 mm thick layer of Metvix® is applied on the lesion, till 1 cm around. The wound is covered with an opaque dressing and it remains so for three hours. After that the remaining photosensitizer is removed with saline solution and illuminated by a red light lamp at 636 nm, with a distance to the tissue between 5 and 8 cm. The usual dosimetry employed is 37 J/cm^2 during 7 to 9 minutes. After illumination, the treated area must remain covered for 48 hours. After that time, the patient can leave the dressings, but solar protectors of high factor must be used.

In the particular case of actinic keratosis only one session is needed. In basocellular carcinoma or Bowen disease other session is carried out in one week. There are various advantages of PDT in dermatology over conventional techniques. First of all, it is a non-invasive technique, with a high specificity and selectivity. In this way, healthy tissue is not affected. It is a treatment easily tolerated by patients, because only a slight pain could appear in the treated area, but it is suppressed by the application of air or cold water. Various lesions can be treated in the same session, and the treatment can be repeated as many times as necessary. Having to do with cosmetics, no scars appear in the affected area. No special skills of the practitioner are required due to the simplicity of the procedure, and difficult lesions (multiple or extended lesions) can be treated. Collateral effects are slight, temporary and limited to the treated area. As a disadvantage of PDT, we could mention that there is no histological confirmation about the cure of the tumour. Other disadvantage is that the procedure is slow, due to the fact that the affected area must be well prepared and also due to the fact that after three hours the patient is seen again for the illumination. PDT is not indicated in case of hypersensibility to the photosensitizer or in morpheiphorm basocellular epitheliomas.

The results of the application of PDT in dermatology confirm the ideas previously exposed. In the case of dermatology, PDT is applied mainly to actinic keratosis, Bowen disease and basocellular carcinomas. PDT has also been applied in other disorders like Paget disease or vascular lesions, among others. In actinic keratosis the application of PDT by means of 5-methyl aminolevulinate (MAL) photosensitizer provokes a complete cure in 91% of the cases [8]. Compared with cryotherapy, the conclusions are that one PDT session has the same efficiency (around 70% of cure), but with a better cosmetic result with PDT. However, after two sessions PDT obtains better results, with around 91% of cure and the same good cosmetic results [9]. In the case of Bowen disease, studies show cure rates of 82% with PDT and ALA photosensitizer. The application of one session of PDT is more efficient than cryotherapy, and again the cosmetic result if much better with PDT than with conventional therapies. Basocellular epitheliomas reveal a cure rate of 97% when treated with PDT and MAL, results similar to those of surgery. As usual, cosmetic results of PDT are better than those of the conventional techniques.

5. PHOTODYNAMIC THERAPY MODEL

The application of PDT is based on some protocols, when they exist, that tend to assure the safety of the treatment. As a consequence, these protocols are not dependent on the real disease the practitioner is dealing with. This implies that the treatment parameters are not the most efficient ones to treat that disorder in particular, but rather normalized ones. In this

section, we propose a model for PDT that allows a predictive analysis of the procedure. With this model, it is possible to estimate necrosis extension as a function of tissue, source and photosensitizer parameters. Optical power or exposition time could be changed in order to find the best parameters for the particular disease under treatment.

In the problem we are dealing with, we use the diffusion theory to model optical propagation in tissue [2]. In the diffusion model, tissues are characterized, from the point of view of optical propagation, by the following parameters: refraction index n; reduced scattering coefficient $\mu_s' = (1-g)\cdot\mu_s$, where g is the anisotropy of scattering and μ_s is the scattering coefficient; and the absorption coefficient $\mu_a' = \mu_{a0} + \mu_{aPS}$, where μ_{a0} is the tissue absorption coefficient and μ_{aPS} is that of the photosensitizer. All these parameters allow the calculation of the diffusion constant $D = \dfrac{1}{3(\mu_a' + \mu_s')}$.

The diffusion model is represented by a diffusion equation, which can be expressed in the following way:

$$\frac{\delta\phi(\vec{r},t)}{c\delta t} + \mu_a\phi(\vec{r},t) - \nabla\left[D\nabla\phi(\vec{r},t)\right] = S(\vec{r},t) \tag{1}$$

In this equation, D is the diffusion constant, $\phi(\vec{r},t)$ represents the irradiance in the tissue, and $S(\vec{r},t)$ takes into account the optical source power per unit volume. A finite difference numerical method can be used to obtain a solution for the fluence rate [10].

Equation (1) provides a spatial-temporal solution for the optical distribution inside an irradiated tissue. However, the photosensitizer suffers from the photobleaching effect, and this must be taken into account because it changes the optical absorption of the sample. One approach is to state that the photobleaching kinetics follows a first order function [11]:

$$\frac{d\,\mu_{aPS}(z,t)}{dt} = -\beta.\Phi(z,t).\mu_{aPS}(z,t), \tag{2}$$

where β is the so-called photobleaching rate of the photosensitizer (m^2/J). A very interesting parameter that deals with tissue necrosis is the so-called photodynamic dose D. A parameter called singlet oxygen quantum yield, γ_0, gives an idea of the amount of toxic products created by the reactions. Next equation shows how this dose is modeled:

$$\frac{dD}{dt} = \gamma_0.\Phi(z,t).\mu_{aPS}(z,t). \tag{3}$$

In order to limit the damaged zone, a dose threshold, D_0, must be established for the particular tissue of the PDT treatment. Equations (1), (2) and (3) provide a complete model for PDT damage prediction.

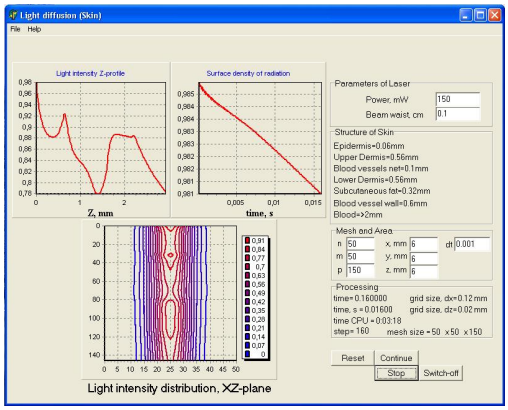

Fig. 2. Screenshot of the program that implements the PDT model for skin diseases.

This model was implemented in a high level language and an executable program was generated in which different optical parameters can be changed. A screenshot of the appearance of the program is shown in Figure 2. The diffusion equation was solved via a numerical explicit finite difference method. The time step was chosen sufficiently low so as to

make the method converge, and the execution time remain reasonably low. After every time step, the optical absorption of the photosensitizer was updated in order to take photobleaching into account.

Any case, this tool allows the adjustment of the source parameters according to the tissue under treatment and the photosensitizer used, by predicting necrosis depth in the particular case of skin disorders.

6. CONCLUSIONS

The increase in skin disorders in the last years has provoked a great amount of cases by the practitioner. The increase of solar exposition on the population, the change in clothing habits that let a greater skin area exposed, the increase of the longevity and the lack of ozone in the atmosphere could be some reasons for this fact. In particular, the nonmelanoma skin cancer is a big health problem in the western countries. Basocelullar carcinoma or squamous cell carcinoma are included in this group. Conventional techniques like surgery, electrocoagulation, cryosurgery, radiotherapy or even pharmacological solutions present some disadvantages that are solved to a great extent by PDT. Among PDT advantages over conventional treatment techniques, we could mention non-invasivity, selectivity and the lack of severe collateral effects.

In this work, we presented the application of PDT on skin diseases and showed the advantages over conventional therapies. The process of PDT was presented in detail, and the increase exit rate of PDT was stated with clinical evidence. As the process of PDT application is carried out by means of protocols in many cases, and in this way the efficiency of the treatment for the particular problem is not assured, we proposed a PDT model for the prediction of the results. It is based on a diffusion approach for the optical propagation, combined with a first order kinetics for the photobleaching rate. The change in optical parameters allows choosing the best power and exposition time for a particular disease, so the procedure efficiency could be increased.

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