BASIC PRINCIPLES OF PHOTODYNAMIC THERAPY IN DERMATO-ONCOLOGY

M. TAMPA[1], CLARA MATEI[2], RODICA-MARIANA ION[3], SIMONA-ROXANA GEORGESCU[4]

[1,2,4] "Carol Davila" University of Medicine and Pharmacy Bucureşti, [3]ICECHIM, Bucureşti, [3] "Valahia" University of Târgovişte

Keywords:
photodynamic therapy, squamous cell carcinoma, actinic keratoses, dermato-oncology

Abstract: *Photodynamic therapy (PDT) is a modern procedure used in dermatology mainly in the treatment of cutaneous malignant tumours (e.g. basal cell carcinoma, squamous cell carcinoma, Kaposis's sarcoma, mycosis fungoides) and premalignant lesions (e.g. actinic keratoses, Bowen's disease, dysplasia and erythroplasia of oral mucosa, erythroplasia of Queyrat). The procedure requires a photosensitiser (PS) able to be selectively accumulated in the tumoral tissue and a light source capable of emitting radiation of an appropriate wavelength in order to activate the photosensitiser. This paper aims at reviewing the basic principles of PDT and the criteria for choosing the photosensitiser, the light source and the adequate values of the physical parameters used in order to obtain optimal therapeutic results with minimal adverse reactions in dermato-oncologic PDT.*

Cuvinte cheie: *terapie fotodinamica, epiteliom spinocelular, keratoze actinice, dermato-oncologie*

Rezumat: *Terapia fotodinamică (PDT) este o procedură modernă utilizată în dermatologie în principal în tratamentul unor tumori cutanate maligne (epiteliom bazocelular, epiteliom spinocelular, sarcom Kaposi, micosis fungoides) şi al unor leziuni precanceroase (keratoze actinice, boala Bowen, displazie şi leucoplazie orală, eritroplazie Queyrat). Metoda necesită utilizarea unui fotosensibilizator (PS) care să aibă proprietatea de a se acumula selectiv la nivelul ţesutului tumoral şi a unei surse de lumină capabile să emită radiaţii cu o lungime de undă adecvată activării fotosensibilizatorului. Articolul de faţă îşi propune să treacă în revistă principiile generale ale PDT şi criteriile care stau la baza alegerii fotosensibilizatorului, a sursei de lumină şi a valorilor optime ale parametrilor de utilizat în vederea obţinerii unor rezultate terapeutice cât mai bune, însoţite de reacţii adverse minime, în terapia fotodinamică dermato-oncologică.*

Photodynamic therapy (PDT) is a modern treatment in dermato-oncology, based on using a chemical photosensitising compound with the capacity to accumulate with good selectivity in the tumoral tissue and a light source of an adequate wavelength, able to initiate, by activating the photosensitiser (PS), a chain of photochemical reactions leading to tumour destruction by the means of tumoral cells apoptosis and local vasculature alteration.(1)

The procedure is used in the field of dermatology mainly in the treatment of malignant skin tumours (e.g. basal cell carcinoma, squamous cell carcinoma, Kaposis's sarcoma, mycosis fungoides) and premalignant lesions (e.g. actinic keratoses, Bowen's disease, dysplasia and erythroplasia of oral mucosa, erythroplasia of Queyrat). PDT can be employed with excellent therapeutic and cosmetic results and minimal adverse reactions in the patients who are not able to undergo surgical excision, present numerous skin lesions or have been submitted to multiple conventional treatments in the past, that led to failure.(2)

The mechanism of photodynamic therapy

Following the absorption of an energy quantum by a PS molecule in fundamental state, one of the two electrons in the peripheral molecular orbital suffers an energetic transition to a superior energy level in a so-called *excited state*. The excited state in which the spins of the two electrons are opposite is called *singlet excited state*, whilst the excited state in which the spins are parallel is called *triplet excited state*. The fundamental (ground) state of the majority of molecules is *singlet state*; the *triplet states* are states of low quantum probability of formation but with long lifespan of about 10^{-3}s-1s, necessary and sufficient for initiating the photochemical processes. The PS is a chemical compound with high quantum yields and an increased probability of triplet state formation.(3)

An electron from a superior excited state may return to a lower energetic state by vibrational relaxation, by fluorescence or by inter-system crossing - a process in which the molecule from an *excited singlet state* is shifting to an *excited triplet state*, after which it will give up the accumulated energy either by phosphorescence or by initiating *photodynamic reactions* – the main physical processes in PDT. There are two types of photodynamic processes in biological systems: *type I photodynamic reactions* - a chain of successive redox chemical reactions - and *type II photodynamic reactions* - of utmost importance in PDT-reactions of energy transfer between the excited triplet PS molecules and the molecular oxygen, whose ground state has the characteristic configuration of triplet, the last being transformed in singlet oxygen. The photodynamic reactions eventually lead to the formation of reactive oxygen species (ROS): superoxide anion O_2^-, hydroxyl radical OH and singlet oxygen $^1O_2$, the latter being the most aggressive of them, all being considered the main promoters of the destructive effects of PDT.(1,3)

PDT comprises a succession of phases: **the administration of the pharmacological compounds**, **a time interval of accumulation or synthesis of photosensitising compounds** in the tumoral cells and **the irradiation of the**

[1]Corresponding author: Mircea Tampa, Sos. Mihai Bravu 281, Sector 3, Bucuresti, E-mail:tampa_mircea@yahoo.com, Tel: +40758 040752
Article received on 28.05.2011 and accepted for publication on 31.07.2012
ACTA MEDICA TRANSILVANICA September 2012;2(3):263-265

tumour.(4)

Choosing the adequate photosensitiser

Photosensitisers (PS) are chemical compounds able to form, upon the absorption of an energy quantum, excited triplet states with a greater probability than other substances. The ideal PS should exhibit the following characteristics: is inocuous/non-toxic in the absence of light, non-allergic, non-teratogenic, well tolerated, with good propensity for efficient and fast accumulation in the tumoral cells and bears the capacity to absorb the light at a particular wavelength where radiation is not absorbed by other skin chromophores (i.e. haemoglobin, oxyhaemoglobin, water or melanin).(4) Each of the existing PS has its own particular advantages and disadvantages. The dermatologist has to choose between the existing PS the one which is the most suitable for each particular clinical situation, therefore it is important to know the basic characteristics of the PS.

There are two main classes of chemical compounds employed as PS in PDT:

-porphyrins and porphyrin-related compounds: hematoporphyrin derivative, porfimer sodium, chlorines, phthalocyanines and various sulphonated porphyrins sharing a more or less similar tetrapiloric macrocycle heterocyclic structure. These compounds are administered intravenously and will concentrate selectively in the tumour cells using various mechanisms: increased permeability of the tumoral blood vessels, increased number of tumour associated macrophages - that concentrate up to 9 times more PS than the tumoral cells- and increased LDL receptor density, as circulating LDL acts like a carrier for the majority of porphyrinic PS.(1,5)

-porphyrin precursors, mainly 5-amino-levulinic acid (ALA) and its esters, of which the most used is its methylic ester, methyl-amino-levulinate (MAL). They are the most used compounds in dermato-oncologic PDT. The prophyrin precursors are topically administered and have good transcutaneous penetration. In the tumoral cell cytoplasm, the ALA esters are hydrolised into ALA, which will be taken over by the skin cell enzymatic apparatus of haem synthesis and consequently transformed into protoporphyrin IX, a photosensitising compound that accumulated in the tumour cell; portoporphyrin IX is the actual PS in PDT, as the porphyrin precursors do not have photosensitising properties *per se.*(4)

Choosing the appropriate wavelength

The wavelength employed for PDT must be chosen so that to overlap to a peak of the absorption spectrum of the particular PS used in that clinical situation. Moreover, the dermatologist must consider the optical window, the wavelength interval where light is not absorbed by other skin chromophores. The wavelength must be less than 850 nm, so it could hold sufficient amount of energy as to be able to generate singlet oxygen ($^1O_2$).

In dermatological practice, in consideration to each clinical situation encountered, the blue light of 415 nm is usually preferred for a maximum of absorption by most used PS and the red light of 630 nm is employed for its ability to penetrate more into the skin depth.(6)

Choosing the appropriate light source for PDT

PDT in dermato-oncology employs sources that emit light in visible and near-UV and near-infrared spectra. Choosing the appropriate light source must consider its technical parameters (especially the emitted spectrum), reliability, portability and acquisition and maintenance cost. Nowadays, the following categories of light sources are available for PDT:

-Incoherent light sources: are based on xenon arcs (400-1400 nm), tungsten filaments, on various halide-metal combinations or they could be fluorescent lamps. They allow dermatological applications and are cheap and reliable but they also comprise an important undesirable thermal effect. Such sources used in dermatology are Versa-Light™ or Curelight™-sources with wide spectrum situated between 580 and 1400 nm.(7)

-LED (acronym for "light emitting diode") sources: are light sources embracing the advantage of having a narrow emission spectrum and therefore, they have consequently decreased thermal effects. Examples of LED lamps used in PDT are Aktilite™ (590-670 nm) and Omnilux PDT™ (630-636 nm).(8)

New flexible *organic LED (OLED) sources* have been recently added to the therapeutic arsenal; these sources are placed directly on the patient's skin surface and will emit radiation from a battery source following a 3-hour interval; meanwhile the patient is able to follow his daily routine. An example of such an OLED light source is Ambulight PDT™, which emits red light with an irradiance of 5-7 mW/cm^2 and a fluency of 45-75 J/cm^2. The procedure uses MAL or ALA for PS and embraces the usual indications of PDT; the level of pain perceived by the patient is lesser than that implied in other forms of PDT.(9,10)

-LASER sources. Laser radiation is coherent, collimated and monochromatic. The power of laser radiation is higher than that of other light sources, but the laser sources are less reliable and are more expansive in terms of acquisition and maintenance costs. Dye lasers are widely used in present-times PDT, and more recently, diode lasers of a wavelength comparable to that of the most frequently used PS; moreover, the latter are cheaper, more reliable for clinical applications and have a good portability.(11)

Choosing the energetic parameters for PDT irradiation

The fluency is defined as the energy delivered per surface unit and is usually expressed in J/cm^2. The fluency rate (irradiance), expressed in W/cm^2, is defined as the power (energy per second) delivered to each surface unit. The fluency and irradiance values vary widely with the type of skin lesion to be treated, its surface and thickness. In general terms, an elevated irradiance leads to a higher temperature of the target-area, therefore fluency rates over 200mW/cm^2 are not advisable. Fluency values more than 40J/cm^2 lead to tissular oxygen depletion, inhibiting the photodynamic processes.(11)

The photosensitiser (PS) concentration and the pre-irradiation interval

The majority of studies regarding the use of MAL in PDT employ a concentration of 160 mg/g, applied for 3 hours under occlusive dressing before PDT irradiation.(12) However, in a randomised study on 112 patients with 384 actinic keratoses, Braathen et al. have proven that PDT with MAL is efficient even one hour after the topical application of the PS.(13) As for using ALA for a PS in dermato-oncologic PDT, there is no consensus in respect to the employed parameters.(12) ALA is usually topically applied in 20% concentration under occlusion, or, more recently, it can be incorporated in self-adhesive patches.

Warren et al. have shown that the production of protoporphyrin IX in actinic keratoses keratinocytes is maximal at 2 hours post-application of ALA; longer pre-irradiation intervals do not bring a plus in the efficiency of the procedure.(14) Alexiades-Amenekas has shown that there are no significant differences between the effects of 595 nm pulsed-lased PDT with ALA, effectuated after pre-irradiation intervals of 3 or 18 hours.(15)

Conclusions:

PDT is a recent acquisition in the treatment of non-melanoma skin tumours. Optimal values of main parameters

employed in dermato-oncologic PDT depend on the type of skin lesion to be treated and various characteristics of the lesions (e.g. thickness of the lesion, total lesion surface); many studies all over the world are trying to assess these values into well-established treatment protocols. Knowing the basic principles and the optimal parameters used in PDT is crucial for the dermatologist, enabling him/her to obtain optimal therapeutic results with minimal adverse reactions.

REFERENCES

1. Moan J, Peng Q. An outline of the history of PDT" in Thierry Patrice. Photodynamic Therapy. Comprehensive Series in Photochemistry and Photobiology, The Royal Society of Chemistry. pp. 1-18. doi:10.1039/9781847551658; 2003.
2. Allison RR, Mang TS, Wilson BD. Photodynamic therapy for the treatment of nonmelanomatous cutaneous malignancies. Semin Cutan Med Surg. 1998;17(2):153-163.
3. Ion RM. Porfirinele si terapia fotodinamica a cancerului, Editura Stiintifica FMR; 2003.
4. Josefsen LB, Boyle RW. Photodynamic therapy and the development of metal-based photosensitisers. Met Based Drugs. 2008;2008:276109.
5. Korbelik M, Krosl G, Olive PL, Chaplin DJ. Distribution of Photofrin between tumour cells and tumour associated macrophages. Br J Cancer. 1991;64(3):508-512.
6. Alexiades-Armenakas M. Laser-mediated photodynamic therapy. Clin Dermatol. 2006;24(1):16-25.
7. Brancaleon L, Moseley H. Laser and non-laser light sources for photodynamic therapy. Lasers Med Sci. 2002;17(3):173-186.
8. Szeimies RM, Radny P, Sebastian M, Borrosch F, Dirschka T, Krahn-Senftleben G, et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a prospective, randomized, double-blind, placebo-controlled phase III study. Br J Dermatol. 2010;163(2):386-394.
9. Moseley H, Allen JW, Ibbotson S, Lesar A, McNeill A, Camacho-Lopez MA, et al. Ambulatory photodynamic therapy: a new concept in delivering photodynamic therapy. Br J Dermatol. 2006;154(4):747-750.
10. Attili SK, Lesar A, McNeill A, Camacho-Lopez M, Moseley H, Ibbotson S, et al. An open pilot study of ambulatory photodynamic therapy using a wearable low-irradiance organic light-emitting diode light source in the treatment of nonmelanoma skin cancer. Br J Dermatol. 2009;161(1):170-173.
11. Sibata CH, Colussi VC, Oleinick NL, Kinsella TJ. Photodynamic therapy: a new concept in medical treatment. Braz J Med Biol Res. 2000;33(8):869-880.
12. Calzavara-Pinton PG, Venturini M, Sala R. Photodynamic therapy: update 2006. Part 2: Clinical results. J Eur Acad Dermatol Venereol. 2007;21(4):439-451.
13. Braathen LR, Paredes BE, Saksela O, Fritsch C, Gardlo K, Morken T, et al. Short incubation with methyl aminolevulinate for photodynamic therapy of actinic keratoses. J Eur Acad Dermatol Venereol. 2009;23(5):550-555.
14. Warren CB, Lohser S, Wene LC, Pogue BW, Bailin PL, Maytin EV. Noninvasive fluorescence monitoring of protoporphyrin IX production and clinical outcomes in actinic keratoses following short-contact application of 5-aminolevulinate. J Biomed Opt. 2010;15(5):051607.
15. Alexiades-Armenakas MR, Geronemus RG. Laser-mediated photodynamic therapy of actinic keratoses. Arch Dermatol. 2003;139(10):1313-1320.