ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. LIX, N 2, 192 SECTIO D 2004

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Photodynamic therapy – mechanism and employment

HISTORY OF PHOTODYNAMIC THERAPY

The beginnings of photodynamic therapy go back to ancient times. The oldest centers of phototherapy were situated in ancient Greece where, under the auspices of Herodotus, heliotherapy was created. In modern times, German student, Oskar Raab was the first who dealt with the photodynamic therapy. He described in 1900 the toxic effects of acridine orange combined with the light on the paramecium. In 1903 von Trappeiner and Jesionek showed that locally treatment with eosine activated by the sunlight might be applied in the therapy of skin carcinomas. In the 60's of the 20th century the interest in the photodynamic therapy became wider. In 1966 Lipson et al. used the derivatives of hematoporphyrin as photosensitizing substances in the treatment of breast tumours. In 1975 an attempt was made to use the photodynamic therapy in the management of carcinoma of the bladder. In 1976 the comprehensive studies concerning the usefulness of the photodynamic therapy in oncology and other medicine branches were initiated in the Roswell Park Cancer Institute in Bufallo.

In 1993 the government of Canada for the first time officially recognized the photodynamic therapy as an effective method of treatment in bladder carcinomas. In 1994 the photodynamic therapy was also approved in Europe and Japan and many medical centers became interested in its usefulness. In Great Britain, the photodynamic therapy is a well-recognized and applied method of treatment in actinic keratoses, Bowen's disease and superficial basal cell carcinoma.

MECHANISM OF PHOTODYNAMIC THERAPY

The photodynamic therapy is based on the activation of the photosensitizing substances by visible light, which are deposited in the treated tissue. During this reaction the reactive oxygen forms are produced, which exerts the toxic effect on the cells of treated neoplasma and on the vessels constituting the integral part of the tumor. The treatment results in the death of neoplasmatic cells (18). Singlet oxygen generated during the photodynamic reaction belongs to oxygen free radicals, i.e. the extremely reactive compounds due to the unpaired electrons on their valence orbit. The radicals easily react with proteins, lipids, carbohydrates and nuclein acids causing the damage to the cell and tissue structure and function.

Singlet oxygen reacts with other molecules in a double way: it gives them off the activation energy while converting into a triplet state or reacts with them chemically. From the chemical point of view, there are several main types of reactions of singlet oxygen with organic compounds. It may be: the addition to alkenes and their aliphatic and heterocyclic derivatives; oxidation of alkenes and their derivatives to alkyloperoxides (e.g., oxidation of cholesterol and tryptophan and binding the polyunsaturated fatty acid radicals, which leads to the formation of lipid peroxides); addition to double bonds in alkenes and their derivatives (e.g., degradation reactions of polyunsaturated radicals of fatty acids); oxidation of

sulphides to sulphoxides (e.g., oxidation of methionine to its sulphoxide) and oxidation of phenols. The amino acid radicals of histidine are most susceptible to the damaging effects of singlet oxygen, followed by those of methionine, tryptophan, tyrosine and cystein. Among the constituents of nuclein acids, singlet oxygen preferentially reacts with guanine and other purine derivatives contrary to the hydroxide radical which attacts unselectively all purine and pyrimidine radicals.

Despite their direct destructive effects on cells, oxygen free radicals activate immunological and inflammatory processes acting as secondary cell transmitters. They affect the expression of acute phase protein genes, genes of cytokines and their receptors, growth factors, adhesive molecules and antioxidative enzymes. Furthermore, they activate the cascade of arachidonic acid metabolism, which results in the production of inflammatory mediators: prostaglandines, thromboxane, leukotrienes and lipoxynes. The reactive forms of oxygen are also one of the death signals leading to cell apoptosis.

PHOTOSENSITIZING SUBSTANCES AND SOURCES OF LIGHT

It should be stressed that singlet oxygen formed during photodynamic therapy does not diffuse to remote tissues and free radical reactions are strictly localized. Therefore, the tissue selectivity of the therapy depends on the distribution of photosensitizers and their selective accumulation in the target tissue, which spares healthy cells and results in effective healing, is the essence of the method.

An important element of successful photodynamic therapy is the proper choice of photosensitizer, which should be characterized by the short period of tissue photosensitization and selective accumulation in the treated tissue. The light sensitizing substances used in the photodynamic therapy are the derivatives of porphirins and are characterized by the absorption of various light wavelengths. The first generation photosensitizing substances include the derivatives of hematoporphirin, Photophrin I (HPD) and Photophrin II (P-II-polymer sodium). HPD and PII are usually activated by the 630 nm light when the best photodynamic effect is observed (8). The drawback of the first generation sensitizers is their unselective accumulation in the tissues. The healthy tissues, particularly the reticular-endothelial system may also uptake these substances. The other problem after their use is the sensitivity which persists for 6–10 weeks.

5-aminolaevulinic acid (ALA) belongs to the second generation of photosensitizers. The advantage of (ALA) is its selective accumulation in the treated tissue and short sensitivity to light (about 24 hours after application). ALA is a simple chemical compound, the precursor of photoporphirin IX (Pp IX) in the metabolic cycle of heme. The application of exogenous ALA to the diseased tissue intensifies the intracellular production of endogenous PpIX, and its major accumulation in the displastic and neoplastic tissues. The optimal wavelength in this case is 630 nm (14).

The other photosensitizing substances are: derivatives of benzoporphirin (BPD) for which 690 nm wavelength is used, and the photosensitivity period is 3–5 days (10); m-tetrahydroxyphenylchlorin (mTHPC) activated at 652 nm (16) and chlorine e' aspartate ester (MACE) activated at 660 nm (17).

The photodynamic therapy uses both laser and non-laser light sources. To obtain the source of 630 nm wavelength the argon, copper or gold lasers are used with the first generation photosensitizers. The second generation photosensitizers may be linked with alexandrite, titanium or galena laser light which emit the light within the range of 700–900 nm wave length.

The non-laser light sources, markedly cheaper than laser sources, are halogen and xenon lamps which emit narrow band light of a desirable wave length. The radiation dose depends on the lamp power, length of eradiation and distance between the source and the tissue surface and may range from 30 to 250 J/cm. However, the effective standard dose is still being studied.

EMPLOYMENT OF PHOTODYNAMIC THERAPY

The photodynamic therapy has been used in neoplastic and non-neoplastic diseases. Its effectiveness in the treatment of neoplasms of the digestive system,particularly the oesophagus and stomach (13), of urinary bladder (12) and of the uterine cervix (6) is still clinically tested. In Poland, the therapeutic indications include the palliative treatment of non-small-cell carcinoma of the oesophagus obliterating its lumen. The skin is a convenient organ for the photodynamic therapy. The photosensiting material can be easily locally applied on the skin and the light source may be easily directed at the treated area. The satisfactory therapeutic effects were achieved in the treatment of skin diseases, particularly basalioma, spinocellular carcinoma and Bowen's disease (11). The clinical studies performed in Great Britain involving over 800 patients with non-melanocyte skin carcinoma revealed that the photodynamic therapy is at least as effective as cryotherapy and treatment with 5-fluorouracil and results in less severe side-effects. The photodynamic therapy (PDT) is particularly useful in big and multifocal neoplastic lesions, of difficult anatomical approach or esthetically important, in which the surgical treatment or radiotherapy is difficult to perform. Moreover, there are numerous reports concerning the application of PDT in T-cell skin lymphoma (4), psoriasis (7), lichen planus (9), viral warts (5) common acne (15), nevoid basal cell carcinoma syndrome (Gorlin's syndrome) (3), Kaposi's sarcoma (2), metastases of breast carcinoma to the skin (1).

In conclusion, photodynamic therapy seems to be the medical procedure worth recommending. The advantages of PDT include its low invasiveness, therapeutic selectivity, minimal side-effects and excellent healing of the lesions subjected to radiation. Moreover, the therapy may be carried out in the ambulatory setting and may be repeated since the toxic dose is not cumulated. Additionally, the therapy is convenient for patients and allows to avoid the high psychosocial and economic costs which are usually related with hospitalisation.

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SUMMARY

Photodynamic terapy (PDT) is a new treatment for a wide variery of malignancies and premalignant dysplasias, as well as some non-cancer indications. Therapeutic response to PTD is achieved through the activation of non-toxic photosensitiser located within neoplastic tissue, using visible light tuned to the appropriate absorption band of the photosensitiser molecule. This produces cytotoxic free radical such as singlet oxigen, which result in local photo-oxidation, cell damage and destruction of the tumour cells. Systemic administration of photosensitisers has been used with endoscopic light exposure to treat a variety of internal malignances. A topical drug delivery is used in the skin deseases treatment. The selective distribution of photosensitiser in the target tissue is the fundamental to the process of PDT. This tissue specific photosensitation and normal tissue sparing results in good healing and often very good cosmetic results. Peterson PTD can be used for the treatment of cutaneous lesions (e.g., SCC, BCC, Bowen's disease, mycosis fungoides, erythroplasia of Queyrat, Gorlin's Syndrome, actinic keratoses), lower genital tract neoplasia (VIN and CIN), gastrointestinal tumours, etc., as well as nononcological indications (e.g., acne, condyloma acuminatum, lichen planus, psoriasis, vitiligo, vulval lichen sclerosus, warts and verrucae).

Terapia fotodynamiczna – mechanizm i zastosowanie

Terapia fotodynamiczna (PDT) jest metodą leczenia nowotworów, stanów przednowotworowych jak również innych chorób. Mechanizm terapii fotodynamicznej polega na aktywacji przez światło widzialne substancji fotowrażliwej, umieszczonej uprzednio w leczonej tkance. W wyniku tego procesu dochodzi do zapoczątkowania reakcji chemicznych, podczas których produkowane są reaktywne formy tlenu. Wolne rodniki tlenowe wywierają działanie toksyczne na komórki nowotworowe i na naczynia stanowiące integralną część guza, powodując śmierć komórek nowotworowych. Selektywna dystrybucja substancji fotouwrażliwiającej do tkanki docelowej jest istotą terapii fotodynamicznej, a jednoczesne oszczędzenie zdrowych komórek powoduje efektywne gojenie i dobre rezultaty kosmetyczne. Terapia fotodynamiczna znalazła liczne zastosowania w dermatologii: w leczeniu powierzchownych raków

podstawnokomórkowych i kolczystokomórkowych oraz w chorobie Bowena. Istnieją doniesienia o przydatności PDT w leczeniu chłoniaków T-komórkowych skóry, w łuszczycy, liszaju płaskim, bielactwie, chorobie Dariera, brodawek wirusowych i w trądziku pospolitym. Poza dermatologią istnieją inne onkologiczne wskazania do terapii PDT, między innymi leczenie nowotworów przełyku (*Barrett's oesophagus*), raka pęcherza moczowego, szyjkowej oraz pochwowej neoplazji śródbłonkowej (CIN i VIN) oraz ognisk przerzutów raka sutka do skóry.