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Photodynamic therapy in head and neck cancer

Terapia fotodynamiczna w nowotworach głowy i szyi

Kamil H Nelke^{1, A, B, D, E}, **Wojciech Pawlak**^{1, B, C, D, E}, **Jarosław Leszczyszyn**^{2, B, F, G},
Hanna Gerber^{1, A, B, E, F, G}

¹Department of Maxillofacial Surgery, Wrocław Medical University, Poland

²EMC HC Clinic, 49-51 Parnell Square West, Dublin 1, Republic of Ireland

Summary

Photodynamic therapy (PDT) is a special type of treatment involving the use of a photosensitizer or a photosensitizing agent along with a special type of light, which, combined together, induces production of a form of oxygen that is used to kill surrounding cells in different areas of the human body. Specification of the head and neck region requires different approaches due to the surrounding of vital structures. PDT can also be used to treat cells invaded with infections such as fungi, bacteria and viruses. The light beam placed in tumor sites activates locally applied drugs and kills the cancer cells. Many studies are taking place in order to invent better photosensitizers, working on a larger scale and to treat deeply placed and larger tumors. It seems that PDT could be used as an alternative surgical treatment in some tumor types; however, all clinicians should be aware that the surgical approach is still the treatment of choice. PDT is a very accurate and effective therapy, especially in early stages of head and neck squamous cell carcinomas (HNSCC), and can greatly affect surgical outcomes in cancerous patients. We present a detailed review about photosensitizers, their use, and therapeutic advantages and disadvantages.

Key words: photodynamic therapy • head and neck • cancer • oncology.

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Adres autora: Kamil Nelke, Department of Maxillo-Facial Surgery, Silesian Piast's Medical University, ul. Borowska 213, 50-556 Wrocław, Poland; e-mail: kamil.nelke@gmail.com

INTRODUCTION

Photodynamic therapy (PDT) uses the human body's dendritic cells (DC), the antigen-presenting cells which are the initiators and modulators of the primary immune response in the human body. DC are most common in skin and mucous membranes and can be mature or immature. After DC make contact with an antigen body (virus, fungi, bacteria and others), they start to form peptides on their surfaces, and they are described later as antigen-presenting cells (APC). Bone marrow-derived DC are the most powerful APC. After DC capture one antigen, their ability to capture more antigens declines greatly, but also can induce many cytokines, such as interferon α , IL-1, IL-6, IL-7, IL-12, IL-15, and macrophage inflammatory protein (MIP1g). Mature DC induce IL-12 production, and CD40 and T cell activation.

Mitochondrially localized sensitizers (photosensitizing agents) are able to induce programmed cell death (apoptosis). Appropriate light wavelength activates local agents and it is excited to its singlet state, which leads to production of singlet oxygen or oxyradical formation. Thanks to this, the cell structure changes. This cytotoxic molecular species results in cytotoxicity, intravascular effects that change blood supply to selected areas and leads to cell death. It seems that proper illumination and an adequate photosensitizing agent that targets tissues and cells and induces presence of oxygen are the most valuable to achieve the therapeutic goal. For example, various mixtures of porphyrins (Photofrin) are used in different cancerous conditions. Another well-described agent is hypericin, which is used as an extract of a natural plant, Saint John's wort, that has some anticancer properties and in PDT usage induces protein kinase C, and also induces peroxidation of membrane lipids, with decrease of cellular glutathione levels, and impairs mitochondrial function.

PDT has an immune-modifying impact under sub-lethal conditions. Increasing PDT levels may undergo rapid cell death apoptosis. On the other hand, high doses induce passive cell death, called necrosis. PDT-treated tumor cells are susceptible to macrophage lysis. Biochemical pathways triggered by PDT immune cells are presumably the consequence of oxidative stress placed upon the cell [21].

The authors' main aim of this paper was to evaluate current PDT advances, treatment possibilities and their influence on head and neck cancer (HNC). Because of many factors predicting HNC, photodynamic therapy along with other therapies should be taken into serious consideration in treatment.

PHOTODYNAMIC THERAPY

Photodynamic therapy, PDT, is minimally invasive therapy, used in cancer and non-oncological disorders. Because of many clinical indications for treatment and usage of various light sources and light absorbents, this therapy can be used in different sites of the human body. A special type of light pipe is described by Canavesi et al., and is an in-

teresting treatment alternative [7,9]. An essential part of the therapy is that neither the photosensitizer nor light alone is cytotoxic. On the other hand, produced cytotoxic singlet oxygen (1O_2) in the radiated field leads to cancer or other non-cancerous tissue death because of oxidative damage. Cell death is more likely related to apoptosis, but other mechanisms are still being discovered and are the focus of many scientific studies. [11,67] Usage of PDT in the early stage of squamous cell carcinoma of the head and neck (SCCHN) has a great effect on therapy; however, another generation of photosensitizers less absorbed by skin is currently being developed. 5-aminolevulinic acid (ALA) as a porphyrin and verteporfin as a benzoporphyrin, and the pheophorbide 9-hydroxypheophorbide- α (9-HPbD), represent a new branch of lower skin photosensitivity. Studies by Chung et al. investigated the mitochondrial events and endoplasmic reticulum (ER) stress induced by 9-HPbD-PDT, which led to cell apoptosis [13,77]. According to the authors, cells treated with 9-HPbD alone or light with absence of 9-HPbD suggested that 9-HPbD is very similar to other photosensitizers and might lead to less negative effects on normal healthy tissue during treatment. A study performed on AMC-HN-3 human head and neck carcinoma cells using 9-HPbD-PDT showed that the use of a higher dose of photosensitizer 9-HPbD-PDT from 0.59 $\mu\text{g}/\text{ml}$ to 2.34 $\mu\text{g}/\text{ml}$ changed the cell mechanism from apoptosis to necrosis, and also showed that the intracellular localization of the sensitizer is essential. Photodamage seems to be more accurate if mitochondria (MMP, mitochondrial membrane) of tumor cells are under the influence of PDT, because of initiating a cascade of events such as release of cytochrome c and activation of caspases [43]. A special type of microinvasive carcinoma is also an indication for treatment, and studies performed by Quon et al. seem to confirm that [60].

PDT has many advantages in treating head and neck cancer. Hung et al. investigated three human HNSCC cell lines: UM-SCC1, UMSCC14A, UMSCC22A. Light and mitochondrial photosensitizer Pc4 and mitoferrin-2 (Mfm2) were used in the study focused on mitochondrial iron uptake through Mfm2-enhanced PDT. The authors suggest that Mfm2 might be a biomarker of sensitivity of head and neck cancers, mostly because of Mfm2-dependent mitochondrial iron uptake that induces PDT, and cell killing [33].

Head and neck squamous cell carcinomas (HNSCC) are very common in the upper part of the aerodigestive tract. Seshadri et al. explored the potential of vascular-targeted (vascular-disrupting agent, VDA) therapy in HNSCC using 5,6-dimethylxanthone-4-acetic acid (DMXAA) on two HNSCC xenografts on nude mice bearing subcutaneous FaDu (human pharyngeal squamous cell carcinoma) and A253 (human submaxillary gland epidermoid carcinoma) [65]. Both were treated with a single dose of DMXAA, 30 mg/kg, and after 24 hours contrast magnetic resonance MRI and immunohistochemistry (CD31) were performed. Studies showed that DMXAA decreased tumor growth and vascular perfusion was reduced at 78% in FaDu and 49% in A253 xenografts. This study was performed to show a greater change in vascularization than in tumor size, which was seen at

the 30th day after treatment. However, it is necessary to be aware that the study was performed on implanted subcutaneous tumors. Another vascular-targeting agent (ZD6126) described by Davis et al., used in HNSCC xenografts, has similar properties [18].

Head and neck cancer along with other non-tumor-like disorders can not only be treated with standard radical dissection combined with chemoradiotherapy (CRT) but also alternative treatments are useful. In this case, PDT will be closely compared and described [19].

Therapy might consist of a photosensitizer agent or might be combined with other chemical substances, such as cisplatin or carboplatin. The most common are ALA (5-aminolevulinic acid, 5-ALA), methyl aminolevulinate (MAL), 9-hydroxyphosphoribide (9-HPbD), erythrosine B, porfimer sodium (Photofrin), Foscan (temoporfin; meta-tetrahydroxyphenyl chlorine, mTHPC), verteporfin (BPD, benzoporphyrin derivative), hyperbranched poly(ether-ester) (HPEE), 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a (HPPH), and hypericin-mediated (HY). Other agents can also be used.

5-Aminolevulinic acid (ALA, 5-ALA) induces synthesis of porphyrin, the protoporphyrin IX (PpIX). Studies show that malignant tissues have accumulated PpIX, which is important for photodynamic therapy in cancer. Allman et al. investigated the treatment of head and neck carcinoma cell lines with the use of ionizing radiation and PDT with the use of 5-ALA [4]. The authors used three cell lines from human squamous cell carcinoma: V134, V175, SCC-61. All cells were incubated in serum-free medium containing 1 mM/l 5-ALA and in 24 hours' time showed an increase of fluorescence. γ -irradiation of 8 Gy performed on three cell lines before 3 minutes PDT cumulates the effects of therapy; however, cell sensitivity varies depending on the cell cycle, G1 or G2. For example, increased accumulation of PpIX occurs during S-phase and G2 phase. The authors also conclude that interaction between γ -irradiation and PDT might be complicated by the dose and timing of variant treatments, and still this combined therapy requires further investigation [13,15].

5-ALA is also used in oral leukoplakia treatment. Shafirstein et al. additionally used a pulsed dye laser in his pilot study, with 585 nm light. In some cases a diode laser with 635 nm could be used, to penetrate deeper than 1-1.5 mm [66]. In the study 23 patients were included, with leukoplakia at least 10 mm wide. 8 J/cm² seems to be an adequate exposure dose in this study, although other authors have their own techniques [48,63]. Shafirstein also suspects that increased p53 levels, and decreased Ki-67 levels, are related to oral leukoplakia DNA damage during PDT.

In some cases a hexenyl ester of 5-ALA (5-ALA-hx) can be used, especially in salivary gland adenocarcinoma SGT cells. A study by Park et al. showed that this therapy induced necrotic cell death rather than apoptosis in SGT cells, and flow cytometry with LDH assay seems to confirm that [59]. This treatment method seems to be a great alternative to the standard surgical approach to salivary glands.

Usage of ALA and MAL might vary depending on clinical cases, and also have different scales of pain. They both seem to have a great influence on therapy success rate.

Skin lesions and cancers, such as actinic keratosis (AK), superficial basal cell carcinoma (BBC) and Bowen's disease (BD), should be treated with PDT. Gaál et al. performed a study to evaluate the degree of treatment-associated pain during PDT while using 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) in different anatomical regions [23]. 182 treated skin cancers consisted of 80 AK, 97 BBC and 5 BD, and 111 of all were located in the head and neck region and involved the cheeks, forehead, temporal area, nose, auricular region, lips, scalp and neck. According to the study, ALA-PDT causes more pain than MAL-PDT treatment in the head region, and patients suffer more pain in AK treatment. Both ALA and MAL are very commonly used photosensitizers; this finding might be related to peripheral nerve endings that trigger nerve stimulation during the procedure, and studies performed by Steinbauer et al. seem to confirm this. It is also worth noting that patient pain sensation may differ [68].

A different approach with ALA is applied when using it on a gentle and thin skin layer, such as in the eyelid.

Basal cell carcinoma (BCC) and papillomas seem to be common in eyelids; therefore various treatment techniques are available. According to a study by Togsyerd-Bo et al., use of topical methyl aminolevulinate (Metvix cream, 16%) is a safer, noninvasive treatment, has better cosmetic results and is less invasive for surrounding tissues [72]. Because of PDT the eyelid and eye could be damaged, but the authors present a different approach. After using 0.4% oxybuprocaine, a protective ocular shield is inserted under the eyelid with clamps or another tool to properly fix the protective plate to the eyelid. Also an adhesive film covers the eye along with a 5 mm margin around the tumor, and an additional light-impermeable eye patch is used. A 37 J/cm² diode lamp with 632 nm was used. After the procedure the patient used an eye patch for 24 hours and eye drops for 3 days after therapy. This method seems to have a great success rate, with about 75% of all 12 treated patients, but still more studies need to be performed in order to evaluate this type of treatment of very difficult tumors [74].

ALA and their ester agents are used commonly worldwide with a great rate of success. Nevertheless, some other enzymes have a great influence on PDT treatment and cell apoptosis.

According to Separovic et al., ceramide synthase 6 (CERS1) is an important enzyme taking part in apoptosis and might lead to apoptosis resistant cells after PDT. Therefore leveling CERS1 can enhance anticancer drug properties, because CERS1 is a molecular factor regulating resistance to PDT [64].

He et al. studied cytotoxic and apoptotic effects of combined 9-hydroxyphosphoribide (9-HPbD)-mediated PDT and CB-

DCA (carboplatin) on the AMC-HN-3 human head and neck cancer cell line in *in vitro* studies [28]. CBDCA was photosensitized at 37°C with 9-HPbD for 6 hours with a diode laser at intensity of 2.0 J/cm² for activating 9-HPbD for 15 minutes. Special tests were used to measure cytotoxicity and apoptotic cell death, which was found higher in combined PDT and CBDCA, but in order to avoid side effects on normal cells, a lower dosage of 9-HPbD should be used. Furthermore, the authors' study on AMC-HN-3 (human head and neck cancer cell line) cells *in vitro* suggests that synergistic cytotoxic combined treatment leads to increased early and late stages of apoptosis in cells; therefore more studies need to take place.

Erythrosine B is another photosensitizer used in PDT in treatment of oral malignancies. The study by Garg et al. presents its efficacy and subcellular localization in malignant (H357) and pre-malignant (DOK) oral epithelial cells. In the study a filament lamp with average 550 nm wavelength was used. According to the study both cells have the same uptake of erythrosine but cell killing was 80% in DOK and just 60% in H357 cells, which could be related to mitochondrial membrane accumulation predisposition. It is important that when using high-dose PDT in DOK cells necrosis appeared, but apoptosis was observed at lower doses in both cell lines. The authors also conclude that both cells show a different response to treatment, and H357 cells were more resistant to PDT and might be related to a lower necrotic response in PDT [24].

It seems that mitochondrial membrane predisposition to accumulate different agents and their ability to process agents should be closely evaluated in different type of tumors and tumor-like disorders, and biopsy or histology should be performed before treatment to properly use the treatment.

A study performed on carcinomas *in situ* (CIS) and T1 carcinomas of the oral cavity and larynx using porfimer sodium was carried out by Rigual et al. The authors used porfimer sodium, 2 mg/kg intravenously 48 hours before treatment, with a 630 nm argon laser with a dose of 50 J/cm² for dysplasia and CIS and 75 J/cm² for carcinoma [61]. It is important that porfimer sodium has prolonged photosensitivity. A study on 35 patients with 15-month follow-up showed that PDT with porfimer sodium has a great effect on local dysplasia and early carcinoma. A very important fact is that second primary cancer sites vary from 3 to 10% after PDT and most of them, according to different authors, vary in standard surgical procedure and after use of PDT [31]. The authors also conclude that the use of PDT in early oral cavity dysplasia responds less well than T1 stage carcinomas, which is essential in proper therapy planning.

Dysplastic lesions in the head and neck, according to Civantos, are very common in the oral cavity and laryngeal region. Because of multiple time PDT usage it can be used in primary and recurrent lesions. The author used PDT among patients with T1 and T2 squamous cell carcinomas (SCC) or dysplasia, but in advanced disease PDT was only used as

an adjuvant treatment. In 45 treated patients, 24 had oral cavity tumors, with SCC in 22 cases, porfimer sodium (Photofrin) intravenously was used as a photosensitizing agent, and therapy was performed after 48 to 72 hours. After treatment of 22 cases with SCC, 11 had a complete response, 2 had a partial response and 9 had no response. The presented data showed a great success rate with use of PDT in treating superficial malignant or premalignant lesions, but a lower success rate was obtained in deeper tumors [14].

When therapy or surgery is not radical, HNC might reoccur. Therefore planning before surgery is essential, and describing surgical margins should be also considered wisely.

Recurrent head and neck cancer is always a major problem for both patients and doctors. In some cases after major surgery with chemotherapy and/or radiotherapy it is not possible to gain access to the recurrent cancer side. Therefore a special type of PDT, interstitial PDT (IPDT), is more accurate to treat inaccessible surgical sites, because of local fibers applied deeper into tissue. Lou et al. reported the use of IPDT. All studies were performed after confirmed biopsy of persistent or recurrent head and neck cancers (HNC). The studied patients were sensitized with 0.15 mg kg⁻¹ intravenous mesotetrahydroxyphenyl chlorin (mTHPC, Foscan) and were treated 4 days later with a 652 nm diode laser used with four treatment fibers positioned at 1.5 cm intervals. With USG, MRI or MRI guidance fibers were placed transorally (or percutaneously) near deeper tumors (also near vital anatomical structures) using 20 J energy. After the procedure patients were scheduled for follow-ups. Lou et al. reported 50% tumor volume decrease with no change of tumor size. In a total of 45 patients, 12 patients did not respond to treatment with PDT, and 33 who responded had a median survival rate of 16 months. This method is effective for carcinomas and sarcomas, especially in inoperable patients, and might increase the survival rate [50].

In studies by Copper et al., in 29 studied patients, in 25 of them after use of second-generation photosensitizers such as meta-tetra(hydroxyphenyl)chlorin (mTHPC) (Foscan), complete remission of the primary tumor was achieved; however, 4 patients were treated with conventional therapy [16].

A review of the literature by Visscher et al., concerning mTHPC in PDT therapy, concluded that more randomized studies are needed to compare the treatment efficacy; however, PDT with mTHPC seems to increase the quality of life (QOL) in palliative care of untreatable patients [17].

Long-term outcomes in BCC performed by Betz et al. show that mTHPC-PDT (FOSCAN, with a low dose of 0.05 mg/kg) is an effective factor in treatment. After analyzing 117 patients with 460 BBC, the success rate was 90.7%. According to the authors, treatment with low dosage Foscan 0.05 mg/kg with at least 40 J/cm² and 48 hours DLI (drug light interval) has the same value of success as the conventional regime in treating BBC with 0.15 mg/kg, 20 J/cm² 96 hours DLI [6].

A study performed by Karakullukcu et al. describes usage and indications for PDT in early neoplasms of the oral cavity and oropharynx. According to the study PDT is more accurate in areas not previously treated, but also might slightly improve treatment in previously treated areas. The total response to PDT treatment rate was 90.7%, defined in the study consisting of 170 patients with 226 lesions, where 95 were primary neoplasms. The authors tried to identify success rates for each group according to T stage in the TNM classification. During the study the authors used mTHPC (temoporfin, Foscan) at a dose of 0.15 mg/kg, and illuminated patients after 96 hours after application, with a laser of 652 nm wavelength and 20 J/cm³, and scheduled routine check-ups up to a 5-years time-frame. According to the authors, the success rate is dependent on T stage, and is related to depth of invasion not more than 5 mm [40].

On the other hand, persistent or recurrent NPC seems to have more therapeutic advantages according to Nyst et al., because of combining temoporfin with PDT. In a study performed on 22 patients, the authors concluded that this therapy can be used to treat recurrent or residual NPC, but only present in the nasopharynx [57].

Tongue base cancer (TBC) treated with mTHPC-PDT 0.15 mg/kg has a high success rate. According to studies performed by Jerjes et al., this minimally invasive surgical tool is the best alternative, and compared to other tongue base cancer methods has lower morbidity and mortality. 33 patients treated with recurrent tongue base carcinoma stage IV were involved in the study. In general anesthesia after ultrasound examination IPDT with use of an 18 gauge needle and 652 nm diode laser illumination of 20 J/cm³ was performed. After treatment statistical analysis was performed showing that there was improvement of breathing, swallowing and speech ($P < 0.001$). Treatment was tolerated by all patients and led to tumor shrinkage and its subsequent control [37,41]. The same authors discussed surgical and PDT margins in tumor control, and agreed that PDT causes much less morbidity than surgery and chemoradiotherapy. Minimally invasive surgical oncology with PDT seems to be a great alternative, especially as a study on T1/T2 oral cancer and three rounds of PDT showed a lower chance of mortality and morbidity [39]. Nevertheless, surgical biopsies should be performed to investigate possible aggressive tumor growth.

Jerjes et al. also described potentially malignant oral disorders such as white and red lesions (leukoplakia, erythroplakia, oral lichen planus, oral submucous fibrosis, actinic cheilitis, xeroderma pigmentosum, Fanconi's anemia, and immunodeficiency syndromes) that can be treated with PDT. In almost all oral cancers and squamous cell carcinomas, first generation photosensitizers are in use, such as Photofrin (porfimer sodium), 5-ALA (5-aminolevulinic acid) and verteporfin (BPD, benzoporphyrin derivative), and the second generation photosensitizer Foscan (temoporfin; meta-tetrahydroxyphenyl chlorine). Oral cavity malignant and premalignant lesions should be treated not only surgically but also with PDT [36,38].

Studies performed worldwide show that oral cavity, nasopharynx and hypopharynx cancers have small differences in photosensitizing agent predisposition rates and this should also be considered before planning usage of PDT in the head and neck region.

Nasopharyngeal cancer cells are more sensitive to temoporfin compared with hematoporphyrin or merocyanine-540 and according to Yow et al. in some cases photosensitizers of the first generation are less accurate to treat cancer cells; therefore second generation and other agents should be considered as useful [79,80].

Considering esophageal cancer PDT with use of talaporfin sodium intravenously 40 mg/m² and diode laser of 664 nm with 50 J/cm² to 100 J/cm² was used by Yano et al. to treat patients with local failure to T2. After failure in chemoradiotherapy, surgery is generally indicated; however, the authors claim that it has a high complication rate [10,71,78].

Oral squamous cell carcinoma (OSCC) treated with PDT seems to have better cosmetic and functional outcomes than standard surgery combined with chemo- or radiotherapy. 121 patients with early stages of OSCC were treated with mTHPC (dose of 0.15 mg/kg) and use of 652 nm laser light. A study by Hopper et al. was performed only in tumors to 0.5 cm depth, to ensure proper laser penetration and treatment. Treatment took place mostly on the mouth floor, lip, tongue and buccal mucosa, and complications occurred only in 6%. The most important matter is that the survival rate (SR) at 1 and 2 years was 89% and 75% respectively. Standard retreatment using surgery repeated in the oral cavity is associated with scarring, tissue loss, and changes after radiotherapy on the oral mucosa, and leads to functional problems. Thanks to PDT tissue loss is smaller and essential functions remain unharmed, and it can be used regardless of patients' age [30].

Skin tumors are also treated with PDT. According to the latest studies basal cell carcinoma (BCC) is almost in 85% of cases localized in facial skin, mostly in the periocular region. Studies showed that even after surgical removal of tumor with margins, some microscopic cells can still be present in surrounding tissues. Garcia et al. described two possible methods of treating BCC in the palpebral region, using PDT and alternative treatment with use of biological response modifiers such as imiquimod (IMQ). Minimally invasive treatments are being considered, mostly because BCC shows less possibility of malignancy and to avoid great tissue loss in the facial region. PDT in BCC mostly requires application of methyl aminolevulinate cream over tumor lesions and surrounding tissues, and leads to better esthetic results and a better treatment rate [51,62,70].

Karakullukcu et al. in 2013 performed a one-institute experience study describing the approach to PDT in 55 patients and in standard surgery in 43 patients as an alternative for patients with early stage oral cavity cancers, but with lesions thinner than 5 mm. According to the authors, overall survival was 83 and 75% for PDT and surgery groups,

but in the PDT group 11%, and the surgical group 26% of patients had additional treatments. It seems that tumors of the tongue and mouth floor are more sensitive to PDT therapy than other oral sites [29]. The authors in their study conclude that PDT in early local stage squamous cell cancer of the oral cavity shows comparable rates of control to trans-oral resection, and furthermore PDT can be performed using local analgesia, while radical surgical excision requires general anesthesia. This might be an alternative way of treatment of patients with lesions smaller than 5 mm, suffering from early stages of oral cavity cancers, but only if careful and scheduled work-up is performed. Especially oral leukoplakia and erythroplakia are in favor of PDT [42].

Nasopharyngeal carcinomas (NPC) in some cases are very hard to properly evaluate and treat. Fang et al. describe PDT while using apoptin, an apoptosis-inducing protein. A study measuring the expression of apoptin in CNE-2 NPC cells showed that combined PDT-apoptin treatment leads to a stronger therapeutic effect, and induces cell apoptosis and several changes in tumor cells. This study might indicate a better alternative to treatment than only use of PDT [20].

Special types of agents are HPPH and HPEE, which could be used in a combined treatment or alone, and it seems that most pharyngeal and esophageal diseases are sensitive to this type of PDT treatment.

Li et al. reported usage of hyperbranched poly(ether-ester) (HPEE)-ce6 nanoparticles, and their use in CAL-27 cancer cells of the tongue. The assay trial showed that higher phototoxicity can be achieved using 12 J/cm² of 660 nm laser illumination. HPEE is the newest class of macromolecule, characterized by many hydroxyl and carboxyl functional groups important in therapy, and could be a great PDT drug carrier. Other studies involving hyperbranched polymers should be performed. It seems that cell-targeted photodynamic nanomedicine will soon be the future of the HNSCC treatment protocol [45,52].

A clinical trial using HPPH-PDT was performed by Sunar et al. to evaluate blood flow, oxygenation, and HPPH photobleaching measured after and before treatment. According to trial studies, the drug is strongly photobleaching and blood flow reduction was essential along with reduced oxygenation. The authors also advise the use of non-invasive diffuse optical spectroscopy in patients with head and neck cancer. In study additionally a biopsy-based molecular marker was used, in order to evaluate photodynamic efficiency [69].

HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a) can also be used in Barrett's esophagus (adenocarcinoma, BE) treatment with PDT. Nava et al. after using porfimer sodium and a light dose of 150 J/cm² at 48 hours and 3-4 mg/m² of HPPH achieved complete study success at 72% at 1 year in high-grade dysplasia and early carcinomas of the esophagus. HPPH-PDT seems to be a safe and promising treatment of Barrett's esophagus [55].

Studies performed on mice by Gil et al. showed that combined PDT with oncolytic vaccinia virus (OVV) has a positive effect on treatment of primary and metastatic tumors. The authors used 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a (a second generation sensitizer) (HPPH)-sensitized PDT along with oncolytic virotherapy in nude mice with implanted syngenic murine NXS2 neuroblastoma and human FaDu head and neck squamous cell carcinoma [27]. Tumor growth and survival were measured, and MRI with immunohistochemistry was used to evaluate vascular function. Studies show that combined PDT with OVV leads to inhibition of metastatic tumor growth and also on the fifth study day a loss of blood flow to the interior of the tumor was diagnosed and cumulated neutrophil infiltration was noted. It seems that combined treatment is a better alternative than standard PDT, but further studies need to be made [47,58].

Also plants and trees naturally accessible in the environment can be used in various treatments.

Hypericin-mediated photodynamic therapy (HY-PDT) presented by Wang et al. is described as a potential way of treating tumors and nonmalignant disorders in the nasopharynx. Hypericin (HY; 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-phenanthro[1,10,9,8-opqra]perylene-7,14-dione) is isolated from the plant *Hypericum perforatum* [75]. Studies involving CNE-2 cells, intracellular caspase, genome-wide expression and cytology tests indicate that HY-PDT therapy could inhibit growth of CNE-2 cells and induce their apoptosis. Because of the highly destructive effect of HY-PDT on the mitochondrial membrane, induced apoptosis is used in various carcinomas, and also activates cysteine-type endopeptidase, which stops cell growth and stimulates apoptosis [1,2,3,14].

Hypericin and the photosensitizer liposomal meso-tetrahydroxyphenyl chlorin derivative (Foslipos[®]) was used in a study performed by Besic Gyenge, showing that combined therapy with both photosensitizers can decrease its toxicity, which can be advantageous in PDT treatments [26].

Dihydroceramide desaturase 1 (DES) is the enzyme responsible for converting dihydroceramide into ceramide, and according to Breen is a potential molecular target for regulating apoptotic resistance to PDT [8].

Thanks to TNM assessment it is quite easy to evaluate cancer state and special treatments are planned. PDT might be useful; however, the upper limit as an indication for treatment with PDT related to TNM is still under consideration.

Furthermore, an extraordinary case of stage T4 nasopharyngeal cancer was described by Indrasari et al. after usage of PDT as a factor of long-term cell response. After 5 years of follow-up the authors reported that the patient's condition was very good and was still being carefully monitored [34].

Not only a special photosensitizing agent is needed to achieve proper therapeutic results, but also diagnostic

tools, and proper illumination of treated head and neck areas. Special tomographic and MRI protocols are further investigated in order to provide an adequate dose and apply agents near tumor sites.

The review of the literature performed by Wildeman et al., referring to PDT in patients with recurrent nasopharyngeal carcinoma, revealed that less invasive treatment than surgery leads to less complications and morbidity [77]. All authors agreed that illumination of the nasopharyngeal cavity requires special techniques. For example, Nyst built a special device that could be easily placed in the upper nasopharyngeal site [56].

Jäger et al. suggested that a special MRI image-guided study is necessary to properly place the IPDT fibers in recurrent head and neck cancers. Patients who were treated with IPDT had previous surgery, radio and chemotherapy or standard treatment limitations, and therefore according to the authors were deemed unsuitable for further surgery [35]. The authors used mTHPC applied intravenously for sensitization and 4 days before IPDT had a daily lighting setting which was increased every 100 lx (60-W) every day. 18-gauge MR-compatible needles were placed in tumor sites according to three-dimensional planes, and due to MRI-guided needles were placed safely and deep into the tumor site. From 4 to 8 days after IPDT contrast-enhanced images were performed in order to properly evaluate tumor necrosis, reduction and success of treatment. It is essential to evaluate IPDT because in some cases additional procedures are necessary. All authors claim that still the prognosis for patients with head and neck tumors remains a mystery, although early stages can be cured [32].

Another author observed that proper deposition into deeper structures requires special imaging tools. Mo et al. described usage of fluorescence diffuse optical tomography (TD-FDOT) with use of a photosensitizer, 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a (HPPH). The study was performed during simultaneous reconstruction of fluorescence yield and lifetime of HPPH was performed before and after PDT. Depth imaging was achieved through three-dimensional mappings of fluorescence and tomographic studies. Studies performed on mice showed that fluorescence changed during time and HPPH accumulated in the tumor 24 hours after injection [53].

Photosensitizing agents could also be made from natural herbs or plants or made from modified silica or other substances.

Lim et al. described a naturally produced photosensitizer, 15^l-hydroxypurpurin-7-lactone ethyl methyl diester (compound 1) from an Araceae plant and it is compared to pheophorbide-a (Pha) used in head and neck cancer therapies. Research was performed on HSC2 (oral cavity), HSC3 (tongue) and nasopharyngeal HK1 and C666-1 cancer cell lines. Studies showed that compound 1 induced more apoptosis and was more accurate especially in G₂/M cell cycle block [46].

On the other hand, Uppal et al. presented Rose Bengal, an anionic photosensitizer from organically modified silica nanoparticles with 3-amino propyl groups. The study was performed on oral (4451) and breast (MCF-7) cancer cells, and showed that Rose Bengal is less phototoxic, but modified with silica nanoplates with 3-amino propyl groups (FTIR) has greater phototoxicity [73].

CONCLUSIONS

Because of targeting only pathological cells, normal structures are unharmed. Light length about 630–650 nm combined with local photosensitizers is the right choice of treatment; however, greater length of light is more accurate only if combined with different photosensitizers applied intravenously [22]. Usage of 5-aminolevulinic acid (5-ALA) or its derivatives seems to be adequate for dermatological diseases, such as malignant skin lesions, Bowen's disease, actinic keratosis, basal cell carcinomas and some types of inflammatory dermatosis.

Lee and Moon described experimental therapeutics for head and neck cancer. It seems that early detection and proper diagnosis is a key to success. Because of treatment limitations in head and neck regions, major surgery is the way of choice. In most cases squamous cell carcinomas of head and neck (SCCHN) treatment consisted of a combination of surgery with either chemo-, radiotherapy or both. Authors describe other possible therapies, such as monoclonal antibodies, molecular inhibitors, gene therapy and photodynamic therapy. It seems that targeted therapy in patients with SCCHN might be important in the future, along with combined therapy, which might lead to overcoming some basic surgical limitations [44].

PDT can also be used in other regions of the human body, not only in the head and neck. Many studies concern usage in esophageal cancer and Moighissi's study seems to confirm it. Early stage esophageal cancer not treated surgically is a good group for potential PDT usage, but still no accurate randomized trials have been performed [54].

Studies worldwide are taking place in order to fully describe the pathology and mechanism of human head and neck cancer cells [12].

It is also essential to remember that dosage of photosensitizer should be related to the variety of light wavelength that should be used carefully in different regions.

Different authors report different PDT success rates [7,18,49]. PDT is a great alternative for standard surgery but requires special diagnostic tools with a photosensitizer working in various limits. Because of many tumors and tumor-like disorders in the head and neck PDT should be considered as favorable in the first stage of treatment; however, without first performing biopsy and histological evaluation, use of this therapy is in vain [25,81].

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