The application of Levulan®-based photodynamic therapy with imiquimod in the treatment of recurrent basal cell carcinoma

Beata Joanna Osiecka 1, Kamil Jurczyszyn 2, Piotr Ziolkowski 1

1 Photodynamic Therapy Laboratory, Department of Pathology, Wrocław Medical University, Wrocław, Poland
2 Department of Dental Surgery, Wrocław Medical University, Wrocław, Poland

Source of support: Financial support from the Ministry of Science and Higher Education is kindly acknowledged (grant N401 015 32/0251)

Summary

Background: Common skin tumors like basal- and squamous-cell carcinoma present a serious problem in modern medicine. Exposure to ultraviolet solar radiation is the main cause of these lesions. Since application of Aldara® and PDT separately is well documented, we decided to use both methods together. The aim of our study was to evaluate the effectiveness of local photodynamic therapy supplemented with topical application of Aldara® in basal-cell carcinoma.

Material/Methods: Thirty-four patients ages 50 to 68 years were enrolled to the trial and underwent PDT treatment. Each case of BCC was histopathologically confirmed. Ten patients were subjected to local Levulan®-PDT and placebo (Eucerin as vehicle cream), and 24 patients were subjected to Levulan®-PDT and imiquimod. Photodynamic diagnosis (PDD) was used to detect and visualize suspicious foci (including cancer lesions).

Results: In the group of patients who were treated using Levulan®-PDT and placebo, 6 patients (60%) were totally cured and 4 lesions (40%) significantly decreased in size. In the group of patients treated with Levulan®-PDT and imiquimod, 18 lesions totally disappeared (75%), 6 lesions significantly diminished, and in 1 patient small foci of previously excised BCC developed again in scar tissue 10 month after the first control examination.

Conclusions: Cure was achieved without any scarring and with very good cosmetic effects. Although this is the preliminary report, the presented modification of PDT seems to be reasonable and promising in treating basal-cell carcinoma.

key words: photodynamic therapy • Levulan® • imiquimod • Aldara® • basal-cell carcinoma

Full-text PDF: http://www.medscimonit.com/fulltxt.php?ICID=882449

Word count: 2234
Tables: 1
Figures: 2
References: 33

Author’s address: Beata Osiecka, Photodynamic Therapy Laboratory, Department of Pathology, Wrocław Medical University, Marcinkowskiego 1 St., 50-368 Wrocław, Poland, e-mail: bjos@magma-net.pl

Received: 2011.04.03
Accepted: 2011.07.20
Published: 2012.02.01
**BACKGROUND**

Common skin tumors like basal- and squamous-cell carcinoma present a serious problem in modern medicine. Exposure to ultraviolet solar radiation is the main cause of these lesions. It is confirmed that a variety of biological consequences such as increases in skin cancer or cataract may result from the increased UV exposure due to ozone depletion and atmospheric ozone hole [1,2]. Sunlight is not the only source of ultraviolet rays. UV radiation may also be produced by artificial sources, for example by quartz lamps frequently used in tanning parlors. Carcinogenesis of skin tumors is very often associated with chronic exposure to UV radiation, and frequent sunburns in childhood may lead to skin cancer in later age. UV-A and UV-B radiation are responsible for photoaging, an accelerated aging of skin [3]. Photoaging is characterized by loss of skin elasticity, roughness, deep wrinkles and pigmentation. The pathogenesis of these changes is associated with free radical generation upon UV irradiation. Free radicals are responsible for damage of cellular DNA that may lead to carcinogenesis.

One of the most common malignant skin tumors is basal cell carcinoma (BCC). This constitutes a majority (70%) of all malignant skin tumors. BCC most commonly occurs in middle-aged and elderly persons (50–70 years old), mainly in Caucasians who were exposed to sunlight radiation. One of the most important biological features is low degree of malignancy and low rate of local growth; however, over time it may contribute to local destruction of surrounding tissues, resulting in deep ulcerations. BCC is mainly located on the skin exposed to UV light, especially on the head, neck and limbs. More dynamic growth is characteristic of lesions located on the nose and on eyelids. These lesions more often recur after incomplete surgical treatment, but generally BCC has a good prognosis. Surgery, cryosurgery, electrodissection and CO₂ laser therapy are typical treatment methods [4–8].

Photodynamic therapy (PDT) comprises 2 main agents: light and a specific chemical compound called a photosensitizer. Photosensitizers have a high affinity to malignant cells and after absorption of energy from light they shift into an excited state. A photosensitizer in the excited state causes photochemical reactions that lead to necrosis and apoptosis in pathological tissues. For many years PDT was used to detect and to treat different lesions located in the skin and mucosa [9–13]. Porphyrins are the most commonly used photosensitizers. Other widely used compounds are chlorins and Le vulan®. Photosensitizers show a high affinity to rapidly proliferating cells such as atypical and cancer cells.

In the present study we used Le vulan® as a natural precursor of porphyrins, which is metabolized in vivo into protoporphyrin IX (Pp IX). Protoporphyrin IX is an acting photosensitizer in this case. Since 1990, aminolevulinic acid (ALA) as a precursor of Protoporphyrin IX was frequently used in local PDT. At present, ALA is successfully applied in treatment of basal cell carcinoma, squamous cell carcinoma (SCC), solar keratosis, and urothelial cancer of the urinary bladder [14–16].

Aldara® is a commercial name of 5% imiquimod cream. Imiquimod belongs to the imidazocinolon family. Topical application on the skin results in inflammation due to activation of immunological response. Toll-like receptors of dendritic cells and macrophages under the influence of imiquimod respond with secretion of cytokines and chemokines such as interferon (INF-α, INF-γ), TNF-α, and interleukins (IL-1, IL6, and IL-8). Moreover, imiquimod stimulates Langerhans cells to present antigens of transformed cells to lymphocytes T in regional lymph nodes. Using natural mechanisms of the immune system, Aldara® eliminates pathologic cells. At present, Aldara® is approved for treating condyloma of the genital organs, solar keratosis and superficial form of basal cell carcinoma (BCC). Imiquimod efficiently destroys clinical and subclinical lesions via its dual immune-modifying properties. Uniquely, imiquimod abolishes immunosuppressive phenomena generated by exogenous factors that allow precancerous and cancerous lesions to propagate.

Since the uses of imiquimod and PDT separately are well documented, we decided to combine both methods. The aim of our study was to evaluate the effectiveness of local photodynamic therapy supplemented with topical application of Aldara® in treatment of basal cell carcinoma.

**MATERIAL AND METHODS**

Thirty-four patients ages 50 to 68 years were enrolled into the trial and underwent PDT treatment. Each case of BCC was histopathologically confirmed. All these cases were previously treated using routine methods (cryosurgery, laser therapy or surgical excision) without satisfactory results. All patients were in good health without any systemic diseases. Patients did not use steroids (locally or systemically), interferon or chemotherapy. Lesions were located on the skin of the face (nose, nasolabial sulcus, cheek, suborbital region) with common BCC features: small, pearl-like nodules, with medium diameter of 0.5 cm, sometimes with erosions on the surface, with bleeding upon rubbing. Some lesions were located in the scar left after previous surgical treatment.

A double-blind, placebo-controlled group was used. Patients were divided into 2 random groups: 10 patients were subjected to local PDT and placebo (Eucerin as vehicle cream), and 24 patients were subjected to PDT and imiquimod. We used Le vulan® (DUSA Pharmaceuticals, Inc) as the photosensitizer precursor. The photosensitizing agent was prepared immediately prior to its use. Lesions after Le vulan® application were protected from direct light exposure using an occlusion dressing which was removed before irradiation. Irradiation was performed after 4 hours using halogen lamp (Teclas, Switzerland). Total time of irradiation was 30 minutes (2×15 minutes), wavelength was 635±20 nm and total energy dose was 100 J/cm². PDT was repeated after 48 hours. Imiquimod (Aldara®) was topically applied in 24 patients 72 hours after irradiation and then applied again twice a week before sleep for 5 weeks. Ten patients received placebo (vehicle only), which was applied in the same manner as imiquimod.

Photodynamic diagnosis (PDD) was used to detect and visualize suspicious sites (including cancer lesions) that were not seen during the routine examination using white light. It comprised local application of precursor, which, after an uptake by cancer cells and irradiation at 405 nm
wavelength, emitted red fluorescence. PDD was performed using Levulan®. The source of irradiation was a Wood lamp. Lesions after application of precursor were covered using occlusion dressing and after 2 hours irradiated for 3–4 minutes. Each patient was subjected to PDD after 6 weeks from the end of therapy. PDD was repeated every 2 months during the next 14 months. Upon UV irradiation, cancer sites emitted red fluorescence and the tumor borders were found to spread beyond the area seen in the white light.

**RESULTS**

The size of lesions was estimated during routine examination in white light and during the PDD session. The result of white light examination is shown in Figure 1, and the effect of the PDD session is shown in Figure 2. The size of lesion during the PDD session was found to be larger and more irregular than during the white light examination.

Most patients during and after PDT complained of erythema and edema that persisted for several days. Patients complained of increasing symptoms such as burning sensation, itching, painful and large edema, and strong irritation of skin, with erosions, after each application of imiquimod. Our study reveals that combination of PDT and Aldara® may increase adverse effects of PDT, such as burning and edema. The skin erosion is attributed to Aldara® application. Due to previously mentioned reasons, 4 patients had to apply imiquimod only once a week. These adverse effects disappeared after completion of therapy with imiquimod, and treated sites scabbed. Local adverse effects typical for imiquimod in the group of patients treated with PDT and placebo were not observed. Results of treatment are shown in Table 1.

In the group of patients who were treated using PDT and placebo, 6 patients (60%) were totally cured and 4 lesions (40%) significantly decreased in size. BCC located on the nose increased after 6 months in 2 patients and recurrent tumor in the scar left after previous surgical excision was observed in 1 patient (Table 1).

In the group of patients treated with PDT and imiquimod, 18 lesions (75%) totally disappeared, and 6 lesions significantly diminished. In 1 patient small foci of previously excised BCC developed again in the scar after 10 months from the first control examination.

Cure was achieved without any scarring and with very good cosmetic effects.

**DISCUSSION**

There is ample evidence supporting the dangers of UV radiation, especially within the context of skin cancer [17]. The popularity of sunbathing and tanning parlors, and chronic sun exposure associated with professional activity results in an increase in a high morbidity rate of skin cancer in middle-aged people [18]. Localization of lesions in the exposed parts of the body, especially on the face, is an important esthetic problem. Patients who are still professionally active expect to receive dermatology treatment that gives
the best cosmetic effects. The main method of skin cancer therapy for decades was surgical excision, very often associated with skin graft transplantation. The main complication after surgical excision is scarring. CO2 laser and cryosurgery were added to the arsenal of methods used against skin cancer in recent years, but each of these methods leaves scarring. Unfortunately, skin cancers are very often irregular in shape and invade beyond the tumor borders that are clearly visible in routine examination. This irregular shape and difficulties in complete removal of a lesion using standard methods may result in frequent recurrences. Surgical excision usually requires a margin 3 to 10 mm wide, but using dermoscopy-guided surgery this may be reduced to 2 mm [19]. Some authors, however, presume that wide margins of excision are not necessary [20]. Moreover, BCCs located on the nose and around the orbit are usually more aggressive than tumors located in other sites. Therefore, it is very important to find an effective therapy that also yields good cosmetic effects.

PDT, as a local treatment method, was used for many years with success in cases of skin precancerous lesions and skin cancers. Levulan®-based PDT (Levulan®-PDT) enables destruction of pathological lesions which are too small to be visible on routine examination. Singlet oxygen and free radicals generated during PDT are responsible for cytotoxic effects. PDT is also responsible for destruction of vessels and induction of immunological response against cancer cells. One of many advantages of PDT is the lack of significant adverse effects (besides burning and edema during PDT and within the next 24 hours). Other advantages are the possibility of repeating and healing without scarring and ease of use. A clear disadvantage of Levulan®-PDT is weak penetration of Levulan® into skin.

The other indication for application of Levulan®-PDT is a superficial lesion on the skin, such as solar keratosis. PDT and PDD can be performed at almost the same time. Our study showed that PDD enables estimation of the true shape of a lesion and allows the microfoci of the tumor to be found.

Aldara® is often used in dermatological lesions, such as warts, condyloma of reproductive organs and the superficial form of BCC or SCC [21–24]. Imiquimod is a strong modulator of immunological response. It induces inflammatory reactions and is responsible for synthesis of cytokines such as interferon [25]. Due to its effects on immunological memory, imiquimod may protect patients against recurrences of lesions, and it is used as an additional agent in cases of incomplete surgical excision [26]. Cryosurgery modified by imiquimod application also showed promising results in BCC treatment [27].

Other studies indicated that PDT in treatment of superficial BCC is effective in 76–97% of cases [28–30]. PDT is generally more effective in treating superficial BCC than nodular BCC [31]. In cases of the nodular form of BCC, CO2 laser surgery and PDT appear to play a synergistic role in the treatment of that lesion [32].

In this study we treated patients only with recurrent form of BCC. The BCC in that localization shows more aggressive growth with recurrences, therefore our previous efforts in BCC eradication resulted in only 60% complete responses. We decided to improve PDT efficacy with addition of a local immunomodulator [33]. This combined therapy enables induction of local natural immunological mechanisms. The 75% success rate obtained in the group treated with PDT and imiquimod confirmed our assumption. Moreover, the synergistic effect of Aldara® on immunological response cells seems to decrease the number of BCC recurrences (1 recurrence after 10 months and 1 after 15 months; see Table 1).

The combination of local PDT and imiquimod results in higher efficiency of BCC treatment in cases of previous unsuccessful treatment such as surgery, cryosurgery and laser therapy. There is one more important benefit from combined therapy – the high level of acceptance by treated patients. Very good cosmetic effect without scarring is the most important advantage of this therapy. Moreover, patients enjoyed knowing that PDT may be repeated at any time.

**Conclusions**

Lack of adverse effects after PDT and very good cosmetic outcomes positively influence the psychological condition of a patient. Patients confirmed their readiness to undergo repeated therapy in case of any recurrence, but they refused other treatment methods, such as routine surgical excision. At present, dermatological patients are younger than in the past and physical appearance is very important for such young people. In our opinion the combination of PDT with local immunomodulator seems to be an effective method of treatment in such group of patients.

Although this is a preliminary report, the presented modification of PDT seems to be reasonable and promising in treating basal-cell carcinoma.

**Conflicts of interest**

No conflicts of interest are declared.

**References:**

1. Rao K, Reichrath J: UV damage and DNA repair in malignant melanoma and nonmelanoma skin cancer. Adv Exp Med Biol, 2008; 624: 162–78
2. Green A, Whiteman D, Frost C, Battistutta D: Sun exposure, skin cancers and related skin conditions. J Epidemiol, 1999; 9: 7–13
3. Brooke RC, Newbold SA, Telfer NR, Griffiths CE: Discordance between facial wrinkling and the presence of basal cell carcinoma. Arch Dermatol, 2001; 137: 751–54
4. Seretis K, Thomaides V, Karpouzis A et al: Epidemiology of Surgical Treatment of Nonmelanoma Skin Cancer of the Head and Neck in Greece. Dermatol Surg, 2010; 36: 15–22
5. Unlü RE, Altun S, Kerem M, Koç MN: Is it really necessary to make wide excisions for basal cell carcinoma treatment? J Craniofac Surg, 2009; 20: 1909–11
6. Fattahi A, Pollock J, Maheswaran A, Britto JA: Big Bad BCCs: craniofacial resection and reconstruction for atypical basal cell carcinomata. J Plast Reconstr Aesthet Surg, 2010; 63: 453–41
7. Skelton LA: The effective treatment of basal cell carcinoma. Br J Nurs, 2009; 20: 18–20; 346, 348–50
8. Levin F, Khalil M, McCormick SA et al: Excision of periocular basal cell carcinoma with stereoscopic microdissection of surgical margins for frozen-section control: report of 200 cases. Arch Ophthalmol, 2008; 127: 1011–15
9. Steinbauer JM, Schreml S, Kohl EA et al: Photodynamic therapy in dermatology. J Dtsch Dermatol Ges, 2010; 8(6): 454–64

10. Shamban AT: Current and new treatments of photodamaged skin. Facial Plast Surg, 2009; 25: 337–46

11. Xu CS, Leung AW: Photodynamic effects of pyropheophorbide-a methyl ester in nasopharyngeal carcinoma cells. Med Sci Monit, 2006;12(6): BR257–62

12. Tierney E, Petersen J, Hanke CW: Photodynamic diagnosis of tumor margins using methyl aminolevulinate before Mohs micrographic surgery. J Am Acad Dermatol, 2011; 64: 911–18

13. Lien MH, Sondak VK: Nonsurgical treatment options for Basal cell carcinoma. J Skin Cancer. Avaiable from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3025364/?tool=pubmed

14. Juarranz A, Jaén P, Sanz-Rodríguez F et al: Photodynamic therapy of cancer. Basic principles and applications. Clin Transl Oncol, 2008; 10: 148–54

15. Fotinos N, Campo MA, Popowsycz F et al: 5-Aminolevulinic acid derivatives in photomedicine: Characteristics, application and perspectives. Photochem Photobiol, 2006; 82: 994–1015

16. Berg K, Selbo PK, Weyergang A et al: Porphyrin-related photosensitizers for cancer imaging and therapeutic applications. J Microsc, 2005; 218: 133–47

17. Kötting B, Drexlter H: UV-induced skin cancer at workplace and evidence-based prevention. Int Arch Occup Environ Health, 2010; 83(8): 843–54

18. Veerend MB, Adam HO, Lund E et al: Sun and solarium exposure and melanoma risk: effects of age, pigmenitary characteristics, and nevi. J Eur Acad Dermatol Venereol, 2010; 24(12): 1395–99

19. Caresana G, Giardini R: Dermoscopy-guided surgery in basal cell carcinoma. J Eur Acad Dermatol Venereol, 2010; 24(12): 1395–99

20. Uluhi RE, Altun S, Kerem M, Kos MN: Is it really necessary to make wide excisions for basal cell carcinoma treatment? J Craniofac Surg, 2009; 20: 1989–91

21. Carneiro RC, de Macedo EM, Matayoshi S: Imiquimod 5% cream for the treatment of pernuclear Basal cell carcinoma. Ophthal Plast Reconstr Surg, 2010; 26: 100–2

22. Alessi SS, Sanches JA, de Oliveira WR et al: Treatment of cutaneous tumors with topical 5% imiquimod cream. Clinics (Sao Paulo), 2009; 64: 961–66

23. Tillman DK Jr, Carroll MT: Topical imiquimod therapy for basal and squamous cell carcinomas: a clinical experience. Cutis, 2007; 79: 241–48

24. Vervecken P, Asea A, Ghazem G et al: A therapeutic approach to peri-anal extramammary Paget’s disease: topical imiquimod can be useful to prevent or defer surgery. Med Sci Monit, 2007; 13(6): CS75–77

25. Wagstaff AJ, Perry CM: Topical imiquimod: a review of its use in the management of anogenital warts, acneic keratoses, basal cell carcinoma and other skin lesions. Drugs, 2007; 67: 2187–210

26. Thissen MR, Kuijpers DI, Keeks GA: Local immune modulator (imiquimod 5% cream) as adjuvant treatment after incomplete Mohs micrographic surgery for large, mixed type basal cell carcinoma: a report of 3 cases. J Drugs Dermatol, 2006; 5: 461–64

27. Gaitanis G, Nomikos K, Vara E et al: Immunocryosurgery for basal cell carcinoma: results of a pilot, prospective, open-label study of cryosurgery during continued imiquimod application. J Eur Acad Dermatol Venereol, 2009; 23: 1427–31

28. Tierney E, Barker A, Ahdout J et al: Photodynamic therapy for the treatment of cutaneous neoplasia, inflammatory disorders, and photoaging. Dermatol Surg, 2009; 35: 725–46

29. Foley P, Freeman M, Menter A et al: Photodynamic therapy with methyl aminolevulinate as adjuvant treatment after incomplete Mohs micrographic surgery. Int J Dermatol, 2009; 48: 1236–45

30. Souza CS, Felicio LB, Ferreira J et al: Long-term followup of topical 5-aminolaevulinic acid photodynamic therapy diode laser single session for non-melanoma skin cancer. Photodiagnostics Photodyn Ther, 2009; 6: 207–13

31. Surrenti T, De Angelis L, Di Cesare A et al: Efficacy of photodynamic therapy with methyl amineolevulinate in the treatment of superficial and nodular basal cell carcinoma: an open-label trial. Eur J Dermatol, 2007; 17: 412–15

32. Whitaker IS, Shokrollahi K, James W et al: Combined CO2 laser with photodynamic therapy for the treatment of nodular basal cell carcinomas. Ann Plast Surg, 2007; 59: 484–88

33. Dahl MV: Imiquimod: an immune response modifier. J Am Acad Dermatol, 2000; 43: S1–5