Photodiagnosis and Photodynamic Therapy 27 (2019) 428–432

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Review

Photodynamic therapy in superficial basal cell carcinoma treatment

Itajaí Oliveira de Albuquerque[a], João Nunes[b], João Paulo Figueiró Longo[a], Luis Alexandre Muehlmann[a], Ricardo Bentes Azevedo[a,*]

[a] Laboratory of Nanobiotechnology, Department of Genetics and Morphology, Institute of Biological Sciences, University of Brasília, Brasília DF, Brazil
[b] Service of Clinical Oncology, University Hospital of Brasília (HUB), Brazil

ARTICLE INFO

Keywords:
Photodynamic therapy
Photosensitizers
Basal cell carcinoma
Clinical trials
Nanomedicine

ABSTRACT

Basal cell cancer (BCC) is an epithelial neoplasm that arises from basal cells, which constitute the lower layer of the epidermis. Global statistics have shown the progressive increase in the incidence of skin cancer in several countries. The cumulative exposure to solar radiation (ultraviolet B) in the first two decades of life represents the critical risk for the disease. Preclinical and clinical trials have shown photodynamic therapy (PDT) as a promising innovation for treatment of skin cancers, especially to the non-melanoma group. The authors reviewed trials with photodynamic therapy in superficial basal cell carcinoma with different photosensitizers to better evaluate how PDT modifies the natural history of sBCC. We conclude trials should not assess only the immediate efficacy but the main goal of long-term effectiveness of the protocols in order to generate best evidence for clinical practice.

1. Introduction

Global statistics have shown the progressive increase in the incidence of skin cancer in several countries. The increase in population longevity and the unprotected exposure to Ultraviolet B radiation (UVB) due to work activities or life style have been found to be responsible for the high incidence of skin cancer [1–8].

Basal cell cancer (BCC) is an epithelial neoplasm that arises from basal cells, which constitute the lower layer of the epidermis and presents a slow-growing dermatological lesion with low metastatic potential. Although, locally, the tumor may present an invasive behavior with multicentric, synchronic and metachronic lesions [9–11]. The metastatic BCC (mBCC), the deadly form of the disease, is rare and poorly understood [12–14].

The most frequent subtypes of aggressive growth BCC are the superficial BCC (sBCC) and nodular BCC (nBCC). The most frequent subtypes are superficial and nodular BCC. Infiltrative, metatypical, morpheaform or sclerosing BCC represent more aggressive subtypes. Associations of histological types occur in about 37–43% of the diagnosed cases [4,15]. Despite the overall low aggressiveness, BCC still experience morbidity due to the frequency of lesions on the face, which has high recurrence rates in the so-called Zone H (v.g., nasolabial fold, nasal alar, orbital area and auricular area).

The gold standard treatment of BCC involves surgical excision with safety margins. Preclinical and clinical trials have demonstrated photodynamic therapy (PDT) as a effective choice, especially for undifferentiated BCC group [16].

2. Photodynamic therapy

Photodynamic Therapy is a treatment that involves the combination of three non-toxic components: photosensitizing substance (FS), light at specific wavelength and molecular oxygen. When these elements interact, they produce a chain of reactive oxygen species (ROS) [17–20]. Depending on a plethora of variables, such as the light energy and the type of PS, PDT may induce different death mechanisms on the cancer cells, mainly necrosis and apoptosis, sometimes depending on the intracellular localization of the photosensitizer [21,22]. Also, PDT may lead to tumor elimination by indirect mechanisms, such as activation of the immune system against tumor antigens and collapse of the tumor microvasculature.

Table 1 presents the selected photosensitizers described in this

Abbreviations: MAL, 5-amino levulinic acid; ALA, amino levulinic acid; BCC, basal cell cancer; CR, complete remissions; PHC, cyanines; mBCC, metastatic BCC; mTHPC or Foscan®, meta-tetrahydroxy-phenylchlorin; nBCC, Nodular BCC; PDT, photodynamic therapy; FS, photosensitizing substance; PpIX, protoporphyrin IX; PL, Pulsed lasers; RCT, Randomized controlled trials; ROS, Reactive oxygen species; PC-4, Silicon phthalocyanine; sBCC, superficial BCC; UVB, Ultraviolet B radiation

* Corresponding author at: Laboratory of Nanobiotechnology, Department of Genetics and Morphology, Institute of Biological Sciences, University of Brasilia, Campus Darcy Ribeiro, 70910-900 Brasília DF, Brazil.
E-mail address: razevedo@unb.br (R.B. Azevedo).

https://doi.org/10.1016/j.pdpdt.2019.07.017
Received 27 November 2018; Received in revised form 11 July 2019; Accepted 22 July 2019
Available online 23 July 2019
1572-1000/

Table 1
Photosensitizers and the respective clinical administration route.

Photosensitizer	Administration Route		Target Organelle[a]
	Intravenous Injection	Topical Application	
Photofrin® - Porphyrin Derivate	2 mg/kg [27,28]	–	Mitochondria and Nuclear Envelope [29]
Foscan® - Chlorin Derivate	0.1–0.15 mg/kg [28,30]	–	Endoplasmic reticulum and Golgi apparatus [31]
NPe6 - Chlorin Derivate	1.6–3.5 mg/kg [28]	–	Lysosome [32]
Hypericin	–	0.1% and 0.25% under occlusion [33]	Endoplasmic reticulum
Cyanines	–	0.01–0.1 mg/mL [34]	Cytoplasm [35]
Amino levulinic acid (ALA) - porphyrin precursor	–	20% [36]	Mithocondria and Plasm membrane [37]

[a] In vitro cellular studies.

article with their respectively administration route used in clinical applications. We also present in the main intracellular photosensitizer localization.

The purpose of this review is to evaluate the effectiveness of PDT in the treatment of sBCC, considering the relationship between the natural history of the disease and the protocol applied in the clinical trial.

3. Material and methods

PubMed, Scielo, Ovide and Cochrane Databases were accessed to select articles published in English from 2005 to 2017. The articles should be published in English presenting results of clinical trials with PDT in the treatment of histologically proven superficial basal cell carcinoma, if possible with post-treatment follow up. It were selected trials with the photosensitizers Photofrin®, Foscan®, Nep6, Hipericum, Cyanines, ALA e MAL. Studies related to background and discussion topics were selected with no time limit of publication.

4. Results

4.1. Photofrin® or photoeme® - PDT

Photofrin® is a complex blend of oligomers derived from dihydrochloridehematoporphyrin. Oseroff et al. realized an open-label clinical trial with no randomization and blinding for interventions and outcomes [38]. Complete remission was reported in 90% of lesions and recurrence rates of 12–28% for sporadic BCC at 5-year follow-up. Kavianiand cols combined PDT with Photoeme®, a hematoporphyrin derivative IX, which was applied in six patients with 30 different lesions located on the head and neck, two of them with 4 sBCC [39]. The trial had its results limited to 30 days after the intervention. One incomplete and 3 complete remissions were observed in sBCC lesions.

4.2. Foscan® PDT

Meta-tetrahydroxy-phenylchlorin (mTHPC or Foscan®), is a second-generation FS. The open-label non-randomized study by Betz et al. using mTHPC had the objective to define by escalation the best protocol for BCC treatment [40,41]. Although more than 50% overall recurrences occurred in the first-year of follow-up in a total of 341 treated sBCC. the group who used the optimized protocol experienced rates of 95% cure after 72 months of follow-up. Thickness (> 3 mm) and location of the lesion (Zone H) were considered to be important factors for recurrence.

4.3. NPe6 - PDT

An open assay performed by Chan et al. aimed to study the pharmacokinetics of mono-L-aspartyl chlorine6 (NPe6 [42]. Twenty-four lesions of sBCC were treated with outcomes of 22 complete therapeutic response (92%) and 2 without remission. There was no long follow-up for a better evaluation of the recurrence of post-treatment lesions.

4.4. Hypericin - PDT

Hypericin, a lipophilic compound obtained from Hypericumperforatum, is considered as the most potent natural photosensitizer. The objective of the Kacerovska et al. trial was to evaluate the efficacy of PDT with topical application of *H. perforatum* extract in keratinized actinic lesion, basal cell carcinoma (BCC) and Bowen's disease [43]. Eighteen patients with superficial basal cell carcinoma were treated. The results demonstrated low efficacy due to variability in the purity and concentration of PS in the extract. The overall incomplete response reach to 88%. Only two lesions off 120 showed clinical and histological complete response.

4.5. Cyanines (PHC) - PDT

Cyanines are second generation FS with molecular similarity to porphyrins. The study conducted by Baron et al. evaluated the topical use of PC-4 in the treatment of skin cancer [45]. The clinical trial included 43 individuals, and no tumor remission was observed.

4.6. Metabolic precursors of protoporphyrin IX - PDT

Amino levulinic acid (ALA) is a precursor of photosensitizer Protoporphyrin IX (PpIX) which shows strong affinity for the skin. The 5-amino levulinic acid (MAL) is equally a metabolic precursor of PpIX. The advantage of the precursors of PpIX over functional PS prior to cell internalization is the low ability of the foremost to promote photoreaction [46].

4.7. MAL - PDT

Szeimies et al. performed a randomized, multicentric trial (United Kingdom, Germany, Switzerland and Australia) to demonstrate the non-inferiority of MAL-PDT, considering complete pathological response and cosmetic results, after one year of treatment [47]. One hundred patients were randomized to receive MAL-PDT and 96 were referred for surgery. After three months of treatment, it was observed that MAL-PDT was not inferior to surgery and a mean complete response of 92.2% and 99.2%, respectively was observed in terms of per protocols analysis (PP population). At 12 months recurrence rates were higher in the MAL-PDT group (9.3%) when compared to the surgery group (0%). Regarding cosmetic results, MAL-PDT showed superiority to surgery.

Arits et al. performed a multicenter clinical trial whose outcomes were followed for three years [48]. The objective was to define the effectiveness of the MAL-PDT in the treatment of sBCC when compared with topical fluorouracil and 5% imiquimod cream The primary endpoint was defined as the probability of the patient maintaining complete remission after 3 and 12 months of follow-up. A total of 601 patients with sBCC were randomly assigned to treatment with MAL-PDT, topical imiquimoid, or topical fluorouracil. After 12 months of treatment, respectively 26%, 16% and 20% of the patients allocated to the MAL-PDT, imiquimoid and fluorouracil groups presented residual

tumors or recurrence. In comparative terms, the treatment with imiquimoid was significantly superior compared to MAL-PDT. Pain and burning sensation were frequent adverse effects in MAL-PDT group. The imiquimoid cream had serious adverse effects which led to ulcer and local infections. Aesthetic results were similar in the MAL-PDT, imiquimoid and fluorouracil groups (62.4, 61.4% and 57.5%, respectively), showing equivalence or non-inferiority. Based on the comparative rates of complete remission of sBCC observed in the study, Roseboom et al. extended the follow-up to 36 months, and observed that 58% of patients treated with MAL-PDT were tumor-free after these three years of observation [49]. After this period, the complete tumor remission was 80% in the imiquimod treated group. Considering follow-up after 1 and 3 years, there is a clear decline in the rate of complete remission associated with MAL-PDT.

The clinical trial conducted by Cristensen et al. aimed to evaluate prospectively the complete therapeutic response of PDT combined with MAL in the extended follow-up [50]. A total of 24 lesions were histopathologically diagnosed as sBCC. In long follow-up, 68% of the lesions treated with a single session of ALA-PDT presented complete remission and 91% of those treated with two PDT sessions remained disease free. The groups of single and double PDT sessions presented clinical and histopathological concordance in the evaluation of complete therapeutic response. More than 90% long-term complete response was observed in patients who have two sessions of PDT, only if the lesions remained clear after 3 months of the last session of treatment. The highest recurrence rate was observed in lesions of H-Zone [51]. Wiegell et al. using a daylight-MAL-PDT treated 21 patients with 32 lesions in different locations. The protocol consisted in apply 1-mm layer of MAL cream and allowed the instruct the patient to start daylight exposure within 30 min and to expose themselves continuously to daylight for 2 h. After that they should wiped off MAL cream and stay the rest of the day indoors. After 3 and 12 months, 94% (in 19 patients) and 74% (in 23 patients) of treated lesions, respectively, showed complete response, and after 12 months 21% of lesions (6 lesions) had recurred. The authors concluded that this approach is effective and more convenient, compared to conventional ones, for clinicians and patients [52].

4.8. Aminolevulinic acid - PDT

Vijlder et al. conducted a randomized, open-label prospective trial with the objective of comparing non- Fractionated ALA-PDT with single dose of 75 J/cm^2 and 2-fold illumination of 20 J and 80 J/cm^2 [53]. The long-term response was evaluated after 5 years of follow-up in a total of 195 individuals. After encouraging first results in the latter group, a third one was created with 50 other subjects. The lesions included in single session group were illuminated after 4 h of the application of 20% ALA ointment. and treated with irradiance standardized at 50 mW/cm^2. After 5 years, the 2-fold illumination ALA-PDT group obtained 88% complete remissions (CR), while for the group that used single PDT session, the CR was 75%. The outcomes demonstrated the superiority of ALA-PDT performed with 2 light fractions of 20 and 80 J/cm^2 when compared to a traditional one-session illumination scheme. The complete response rate was comparable to surgery, with the advantage of better cosmetic outcome (Table 2).

5. Discussion

Clinical trials have the best potential to generate robust evidence about therapeutic interventions in humans, its results have internal and external validity when the methodology is based on randomization, blinding assignment of subjects and controlled selection of parameters and outcomes. Clinical trials with BCC in general are quite scarce in the literature and this scarcity influences the guidelines for sBCC treatment, which do not demonstrate a clear consensus on the first choice among non-invasive therapies to treat the neoplasm [49]. The trials selected here evaluated the effectiveness of different FS combined to PDT in the treatment of sBCC, with different designs and methodological qualities. Studies with broad follow-up are important to translational medicine because the longer design allows a parameter to assess complete therapeutic response or the disease-free interval. The PDT clinical trials with Photofrin, Foscan, Nep6 and Hipericum have an uncertain methodology, which compromise the external validity of their results. The absence of randomization and blinding of professionals and patients, the small number of subjects included, the lack of anatomical-clinical correlation of the lesions, the use of a valid biopsy method and the absence of stratified subgroups certainly allowed bias. The scarcity of other trials with PS included in this review makes it impossible for meta-analysis to reach a conclusion regarding their effectiveness. Trials with ALA and MAL associated with PDT and long follow-up admitted better levels of scientific evidence. All of them were randomized controlled trials (RCT) with different degrees of blinding, which evaluated not only the effectiveness of ALA-PDT and MAL-PDT but compared both with other therapeutic modalities in order to answer superiority and inferiority questions.

One point that need to be highlighted is the heterogeneity of the luminous parameters for irradiation. The difference in parameters respond to the chemical characteristics of the PS, administration route, strategies to circumvent photobleaching and downsizing of the adverse effects.

MAL-PDT differences in protocols have consequences in the primary outcomes. The comparison between these randomized trials with a very similar sBCC cohort suggests that more than two PDT sessions design may achieve best therapeutic results (Table 1). Studies with PPIX has demonstrated that PDT repeated at a prefixed time interval in one therapy (fractionated) session induces a higher tissue phototoxicity, because the time gap between irradiations allowed the resynthesis of PpIX and the tissue concentration of FS is a function of fluency rate used in the first stage of PDT session [55].

Considering the timeline of the PDT clinical trials, the photosensitizers most successful are 5-ALA and MAL. Recently an open, uncontrolled study evaluates the efficacy of day-light MAL-PDT in BCC with excellent results [52] after 12 months follow up. But the long follow-up should be for at least 3 years in order to monitor late recurrences. The time for monitoring the PDT-treated lesions and their recurrences should receive more attention in clinical trial designs. The reasons for the recurrence point to the hypothesis of resistant microtumors that escape the phototoxic effects. Preclinical studies have sought to investigate the role of autophagy in tumor resistance, as well as the participation of possible neoplastic stem cells as immortal matrix

Table 2
Complete Response of SBCC to MAL and ALA – PDT.

Type of Study	PS	3 mo CR	12 mo CR	36 mo CR	5 years CR
Randomized, open label, multicentric Trial [44]	MAL	92,2%	–	–	–
Randomized, Partially blinded, multicentric Trial [46]	MAL	–	74%	80%	
Longitudinal prospective study [47]	MAL	–	–	–	81%
Randomized, open-label prospective trial [49]	ALA	–	–		75% (1) 88% (2)

PS: photosensitizer. MAL: 5-amino levulinic acid. ALA: Amino levulinic acid. Mo: month. CR: Complete Remission.
(1) 1 sessions ALA-PDT group. (2) 2 session ALA-PDT group.

of tumor persistence. However, the results are not yet sufficiently consolidated to generate evidence that can lead clinical practice to achieve better results in cancer therapy [22,23].

The natural impermeability of the skin constitutes a barrier to the diffusion of FS into deeper layers. Curettage before PDT, including area of safety margin, is mandatory for better absorption of FS and it significantly impacts on the clearance rate [56]. Certainly, the lack of curettage seen in trials with hypericum and phthalocyanine contributes to the poor results described [57–59].

The Hipericin-PDT, ALA-PDT and MAL-PDT trials demonstrated that disagreement between clinical and histopathological diagnosis may compromise the evaluation of results and the conclusiveness. At this point, the technical limitations of scraping should be highlighted and even punch biopsy in the evaluation of skin cancer. Roseboom analyzes retrospectively 243 primary BCC and concluded that punch biopsy can predict the aggressive BCC pattern only in 84.4% of cases. The finding is similar to the results of studies conducted by Wolberink et al., and Kamiab-Esari et al., who demonstrated extreme pitfalls in specificity and sensitivity of punch biopsy to distinguish between subtypes of BCC [60,61].

6. Conclusion

PDT are important treatment modality of patients diagnosed with sBCC who may prefer the most appropriate cosmetic results or have contraindications to other therapeutic modalities, which are in accordance with the risks of recurrence. Scientific evidences have been continuously produced by in vitro and in vivo studies with focus on PS, lasers and the mechanisms of phototoxicity in cancer cells. Although, in order to better evaluate how the PDT modify the natural history of sBCC, it is necessary to perform randomized controlled trials which should assess not only the immediate effectiveness, but the long-term effects of complete therapeutic response, to generate the most appropriate evidence to guide the clinical practice.

Authors' contribution

IOA, JPL, and LAM were responsible for data collection and analysis; IOA, JN and RBA wrote this article; all co-authors contributed by commenting and approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgements

This study was funded by Fundação de Amparo a Pesquisa do Distrito Federal (FAP-DF) Grant agreement 193.000.846/2015 and Conselho Nacional de Pesquisa (CNPq) – Brasil – National of Science and Technology in Nanobiotechnology (INCT in Nanobiotechnology) Grant agreement 573880/2008-5.

References

[1] U. Leiter, T. Eigentler, C. Garbe, Epidemiology of skin cancer, Adv. Exp. Med. Biol. 810 (2014) 120–140.
[2] A. Lomas, J. Leonardi-Bee, F. Bath-Hextall, A systematic review of worldwide incidence of nonmelanoma skin cancer, Br. J. Dermatol. 166 (2012) 1069–1080.
[3] M.R. Karagas, M.S. Zens, Z. Li, et al., Early-onset basal cell carcinoma and indoor tanning: a population-based study, Pediatrics 134 (1) (2014) e4–e12.
[4] V.P. Chinem, H.A. Miot, Epidemiology of basal cell carcinoma, An. Bras. Dermatol. 86 (2) (2011) 292–305.
[5] L.L. Griffin, F.R. Ali, J.T. Lear, Non-melanoma skin cancer, Clin. Med. Lond. 16 (February (1)) (2016) 62–65.
[6] Z. Apalla, D. Nashan, R.B. Weller, X. Castellsagué, Skin cancer: epidemiology, disease burden, pathophysiology, diagnosis and therapeutic approaches, Dermatol. Ther. (Heidelb) 7 (January (Suppl. 1)) (2017) 5–19.
[7] Brasil. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA), Estimativa 2016: Incidência De Câncer No Brasil/ Estimate 2016: Cancer Incidence in Brazil, INCA, Rio de Janeiro, 2015, p. 122.
[8] Q. Wei, G. Matanoski, E.R. Farmer, M.A. Hedayati, L. Grossman, DNA repair and aging in basal cell carcinoma: a molecular epidemiology study, PNAS 90 (4) (1993) 1614–1618.
[9] V. Madan, J.T. Lear, R.M. Szeimies, Non melanoma skin cancer, Lancet 375 (9715) (2010) 673–685.
[10] M. Tarallo, E. Cigna, R. Frati, et al., Metatypical basal cell carcinoma: a clinical review, J. Exp. Clin. Cancer Res. 27 (1) (2008) 65.
[11] S.J. Miller, Biology of basal cell carcinoma (part I), J. Am. Acad. Dermatol. 24 (1) (1991) 1–13.
[12] M. McCusker, N. Basset-Seguin, R. Dummer, et al., Metastatic basal cell carcinoma: prognosis dependenton anatomic site and spread of disease, Eur. J. Cancer 50 (2014) 774–783.
[13] S.N. Snow, W. Sahl, J.S. Lo, F.E. Mohs, T. Warner, et al., Metastatic basal cell carcinoma report of five cases, Cancer 73 (2) (1994) 328–335.
[14] M. Trakatelli, C. Morton, E. Nagore, Update of the European guidelines for basal cell carcinoma management, Eur. J. Dermatol. 24 (3) (2014) 312–329.
[15] A.N. Crowson, Basal cell carcinoma: biology, morphology and clinical implications, Mod. Pathol. 19 (2006) S127–S147.
[16] D. Straten, V. Mashayekhi, H.S. Bruijn, S. Oliveira, D.J. Robinson, Oncologic photodynamic therapy: basic principles, current clinical status and future directions, Cancers (Basel) 9 (February (2)) (2017) 19.
[17] D. Dolmans, D. Fukuma, R. Jain, Photodynamic therapy for cancer, Nat. Rev. Cancer 3 (2003) 380–387.
[18] C.A. Robertson, D.H. Evans, H. Abrahamse, Photodynamic therapy (PDT): a short review on cellular mechanisms and cancer research applications for PDT, J. Phtochem. Photobiol. B 96 (1) (2009) 1–8.
[19] K. Plaetzer, J. KrammerBerlanda, F. Berr, T. Kiesslich, Photophysics and photochemistry of photodynamic therapy: fundamental aspect, Lasers Med. Sci. 24 (2009) 259–268.
[20] S. Gupta, et al., In vitro and in vivo targeted delivery of photosensitizers to the tumor cells for enhanced photodynamics effects, J. Cancer Res. Ther. 7 (3) (2011) 314–324.
[21] V. Monge-Fuentes, L.A. Muehlmann, R.B. Azevedo, Perspectives on the application of nanotechnology in photodynamic therapy for the treatment of melanoma, Nano Rev. 5 (2014) 24381.
[22] D. Kessel, J. Reiners Jr., Light-activated pharmaceuticals: mechanisms and detection, Isr. J. Chem. 52 (September (8–9)) (2012) 674–680.
[23] B.Q. Spring, I. Rizvi, N. Xu, Tayyaba Hasan, The role of photodynamic therapy in overcoming cancer drug resistance, Photochem. Photobiol. Sci. 14 (2015) 1476–1491.
[27] M.S. Eljamel, C. Goodman, H. Moseley, ALA and Photofrin® fluorescence-guided resection and repetitive PDT in glioblastoma multiforme: a single centre phase iii randomised controlled trial, Lasers Med. Sci. 23 (4) (2008) 361–367.
[28] R.R. Allison, G.H. Downie, R. Cuenca, X.H. Hu, C.J. Childs, C.H. Sibata, Photosensitizers in clinical PDT, Photodiagn. Photodyn. Ther. 1 (1) (2004) 27–42.
[29] J. Saczko, M. Mazurkiewicz, A. Chwiłkowska, et al., Intracellular distribution of Photofrin in malignant and normal endothelial cell lines, Folia Biol. (Praha) 53 (1) (2007) 7–12.
[30] J.S. Friedberg, R. Mick, J. Stevenson, et al., A phase I study of Foscan-mediated photodynamic therapy and surgery in patients with mesothelioma, Ann. Thorac. Surg. 75 (3) (2003) 952–959.
[31] M.H. Teiten, L. Bezdetnaya, P. Morlière, R. Santus, F. Guillemin, Endoplasmic reticulum and Golgi apparatus are the preferential sites of Foscan® localisation in cultured tumour cells, Br. J. Cancer 88 (1) (2003) 146–152.
[32] J.J. Reiners, J.A. Caruso, P. Mathieu, B. Chelladurai, X.M. Yin, D. Kessel, Release of cytochrome c and activation of pro-caspase-9 following lysosomal photodamage involves Bid cleavage, Cell Death Differ 9 (9) (2002) 934–944.
[33] A.H. Rook, G.S. Wood, M. Duvic, E.C. Vonderheid, A. Tobia, B. Cabana, A phase II placebo-controlled study of photodynamic therapy with topical hypericin and visible light irradiation in the treatment of cutaneous T-cell lymphoma and psoriasis, J. Am. Acad. Dermatol. 63 (6) (2010) 984–990.
[34] E.D. Baron, C.L. Malbasa, D. Santo-Domingo, et al., Silicon phthalocyanine (Pc 4) photodynamic therapy is a safe modality for cutaneous neoplasms: results of a phase 1 clinical trial, Lasers Surg. Med. 42 (10) (2010) 888–895.
[35] L.A. Muehlmann, M.C. Rodrigues, J.P. Longo, et al., Aluminium-phthalocyanine chloride nanoemulsions for anticancer photodynamic therapy: development and in vitro activity against monolayers and spheroids of human mammary adenocarcinoma MCF-7 cells, J. Nanobiotechnol. (2015) 13–36.
[36] S.K. Passos, P.E. de Souza, P.K. Soares, et al., Quantitative approach to skin field cancerization using a nanoencapsulated photodynamic therapy agent: a pilot study, Clin. Cosmet. Investig. Dermatol. 6 (2013) 51–59.
[37] A.P. Castano, T.N. Demidova, M.R. Hamblin, Mechanisms in photodynamic therapy: part one—photosensitizers, photochemistry and cellular localization, Photodiagn. Photodyn. Ther. 1 (4) (2004) 279–293.
[38] A.R. Oseroff, L.R. Blumenson, D. Wilson, T.S. Mang, D.A. Bellnier, A dose ranging study of photodynamic therapy with porfimer sodium (Photofrin®) for treatment of basal cell carcinoma, Lasers Surg. Med. 38 (2006) 417–426.
[39] A. Kaviani, L. Ataie-Fashtami, M. Fateh, N. Sheikhbahaee, M. Ghodsi, et al., Photodynamic therapy of head and neck basal cell carcinoma according to different clinicopathologic features, Lasers Surg. Med. 36 (2005) 377–382.
[40] C.S. Betz, W. Rayschning, E.P. Stranadko, M.V. Riabov, V. Albrecht, et al., Optimization of treatment parameters for Foscan®-PDT of basal cell carcinomas, Lasers Surg. Med. 40 (2008) 300–311.
[41] C.S. Betz, W. Rauschning, E.P. Stranadko, M.V. Riabov, V.N. Volgin, et al., Long-

term outcomes following Foscan®-PDT of basal cell carcinomas, Lasers Surg. Med. 44 (2012) 533–540.
[42] A.L. Chan, M. Juarez, R. Allen, W. Volz, T. Albertson, Pharmacokinetics and clinical effects of mono-L-aspartyl chlorin e6 (NPe6) photodynamic therapy in adult patients with primary or secondary cancer of the skin and mucosal surfaces, Photodermatol. Photoimmunol. Photomed. 21 (2005) 72–78.
[43] D. Kacerovska, K. Pizinger, F. Majers, F. Smid, Photodynamic therapy of non-melanoma skin cancer with topical Hypericumperforatum extract—a pilot study, Photochem. Photobiol. 84 (2008) 779–785.
[44] A.C. Tedesco, F.L. Primo, M. Beltrame, Phtalocyanines: synthesis, characterization and biological applications of photodynamic therapy (PDT), nanobiotechnology, magnetohypertermia and photodiagnosis (theranostics), Ref. Module Mater. Sci. Mater. Eng. (2016) 1–6 Current as of 25 July 2016.
[45] E.D. Baron, C.L. Malbasa, D. Santo-Domingo, P. Fu, J.D. Miller, et al., Silicon phthalocyanine (Pc 4) photodynamic therapy is a safe modality for cutaneous neoplasms: results of a phase 1 clinical trial, Lasers Surg. Med. 42 (10) (2010) 728–735.
[46] E. Angell-Petersen, et al., Phototoxic reaction and porphyrin fluorescence in skin after topical application of methyl aminolaevulinate, Br. J. Dermatol. 156 (2) (2007) 301–307.
[47] R.M. Szeimies, S. Ibbotson, D.F. Murell, D. Rubel, Y. Frambach, et al., A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8–20 mm), with a 12-month follow-up, J. Eur. Acad. Dermatol. Venereol. 22 (2008) 1302–1311.
[48] A.H.M.M. Arits, K. Mosterd, B.A.B. Essers, E. Spoorenberg, A. Sommer, et al., Photodynamic therapy versus topical imiquimod versustopical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomized controlled trial, Lancet Oncol. 14 (2013) 647–654.
[49] M.H. Rozeboom, A.H.M.M. Arits, K. Mosterd, A. Sommer, B.A.B. Essers, et al., Three-year follow-up results of photodynamic therapy vs. imiquimod vs. fluorouracil for treatment of superficialbasal cell carcinoma: a single blind,noninferiority, randomized controlled trial, J. Invest. Dermatol. 136 (2016) 1568–1574.
[50] E. Cristensen, E. Skogvoll, T. Viset, T. Warloe, S. Sundstrøm, Photodynamic therapy with 5-aminolaevulinic acid, dimethylsulfoxide and curettage in basal cellcarcinoma: a 6-year clinical and histological follow-up, J. Eur. Acad. Dermatol. Venereol. 23 (2009) 58–66.
[51] E. Christensen, C. Mørk, E. Skogvoll, High and sustained efficacy after two sessions of topical 5-aminolaevulinic acid photodynamic therapy for basal cell carcinoma: a prospective, clinical and histological 10-year follow-up study, Br. J. Dermatol. 166 (2012) 1342–1348.
[52] S.R. Wiegell, V. Skødt, H.C. Wulf, Daylight-mediated photodynamic therapy of basal cell carcinomas—an explorative study, J. Eur. Acad. Dermatol. Venereol. 28 (February (2)) (2014) 169–175.
[53] H.C. Vijlder, H.J.C.M. Seterenborg, H.A.M. Neumann, D.J. Robinson, E.R.M. Haas, Light fractionation significantly improves the response of superficialbasal cell carcinoma to aminolaevulinic acid photodynamic therapy: five-year follow-up of a randomized, prospective trial, Acta Derm. Venereol. 92 (2012) 641–647.
[55] S. Mallidi, S. Anbil, A.L. Bulin, G. Obaid, M. Ichikawa, T. Hasan, Beyond the barriers of light penetration: strategies, perspectives and possibilities for photodynamic therapy, Theranostics 6 (13) (2016) 2458–2487.
[56] H. Wang, Y. Xu, J. Shi, X. Gao, L. Geng, Photodynamic therapy in the treatment of basal cell carcinoma: a systematic review and meta-analysis, Photodermatol. Photoimmunol. Photomed. 31 (2015) 44–53.
[57] F.C. Rossetti, L.B. Lopes, A.R. Carollo, J.A. Thomazini, A.C. Tedesco, M.V. Bentley, A delivery system to avoid self-aggregation and improve in vitro and in vivo skin delivery of a phthalocyanine derivative used in the photodynamic therapy, J. Control. Release 155 (3) (2011) 400–408.
[58] M. Broekgaarden, A.L. Kroon, T.M. Gulik, M. Heger, Development and in vitro proof of concept of interstitially targeted sinc-phthalocyanine liposomes for photodynamic therapy, Photodiagn. Photodyn. Ther. 13 (2016) 148–157.
[59] L.A. Muehlmann, B.C. Ma, J.P.F. Longo, M.F.M.A. Santos, R.B. Azevedo, Aluminum-phthalocyanine chloride associated to poly(methyl vinyl ether-co-maleic anhydride) nanoparticles as a new third-generation photosensitizer for anticancer photodynamic therapy, Int. J. Nanomed. 9 (2014) 1199–1213.
[60] K. Kamyab-Hesari, H. Seirafi, Z.S. Naraghi, M.M. Shah Shahani, Z. Rahbar, M.R. Damavandi, M.M. Naraghi, M. Rezvani, N. Aghazadeh, Diagnostic accuracy of punch biopsy in subtyping basal cell carcinoma, J. Eur. Acad. Dermatol. Venereol. 28 (2) (2014) 250–253.
[61] E.A. Wolberink, M.C. Pasch, M. Zeiler, P.E. van Erp, M.J. Gerritsen, High discordance between punch biopsy and excision in establishing basal cell carcinoma subtype: analysis of 500 cases, J. Eur. Acad. Dermatol. Venereol. 27 (8) (2013) 985–989.