Journal of Lasers in Medical Sciences

J Lasers Med Sci 2022;13:e44

Case Report

http://journals.sbmu.ac.ir/jlms

doi 10.34172/jlms.2022.44

Systemic Photodynamic Therapy With Chlorine e6 as a Photosensitizer for the Treatment of Nodular BCC: A Case Report

Parvin Mansuri[1], Seyed Mehdi Tabaie[1*], Mina Sadat Naderi[2], Katayoun Kebriti[1], Gholamreza Esmaeeli Djavid[3], Afshan Shirkavand[1]

[1]Department of Medical Laser, Medical Laser Research Center, Yara Institute, ACECR, Tehran, Iran
[2]Department of Biophysics, Faculty of Biological Sciences, North Tehran Branch, Islamic Azad University, Tehran, Iran
[3]Department of Photo Healing and Regeneration, Medical Laser Research Center, Yara Institute, ACECR, Tehran, Iran

***Correspondence to**
Seyed Mehdi Tabaie,
Email: smtabaie@yahoo.com

Received: November 14, 2021
Accepted: August 9, 2022
Published online October 11, 2022

Abstract

Introduction: Photodynamic therapy (PDT) is a demonstrated therapeutic method for basal cell carcinoma (BCC), which is the most common human cancer. Here, we present a case report about systemic PDT with chlorine e6 as a photosensitizer (PS) for BCC treatment.

Case Report: A 78-year-old man was diagnosed with a history of a 4-year nodular BCC in the nasal area. The patient was under control and treatment for hypertension and type 2 diabetes. Chlorine e6 was injected intravenously at a 0.08 mg/kg dosage in 500 cc normal saline within 20 minutes. Three hours after injection, laser irradiation was performed with a wavelength of 665 nm, a dosage of 150 J/cm^2, and an irradiance value of 150 mW/cm^2. His nodular BCC was completely cured without any side effects after one session of PDT with chlorine e6.

Conclusion: Systemic PDT with chlorine e6 as a PS may be safe and effective in removing BCC lesions due to the data obtained in a two-month follow-up.

Keywords: Basal cell carcinoma (BCC), Photodynamic therapy (PDT), Chlorine e6

Introduction

Skin cancers, including melanoma and non-melanoma, show a worldwide increasing incidence rate annually, and both of them are currently the most common types of cancer in white populations.[1,2] The rising rate of non-melanoma skin cancer is likely multifactorial: increased exposure to ultraviolet radiation or sunlight due to lifestyle changes, increased outdoor activities, ozone depletion, immune suppression, and genetics in some cases.[3,4] Prolonged exposure to the sun and frequent sunburns seem to be the main risk factors for skin cancers. This is especially relevant to people with lighter skin tone (skin type I-II).[1] Basal cell carcinoma (BCC) is one of the most prevalent cancers worldwide, and its overall prevalence is still rising.[5] BCC has low mortality but can cause significant morbidities due to local invasion.[6] BCC is usually a slow-growing tumor in which metastasis is rare because it occurs in only 0.5% or fewer cases.[7] Although the first treatment for BCC is complete surgery, it is only recommended for high-risk cases.[8] Other treatments include electrodesiccation and curettage, excision, cryosurgery, and Mohs micrographic surgery. Topical therapies and destructive methods such as photoablation or PDT should be considered for a low-risk BCC treatment.[9] Photodynamic therapy (PDT) was discovered 100 years ago by medical student Oscar Raab and his professor Von Tappeiner. The observation showed that incubated paramecia exposure to fluorescent dye and light caused their death, but those kept in the dark remained unchanged. Thus the term "photodynamic reaction" was first coined by Von Tappeiner.[10] PDT is currently used as an alternative treatment for malignant diseases.[11] The pharmacological basis of PDT is through photooxidation in target tissues. The main components of PDT include a photosensitizer (PS), oxygen, and light within the absorbent spectrum of the used PS.[12] Various light sources can be used in PDT, such as light-emitting diodes (red and blue lights), lasers, and fluorescent lamps. Blue light is preferred for maximum absorbance. Red light provides the best tissue penetration.[13,14]

Virtually all the PSs used in cancer therapy are based on the tetrapyrrole backbone, similar to the structure of the protoporphyrin prosthetic group of hemoglobin. Depending on the exact structure, an effective PS can be synthesized between 600 and 800 nm absorption bands. As the light penetration into tissue increases with a wavelength, infrared spectral region PSs such as chlorins, bacteriochlorins, and phthalocyanines tend to make much more effective PSs; however, many other factors are also important. A PS should ideally be a pure unit combined

Please cite this article as follows: Mansuri P, Tabaie SM, Naderi MS, Kebriti K, Esmaeeli Djavid G, Shirkavand A. Systemic photodynamic therapy with chlorine e6 as a photosensitizer for the treatment of nodular BCC: a case report. *J Lasers Med Sci.* 2022;13:e44. doi:10.34172/jlms.2022.44.

with reasonable quality control, low production cost, and high-grade stability during storage. It should have a strong peak between 650 and 800 nm in red to the near-infrared spectral region to provide enough energy to excite oxygen to its singlet state. It should be non-toxic and quickly removable from normal tissues to reduce the phototoxic side effects [15, 16]. Chlorins are the essential PSs, including m-tetrahydroxyphenyl chlorin, benzoporphyrin derivative, and Radachlorin.[17] Chlorine (e6) formulated as the trisodium salt known as Photodithazine or dissolved in polyvinylpyrrolidone has been used.[18] Ce6 is accumulated more effectively in tumors and has a better effect. It is absorbed strongly in longer wavelengths (670 nm) and can be activated by light and ultrasound. It also has a faster clearance function.[19] According to a previous study using PDT with chlorine e6 for the treatment of skin metastases in melanoma, all the metastases were cured completely with no recurrences during the study. There was no necessity to repeat the treatment after one PDT session.[20] Additionally, the review study claims that PDT has recently become a suitable therapy for actinic keratosis and BCC, particularly in large cancerous areas. It is also associated with minimum side effects, excellent performance, and satisfying esthetic results, and satisfying cosmetics.[1,21] In addition, the antimicrobial and antiviral properties of PDT are helpful in the treatment of various infectious diseases.[22]

Case Report

A 78-year-old man was diagnosed with a 4-year history of nodular BCC on the nose area. The patient had been under control and treatment for hypertension and type 2 diabetes. In routine blood tests, FBS and HbA1c were respectively 140 and 7.2. Renal and hepatic function tests were normal. Chlorine e6 was injected intravenously at a 0.08 mg/kg dosage in 500cc normal saline within 20 minutes. Three hours after injection, laser irradiation was performed with a wavelength of 665 nm, a dosage of 150 J/cm^2, an irradiance value of 150 mW/cm^2, and a cross-section of 1 cm (The device was a medical laser, ML7710, from Modulight company with $\lambda = 665$ nm). The patient's 2-cm BCC lesion and 0.5 cm from its peripheral were irradiated. The patient's lesion (2- cm BCC and 0.5 cm from its peripheral) was irradiated Figure 1. The patient was advised to stay at home for at least 48 hours and not be exposed to the sunlight. In the case of going out, covered clothes, a hat, and a suitable sunscreen have to be used.

After PDT, the patient's lesion was bandaged with zinc ointment and mupirocin for 48 hours. The patient was instructed to do wound care, such as daily washing with normal saline, using zinc ointment, taking mupirocin three times a day, and avoiding sun exposure until the wound healed. A weekly visit for two weeks and a visit two months after the operation were performed. On the first visit and the second one after two months, the patient was examined for any signs of infection, such as prolonged pain, swelling, excessive redness, phototoxicity or any other symptoms. The patient had no problem. As seen in Figure 2, the lesion completely went two months after the PDT session for nodular BCC in the nasal area, and acceptable scarring was observed due to the treatment.

Discussion

PDT has advantages in surgical procedures like promoting selective cell destruction. The procedure can be repeated multiple times if necessary. Its cost is more beneficial compared to surgery. Since there is no cumulative toxicity, the treatment is more efficient.[23,24] Over the last 40 years, topical PDT, either using 5-aminolevulinic acid or methyl aminolevulinate, has been approved as an effective treatment for both superficial BCC and thin nodular BCC.[25]

Many new PSs have been investigated in laboratories and also clinical trials, among which Ce6 and its derivatives, such as mono-L-aspartyl chlorin e6 (MACE), diaspartyl Ce6, monoseryl Ce6, and other amino acid derivatives, have improved efficacy and reduced side effects compared to the other PSs for PDT. Ce6 derivatives such as Radachlorin (RADA-PHARMA Ltd., Russia) and Photodithazine (Veta Grand Co., Russia) have been used in clinical trials or approved for some diseases in Russia.[26] Chin et al. indicated that Ce6-PVP had better quality than Ce6 alone in patients with angiosarcoma.[27] Sheleg et al demonstrated that chlorin e6 for skin metastases from melanoma was efficient and well-tolerated in the PDT procedure.[20]

Chlorin e6 contains a higher photodynamic activity under *in vitro* and *in vivo* conditions, and PDT with Ce6 is well sustained and impressive for skin metastases from pigmented melanoma.[28] Son et al demonstrated that a simple structure based on a PS and gelatin could improve

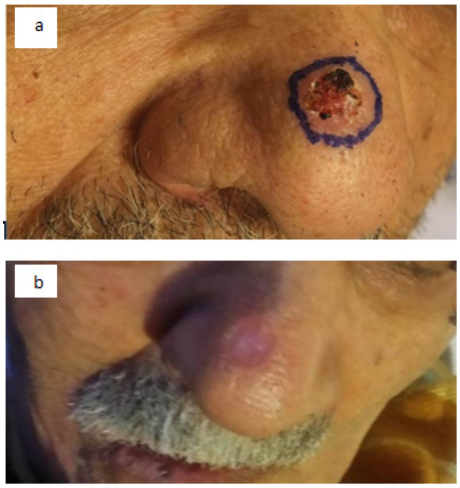

Figure 1. (a) Initial BCC lesion, (b) Follow-up after two months

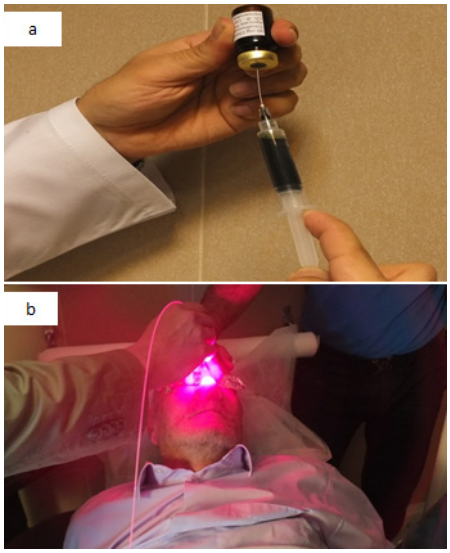

Figure 2. (a) Application of chlorine e6, (b) PDT procedure using laser irradiation (medical laser ML7710, with λ = 665 nm)

water solubility and stability. This structure could increase therapeutic efficacy during *in vivo* PDT and showed its high potential for clinical usage.[29] In this PDT procedure, the concentration of the Ce6 PS, laser power intensity, and contact time were optimally set for the optimized results. Chlorine e6 has maximum absorption in the 665-nm region (optical window for PDT).

In sum, Chlorine e6 may be a helpful method for the treatment of basal cell epitheliums and more efficient than placebo-PDT. This is the first case report on the treatment of nodular BCC with systematic PDT with chlorin e6 in Iran. More extensive identification using the applied and other novel PSs in removing BCC lesions and the design of a new therapeutic protocol are suggested for more accurate PDT efficiency in treating BCC.

Acknowledgments

This work has been financially supported by the Research Council of Medical Laser Research Center, Yara Institute. The authors would like to thank Farhad Seif and Arezoo Aghazadeh for their significant contributions.

Conflict of Interest

No conflict of interest

Ethics Considerations

Due to the report about the successful treatment of a patient with cutaneous BCC by the PDT method, the publication of the report, according to the Ethics Committee of Medical Laser Research Center, Yara Institute, has been unimpeded while preserving the patient's privacy.

References

1. Ericson MB, Wennberg AM, Larkö O. Review of photodynamic therapy in actinic keratosis and basal cell carcinoma. Ther Clin Risk Manag. 2008;4(1):1-9.
2. Shirkavand A, Mohajerani E, Farivar S, Ataie-Fashtami L, Ghazimoradi MH. Quantitative autofluorescence imaging of A375 human melanoma cell samples: a pilot study. J Lasers Med Sci. 2021;12:e4. doi: 10.34172/jlms.2021.04.
3. Gordon R. Skin cancer: an overview of epidemiology and risk factors. Semin Oncol Nurs. 2013;29(3):160-9. doi: 10.1016/j.soncn.2013.06.002.
4. Leiter U, Eigentler T, Garbe C. Epidemiology of skin cancer. Adv Exp Med Biol. 2014;810:120-40. doi: 10.1007/978-1-4939-0437-2_7.
5. Lanoue J, Goldenberg G. Basal cell carcinoma: a comprehensive review of existing and emerging nonsurgical therapies. J Clin Aesthet Dermatol. 2016;9(5):26-36.
6. Kim DP, Kus KJB, Ruiz E. Basal cell carcinoma review. Hematol Oncol Clin North Am. 2019;33(1):13-24. doi: 10.1016/j.hoc.2018.09.004.
7. Lo JS, Snow SN, Reizner GT, Mohs FE, Larson PO, Hruza GJ. Metastatic basal cell carcinoma: report of twelve cases with a review of the literature. J Am Acad Dermatol. 1991;24(5 Pt 1):715-9. doi: 10.1016/0190-9622(91)70108-e.
8. Peris K, Fargnoli MC, Garbe C, Kaufmann R, Bastholt L, Seguin NB, et al. Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. Eur J Cancer. 2019;118:10-34. doi: 10.1016/j.ejca.2019.06.003.
9. Chren MM, Linos E, Torres JS, Stuart SE, Parvataneni R, Boscardin WJ. Tumor recurrence 5 years after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma. J Invest Dermatol. 2013;133(5):1188-96. doi: 10.1038/jid.2012.403.
10. Hamblin MR. Fullerenes as photosensitizers in photodynamic therapy: pros and cons. Photochem Photobiol Sci. 2018;17(11):1515-33. doi: 10.1039/c8pp00195b.
11. dos Santos AF, de Almeida DR, Terra LF, Baptista MS, Labriola L. Photodynamic therapy in cancer treatment-an update review. J Cancer Metastasis Treat. 2019;5:25. doi: 10.20517/2394-4722.2018.83.
12. Fien SM, Oseroff AR. Photodynamic therapy for non-melanoma skin cancer. J Natl Compr Canc Netw. 2007;5(5):531-40. doi: 10.6004/jnccn.2007.0046.
13. Morton CA, Szeimies RM, Sidoroff A, Braathen LR. European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications - actinic keratoses, Bowen's disease, basal cell carcinoma. J Eur Acad Dermatol Venereol. 2013;27(5):536-44. doi: 10.1111/jdv.12031.
14. Tabaie SM, Berenji Ardestani H, Azizjalali MH. The effect of one session low level laser therapy of extracted follicular units on the outcome of hair transplantation. J Lasers Med Sci. 2016;7(1):26-9. doi: 10.15171/jlms.2016.06.
15. Allison RR, Sibata CH. Oncologic photodynamic therapy photosensitizers: a clinical review. Photodiagnosis Photodyn Ther. 2010;7(2):61-75. doi: 10.1016/j.pdpdt.2010.02.001.
16. Aziz-Jalali MH, Tabaie SM, Djavid GE. Comparison of red and infrared low-level laser therapy in the treatment of acne vulgaris. Indian J Dermatol. 2012;57(2):128-30. doi: 10.4103/0019-5154.94283.
17. Wagner A, Denzer UW, Neureiter D, Kiesslich T, Puespoeck A, Rauws EA, et al. Temoporfin improves efficacy of photodynamic therapy in advanced biliary tract carcinoma: a multicenter prospective phase II study. Hepatology. 2015;62(5):1456-65. doi: 10.1002/hep.27905.
18. Abrahamse H, Hamblin MR. New photosensitizers for photodynamic therapy. Biochem J. 2016;473(4):347-64. doi: 10.1042/bj20150942.
19. Shi H, Liu Q, Qin X, Wang P, Wang X. Pharmacokinetic study of a novel sonosensitizer chlorin-e6 and its sonodynamic anti-cancer activity in hepatoma-22 tumor-bearing mice. Biopharm Drug Dispos. 2011;32(6):319-32. doi: 10.1002/bdd.761.
20. Sheleg SV, Zhavrid EA, Khodina TV, Kochubeev GA, Istomin YP, Chalov VN, et al. Photodynamic therapy with

chlorin e6 for skin metastases of melanoma. Photodermatol Photoimmunol Photomed. 2004;20(1):21-6. doi: 10.1111/j.1600-0781.2004.00078.x.
21. Tabaie SM, Nasr E, Naderi MS, Rezvan M. Treatment of striae distensae using fractional ablative CO2 laser in skin types II-IV: a retrospective case series study. J Cosmet Laser Ther. 2018;20(6):330-4. doi: 10.1080/14764172.2018.1493512.
22. Tampa M, Sarbu MI, Matei C, Mitran CI, Mitran MI, Caruntu C, et al. Photodynamic therapy: a hot topic in dermato-oncology. Oncol Lett. 2019;17(5):4085-93. doi: 10.3892/ol.2019.9939.
23. da Mota AC, Leal CR, Olivan S, Leal Gonçalves ML, de Oliveira VA, Pinto MM, et al. Case report of photodynamic therapy in the treatment of dental caries on primary teeth. J Lasers Med Sci. 2016;7(2):131-3. doi: 10.15171/jlms.2016.22.
24. Diniz IM, Horta ID, Azevedo CS, Elmadjian TR, Matos AB, Simionato MR, et al. Antimicrobial photodynamic therapy: a promise candidate for caries lesions treatment. Photodiagnosis Photodyn Ther. 2015;12(3):511-8. doi: 10.1016/j.pdpdt.2015.04.006.
25. Collier NJ, Rhodes LE. Photodynamic therapy for basal cell carcinoma: the clinical context for future research priorities. Molecules. 2020;25(22):5398. doi: 10.3390/molecules25225398.
26. Spikes JD. Chlorins as photosensitizers in biology and medicine. J Photochem Photobiol B. 1990;6(3):259-74. doi: 10.1016/1011-1344(90)85096-f.
27. Chin WW, Heng PW, Thong PS, Bhuvaneswari R, Hirt W, Kuenzel S, et al. Improved formulation of photosensitizer chlorin e6 polyvinylpyrrolidone for fluorescence diagnostic imaging and photodynamic therapy of human cancer. Eur J Pharm Biopharm. 2008;69(3):1083-93. doi: 10.1016/j.ejpb.2008.02.013.
28. Kostenich GA, Zhuravkin IN, Zhavrid EA. Experimental grounds for using chlorin e6 in the photodynamic therapy of malignant tumors. J Photochem Photobiol B. 1994;22(3):211-7. doi: 10.1016/1011-1344(93)06974-8.
29. Son J, Yi G, Kwak MH, Yang SM, Park JM, Lee BI, et al. Gelatin-chlorin e6 conjugate for in vivo photodynamic therapy. J Nanobiotechnology. 2019;17(1):50. doi: 10.1186/s12951-019-0475-1.