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Ocular preservation through limited tumor excision combined with ALA-PDT in patients with periocular basal cell carcinoma

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ABSTRACT

Background: In recent years, photodynamic therapy (PDT) has emerged as a successful technique for treating early non-melanoma skin cancers compared with traditional methods such as surgical operation, chemotherapy, radiotherapy, and immunity treatment, etc. PDT offers excellent aesthetic results and skin function preservation effects, especially so for tumor in difficult-to-treat areas. The purpose of this article was to study the anti-tumor effect of ALA-PDT combined with limited excision in periocular basal cell carcinoma (BCC) and its role in improving the effect of the operation.

Methods: In our study, 8 patients with periocular basal cell carcinoma were treated with topical aminolevulinic acid photodynamic therapy (ALA-PDT) combined with surgery. After removal of tumor mainly with normal tissue saved, each tumor region was irradiated with 177 J/cm^2 using a 635-nm laser for 15 min. A total of 3 times of assisted ALA-PDT was applied during and after operation. BCC was confirmed by pathological examination and the structure of tumor tissues was observed by transmission electron microscopy.

Results: Transmission electron microscopy showed that PDT had inhibitory effects on the growth of BCC by causing necrosis of tumor cells. There was no recurrence in the follow-up of 2.8 years (range, 0.6–5 years). The patients with infiltrative orbital BCC were able to complete the treatment protocol with good cosmetic results and no significant side effects.

Conclusions: PDT in combination with limited surgery is a safe, effective and minimally-invasive approach for treating orbital BCC. Topical PDT during and after operation can reduce the excision range of the tumor lesions. Therefore, PDT may play a positive role in the treatment of periocular basal cell carcinoma.

1. Introduction

Basal cell carcinoma (BCC) comprises approximately 90% of malignant periocular cancers [1]. Depending on the tumor size, location, and histologic type, the guideline-based therapies for BCC include surgery, radiotherapy, freezing and chemotherapy [2]. These therapies raise concerns towards cosmetic effects, especially when periocular area is in the BCC diagnosis and treatment region. Moreover, the formation of scar after treatment may impair the eyelid function and lead to chronic conjunctival irritation. Meanwhile, these therapies may have severe cosmetic effects. Mohs micrographic surgery is preferred because it minimizes recurrence risk and aims for less damage to normal tissues. However, this methodology is restricted due to the lack of skilled Mohs surgeons. How to retain the morphology and function of the eyelid of these patients is one of the clinical challenges.

PDT, a form of therapy involving light and a photosensitizing chemical substance, produces reactive oxygen species to selectively destroy these lesions. The photosensitiser is activated by exposure to light for a specified wavelength. This specific light supplies sufficient energy to stimulate the photosensitiser till the reactive oxygen induced cytotoxicity of malignant cells, to kill the target cells [3]. While ideally they are not strong enough to permanently damage neighbouring healthy tissues. In addition, PDT combined with excision can be used multiple times without resistance, severe side effects and scar formation. Considering that the traditional therapy for eyelid BCC usually can lead to dysfunction and poor appearance of eyelid, we tried to provide a new protocol. Therefore, we used topical PDT combined with limited excision for treatment of these patients and assessed the outcomes.

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2. Patients and methods

In our study, 8 patients (age 54 to 81) with periocular BCC in our department were randomly selected, six males and two females. We informed to the patients about the details of operation methods, PDT indications, treatment principles, therapeutic effect, possible complications and preventive measures. To preserve function of the eyelid, excision was limited to the size of the lesions. The protocol was carried out including surgery combined with topical PDT for the treatment of eyelid BCC. Written informed consent from patients was obtained. All the tumors were verified as BCC by means of a frozen section biopsy then PDT was given in the following way.

Fresh wounds (2.0 cm beyond the visible lesions) were covered with 10% 5-ALA (Fudan Zhang Jiang Biomedical Corp., Shanghai, China) in an oil-in-water emulsion for a 4 h incubation period under a light-shielding dressing. The laser beams of a 635-nm wavelength emitted by a diode laser type XD-635AB (manufactured by Xingda Photoelectricity Medical Equipment Corp., Guilin, China) were directed onto the therapy area at the same energy density (120 J/cm^2) within the exposure time of 15 min for each 3cm^2 field; power output was set to 177 mW/cm^2. The light exposure was adjusted to keep a constant distance from lesions vertically. The PDT treatment session was repeated 1 week and 3 weeks later.

The efficacy of treatment was followed-up post the full treatment 1 and 3 months respectively with information collected including lesion response and recurrence, cosmetic outcome and the function of eyelid. The following figure illustrates the treatment results of one of those patients. The pathological sections obtained from BCC before and after PDT were studied under light and transmission electronic microscopy.

3. Results

PDT did have transient local reactions although resolved spontaneously in 1–2 days, such as burning sensation on the skin, pain or erythema, symptoms that are commonly associated with the way the therapy performed. The group all completed the three PDT sessions. All reactions were tolerated well in all patients with no serious complications and scar formation observed.

All 8 patients had biopsy-proven BCC of the periocular region (Fig. 1). Infiltrative BCC with marked pleomorphism was exhibited in TE microscope (Fig. 2). Eelectron microscope tests were done immediately post-operation (Fig. 3), 4 days after PDT (Fig. 4). Results indicated that PDT had changed the ultrastructure of tumor cells (including PDT-induced cellular edema) and has decreased the tonofilament expression. With increasing duration after therapy, necrosis of tumor cells noticed in ongoing therapy with macrophage and lymphocytes engulfing dead tumor cells which might be induce powerful antitumor immunity. The therapeutic results, including functional and cosmetic outcomes, were demonstrated by photographs during the follow-up (Fig.5a-d), and the mean duration of follow-up was 2.8 years (range, 0.6–5 years). Histological specimen will be taken if there were any suspicions of recurrence. Curative effect of these cases that adopted the combined therapies early were satisfying, no recurrence by follow-up visit.

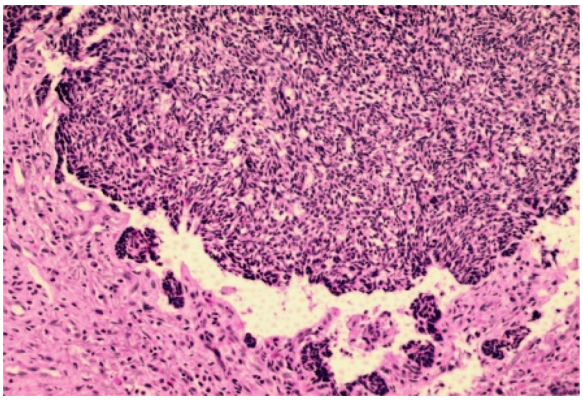

Fig. 1. Histological analysis shows basal cell carcinomas with basal cell like cells hyperplasia, dark stained nuclei, less nuclear disintegration.

4. Discussion

The most common tumors occurring in periocular area were BCC, accounting for 84%–96% [4]. Involved areas include the lower lid, medial canthus, upper lid, and lateral canthus [5]. However, eyelid malignancies require different treatments than other skin tumors, due to the unique anatomical factors in the periocular region. Special consideration thus needs to be taken for functional impact of surgical resection and reconstruction for optimal visual acuity and cosmetic effect preservation. [4]. As both functional and cosmetic outcomes are visible, therefore the eyelid area is challenging for high risk when treating cutaneous carcinoma.

The standard BCC treatment is radical surgery. However, medial canthus location is associated with a higher rate of incomplete resection and possible intra-orbital involvement can not only cause local recurrence but also require the intra-orbital resection [6,7]. There are studies show that the rate of local recurrence is less than 1% after total removal of BCC with negative margins in 5-year follow-ups, where's up to 38% with incomplete excisions [8,9]. Moreover, expanded resection may require skin flaps or free skin grafts in eyelid area, which not only affects the eyelid function and aesthetics, but also may cause complications such as infection and scar. Mohs micrographic surgery is widespread treatment modality, followed by eyelid reconstruction, which both demand highly experienced and skilled surgeons [10]. Radiation has always been used for adjuvant treatment of high-risk tumors in the therapy of eyelid malignancies. However, it has side effects including conjunctival keratinization, chronic dry eye, exposure keratopathy, cataract, optic neuropathy and retinopathy [11]. Imiquimod is a medication that acts as an immune response modifier. This drug provides hope of a treatment to nodular BCC. However, its impact on infiltrative BCC are inconsistent. Vismodegib is the first molecularly targeted therapy for advanced and metastatic BCC [12]. The most commonly reported side effects are leg cramps, dyspepsia, weight loss, alopecia, and lower back pain. A research has indicated that 14 of 26 patients (54%) with BCC treated with vismodegib had to stop therapy due to side effects. Therefore, recurrence rate, preserving function of eyelid, expectations of patients and potential moderate interactions must be carefully analyzed when we select optimal management for periocular BCC [13]. At present, ALA-PDT is a new life-extending treatment which has minimal damage to surrounding normal tissues and with no negative effects on quality of life.

PDT is a novel non-invasive therapeutic technique, which can be curative, particularly in early stage tumors that have been revealed by clinical studies [14]. Exposure of specific wavelength light at tumor sites can activate photosensitizers (5-ALA) which selectively accumulate in tumor tissue, it can trigger photochemical reactions that damage tumor tissue and little damage to adjacent normal tissue structure [15]. This treatment has minimal normal tissue toxicity, negligible systemic effects, significantly reduced long-term morbidity, good cosmetic and related function preservation. PDT combines photosensitizers, oxygen molecules and light stimulation to treat tumors. The main cytotoxic material in PDT is the excited state of the molecular oxygen, singlet oxygen ($^1O_2$), a highly active ROS that oxidizes biological substrates [16]. The singlet oxygen or ROS produced within the cell membrane can cause photo-oxidation damage to proteins and lipids within the photosensitive binding site, which induce oxidative damage in the target cells, leading to induction of apoptosis, necrosis, and the damage of tumor vasculature system [17]. Inflammatory response at the same time can be triggered and anti-tumor immune response indirectly

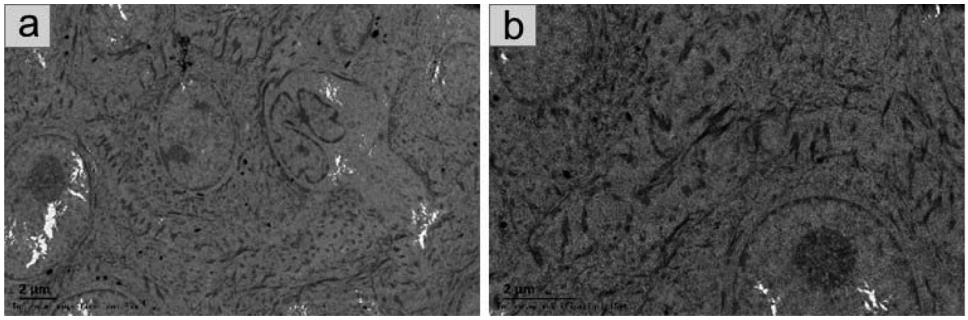

Fig. 2. Tissues from a BCC patient. (a) Tumor cell atypia was obvious; melanin granules and many tonofilaments in the cell. (b) Tumor cells infiltrating stroma; basal lamina lost and desmosome lacking.

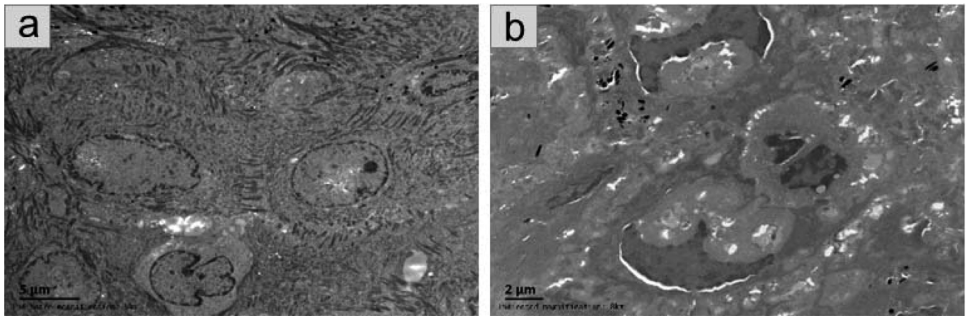

Fig. 3. Tissues from a PDT-treated patient (immediately after) (a) No clear boundary in tumor cells; BCC and tonofilament partly disassembled. (b)Three basic alterations are evident: cellular edema; vacuoles were seen in the nucleus and cytoplasm; cell nuclei showed irregular shape like crescent.

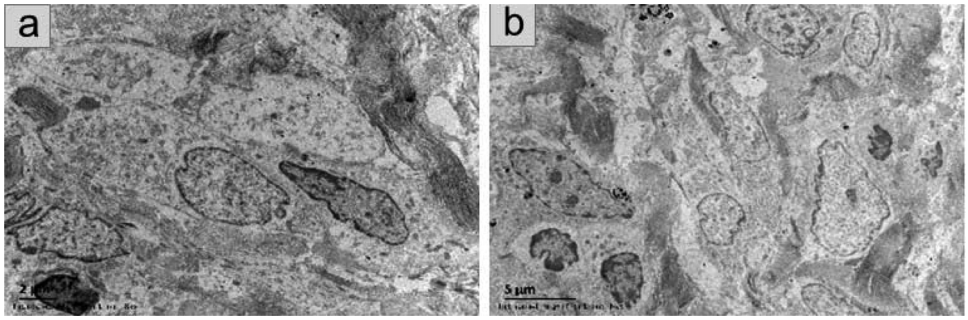

Fig. 4. Tissues from a PDT-treated patient (Day 4) (a) Though the cellular outlines vaguely remain, the tumor cells have lost their nuclei. (b) Macrophage and lymphocytes engulfing the dead tumor cells.

stimulated. The combination of these three mechanisms may lead to long-term tumor control through anti-tumor effects on primary and metastatic tumors [18]. Currently, it received approval in the authoritative cancer treatment guidelines as a second-line treatment for patients with skin cancer [19], especially for nonmelanoma skin cancer like Bowen's disease and superficial basal cell carcinoma. However, clinical experiences of PDT on the treatment of infiltrative BCC are still lacking.

In this study, surgical removal of visible lesions followed by PDT shows suppression of the development of periocular infiltrative BCC. The laser with a wavelength of 635 nm has a less than 6 mm of penetration depth in the skin tissues, which limited the downward penetration of photosensitive reactions and inevitably influenced the therapeutic depth. Thus, it normally requires 3 sessions of PDT to achieve complete regression of the cancer. In these cases, the visible lesions (1 cm beyond the edge) were completely removed in 8 cases. Selecting a suitable treatment method is particularly important for patient with periocular BCC due to its prominent position for which only lesions with significant hyperplasia and those obviously affected are removed surgically in the group to minimize risk of periocular deformation. We have adopted PDT to eliminate the tumor cells remaining in the primary site for low recurrence rate and function preservation. Electron microscopy observations also show that photodynamic therapy in infiltrative BCC can induce tumor cell necrosis which may activate anti-tumor immunity to achieve long-term tumor regression through DAMPs pathway [20]. What we aim for in this study is that: complete or partial removal of the lesions to enable effective penetration of laser, thus better therapeutic depth penetration and then shortened treatment time frame. The lesions are completely subsided after three sessions of PDT for all patients in the study.

In conclusion, the superiorities of PDT lessen the need for delicate surgery of the tumor, improve rapid rehabilitation, reserve the function of eyelid and minimize formation of scar tissue and disfigurement. ALA-PDT combined limited lesion excision may be more suitable for the treatment of periocular tumors as optimal eyelid function and cosmetic effects are an important clinical consideration.

Acknowledgments

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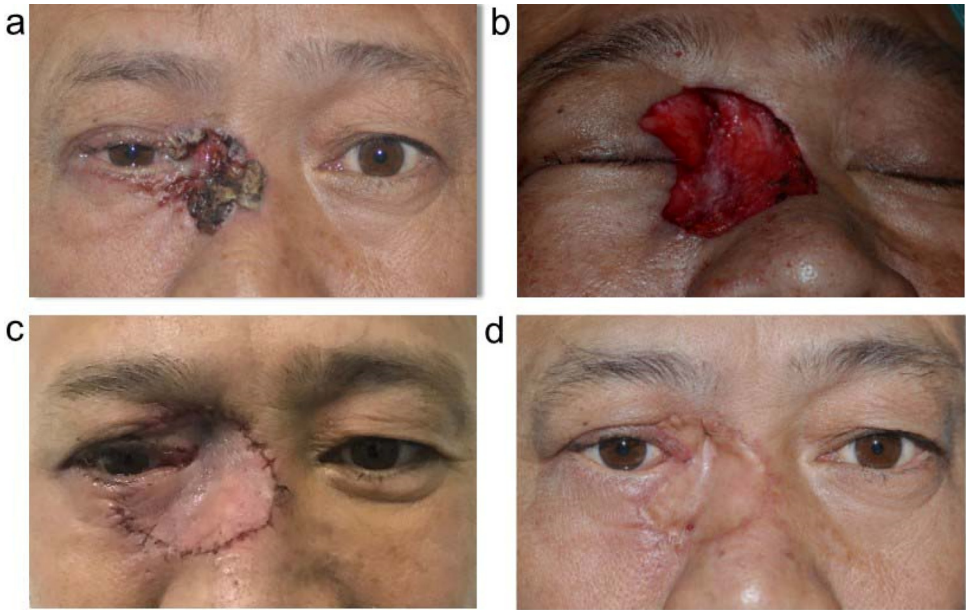

Fig. 5. (a) Periocular BCC patient before treatment. (b) Tumor resection and skin grafting. (c) Presentation after 5 days of tumor resection. (d) 3 months after resection and PDT.

References

[1] B.E. Cook Jr., G.B. Bartley, Epidemiologic characteristics and clinical course of patients with malignant eyelid tumors in an incidence cohort in Olmsted County, Minnesota, Ophthalmology 106 (4) (1999) 746–750.

[2] C.K. Bichakjian, et al., Basal cell skin Cancer, version 1.2016, NCCN clinical practice guidelines in oncology, J. Compr. Cancer Netw. 14 (5) (2016) 574–597.

[3] L.B. Josefsen, R.W. Boyle, Photodynamic therapy and the development of metal-based photosensitisers, Met. Drugs 2008 (2008) 276109.

[4] V.T. Yin, et al., Eyelid and ocular surface carcinoma: diagnosis and management, Clin. Dermatol. 33 (2) (2015) 159–169.

[5] F. Weesie, et al., Recurrence of periocular basal cell carcinoma and squamous cell carcinoma after Mohs micrographic surgery: a retrospective cohort study, Br. J. Dermatol. (2018).

[6] A.Y. Nemet, et al., Management of periocular basal and squamous cell carcinoma: a series of 485 cases, Am. J. Ophthalmol. 142 (2) (2006) 293–297.

[7] R. Shinder, Risk factors for orbital exenteration in periocular basal cell carcinoma, Am. J. Ophthalmol. 154 (1) (2012) 212 author reply 212-3.

[8] R.M. Conway, S. Themel, L.M. Holbach, Surgery for primary basal cell carcinoma including the eyelid margins with intraoperative frozen section control: comparative interventional study with a minimum clinical follow up of 5 years, Br. J. Ophthalmol. 88 (2) (2004) 236–238.

[9] V.A. Wong, et al., Management of periocular basal cell carcinoma with modified en face frozen section controlled excision, Ophthalmic Plast. Reconstr. Surg. 18 (6) (2002) 430–435.

[10] P. Bonavolonta, et al., Treatment of metastatic eyelid carcinoma, J. Craniofac. Surg. 28 (8) (2017) e722–e725.

[11] A. Hsu, et al., Postoperative adjuvant external-beam radiation therapy for cancers of the eyelid and conjunctiva, Ophthalmic Plast Reconstr Surg 24 (6) (2008) 444–449.

[12] H.S. Gill, et al., Vismodegib for periocular and orbital basal cell carcinoma, JAMA Ophthalmol. 131 (12) (2013) 1591–1594.

[13] M.M. Chren, et al., Quality-of-life outcomes of treatments for cutaneous basal cell carcinoma and squamous cell carcinoma, J. Invest. Dermatol. 127 (6) (2007) 1351–1357.

[14] Y.G. Lu, et al., Efficacy of topical ALA-PDT combined with excision in the treatment of skin malignant tumor, Photodiagnosis Photodyn. Ther. 11 (2) (2014) 122–126.

[15] M. Fujino, et al., 5-Aminolevulinic acid regulates the inflammatory response and alloimmune reaction, Int. Immunopharmacol. 37 (2016) 71–78.

[16] M.M. Kim, et al., On the in vivo photochemical rate parameters for PDT reactive oxygen species modeling, Phys. Med. Biol. 62 (5) (2017) R1–R48.

[17] D.E. Dolmans, D. Fukumura, R.K. Jain, Photodynamic therapy for cancer, Nat. Rev. Cancer 3 (5) (2003) 380–387.

[18] F. Anzengruber, et al., T-cell mediated anti-tumor immunity after photodynamic therapy: why does it not always work and how can we improve it? Photochem. Photobiol. Sci. 14 (8) (2015) 1492–1509.

[19] M.H. Gold, M.P. Goldman, 5-aminolevulinic acid photodynamic therapy: where we have been and where we are going, Dermatol. Surg. 30 (8) (2004) 1077–1083 discussion 1083-4.

[20] Y. Zheng, et al., Photodynamic-therapy activates immune response by disrupting immunity homeostasis of tumor cells, which generates vaccine for Cancer therapy, Int. J. Biol. Sci. 12 (1) (2016) 120–132.