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Photodynamic therapy in the treatment of oral leukoplakia: A systematic review

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ABSTRACT

Objective: The aim of the present study was to systematically review the efficacy of photodynamic therapy (PDT) in the management of oral leukoplakia (OLK).

Methods: This systematic review aimed to address the following focused question: "Is photodynamic therapy effective in the management of oral leukoplakia?" PubMed/Medline, EMBASE, ISI Web of Knowledge, OVID, CNKI, and WANFANG DATA were searched up to and including June 2018 using different combinations of the following keywords: photodynamic therapy, leukoplakia, oral dysplasia, oral precancers, and oral premalignant lesions.

Results: Sixteen studies were included in the present study. A total of 352 patients was included in this review, with age ranging from 20 to 79 years. Photosensitizers used were aminolevulinic acid, Photofrin, methylene blue, and chlorine-e6. Laser wavelength, duration of irradiation, and power density were 420–660 nm, 60–1000 s, and 100–150 mW/cm^2, respectively. On the whole, the rates of complete response and partial response were 32.9% and 43.2%, and the sum was 76.1%. The follow-up period ranged from 1 month to 119 months. The recurrence rate of OLK was 0–60%.

Conclusion: PDT appears to be a useful therapeutic strategy in the management of oral leukoplakia as a non-surgical treatment. Further RCTs with long follow-up period, standardized PDT parameters, and comparing efficacy of PDT with various other therapies are needed to acquire definite conclusions.

1. Introduction

Oral leukoplakia (OLK) is defined as a white patch or plaque that cannot be characterized clinically or pathologically as any other diseases. [1] The morbidity rate, as reported previously, ranges from 0.2% to 4.3% [2]. It is one of the most common precancerous lesion of oral mucosa. The rate of malignant transformation ranges from 7.7% to 38.1% [3], which is suggested to be related to population, gender, tobacco habits, lesion size, pathological type, and histological grading of dysplasia [4,5].

Each year 300,400 new cases of oral squamous cell carcinoma (OSCC) and 145,300 cancer-related deaths occur, with an average 5-year survival rate below 60%. [6] However, OSCC is a long-term process, and therefore precautionary measures can be developed to prevent cancerization long before malignancy arises [7]. The standard therapies for OLK range from careful observation to complete resection [8]. But it was reported that the surgical approach applied did not prevent all premalignant lesions from malignant development [9]. Non-surgical treatment is considered to be applied in the management of OLK lesions which involve a large area of oral mucosa or occur in patients with high surgical risks, or when patients refuse surgical treatment.

A variety of treatment strategies has been applied for the management of oral leukoplakia, such as systemic use of drugs (Alfa tocoferol, Beta-carotene, Isotretinoin, Vitamin A, Lycopene, and etc.), topical application of drugs (Bleomycin, Vitamin A, Tretinoin, Isotretinoin, and etc.), and photodynamic therapy [10].

Photodynamic therapy (PDT) is a non-surgical tool with the use of photosensitizing agents which accumulate selectively in target tissue before light delivery. [11] PDT involves 3-components: light source, photosensitizers, and tissue oxygen [12]. In the presence of oxygen, interaction between a light source and photosensitizer (PS) is stimulated, which produces reactive oxygen species (ROS) [13]. The intracellular cytotoxic ROS result in oxidative damage to microbial cell walls as well as pre-malignant and malignant cells [14,15].

In recent years, a number of clinical trials using PDT in the treatment of OLK were reported. In the study by Chen H.M. et al [16], 24

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OLK patients were treated by PDT, with a result of 8 patients showing complete response and 16 patients showing partial response. Only in two cases, OLK recurred during the follow-up period. Kübler A et al. [17] also reported a total of 12 OLK lesions treated by PDT with complete response in 5, partial response in 4, and no response in 3 patients, whereas no recurrence was revealed. Besides, PDT was suggested to be a useful treatment strategy in the management of oral premalignant lesions in the systematic review of Vohra F et al. [18] However, efficacy of PDT in oral leukoplakia has not been systematically reviewed to our knowledge from indexed literature.

The aim of the present study was to systematically review the efficacy of PDT in the management of oral leukoplakia.

2. Materials and methods

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the focused question of the present review was "Is photodynamic therapy effective in the management of oral leukoplakia?"

2.1. Eligibility criteria

(a) Original studies; (b) clinical studies; (c) participants were humans; (d) intervention: photodynamic therapy; (e) clinical and/or pathological diagnosis was oral leukoplakia; (f) articles published in English or Chinese. Review articles, case reports, animal studies, in vitro studies, commentaries, and letters to the Editor were excluded. Study type restrictions were not imposed.

2.2. Search strategy

PubMed/Medline (National Library of Medicine, Bethesda, Maryland), EMBASE, ISI Web of Knowledge, OVID, CNKI (China National Knowledge Infrastructure), and WANFANG DATA were searched from their inceptions till June 2018, using different combinations of the following keywords: "photodynamic therapy", "leukoplakia", "oral dysplasia", "oral precancers", and "oral premalignant lesions".

2.3. Selection and assessment of relevant studies

The eligibility criteria were formulated by two independent raters (He Y. and Li Y.) following the reading of title and abstract of each article and checked for agreement. Thirty-four full texts of selected studies were read and independently assessed with reference to the eligibility criteria. A consensus meeting was held to discuss differences by the reviewers after assessment. Based on the discussion, sixteen articles were included in the present systematic review.

2.4. Data analysis

Two reviewers (He Y. and Li Y.) performed data extraction independently. Information from the accepted studies was tabulated according to subject demographics, site of OLK assessed, follow-up period, main study outcomes, recurrence, quality of studies, and PDT parameters. All extracted data was crosschecked by the reviewers and inconformity was solved by discussion until agreement was reached.

2.5. Assessment of the risk of bias

The assessment of methodological quality and risk of bias of the included studies was done by two assessors (He Y. and Li Y.) based on a modified version of the Downs and Black checklist [19].

2.6. Statistical analysis

As a result of the lack of methodological uniformity of the included studies, a meta-analysis could not be performed. The pattern of the present study was customized to mainly summarize relevant information.

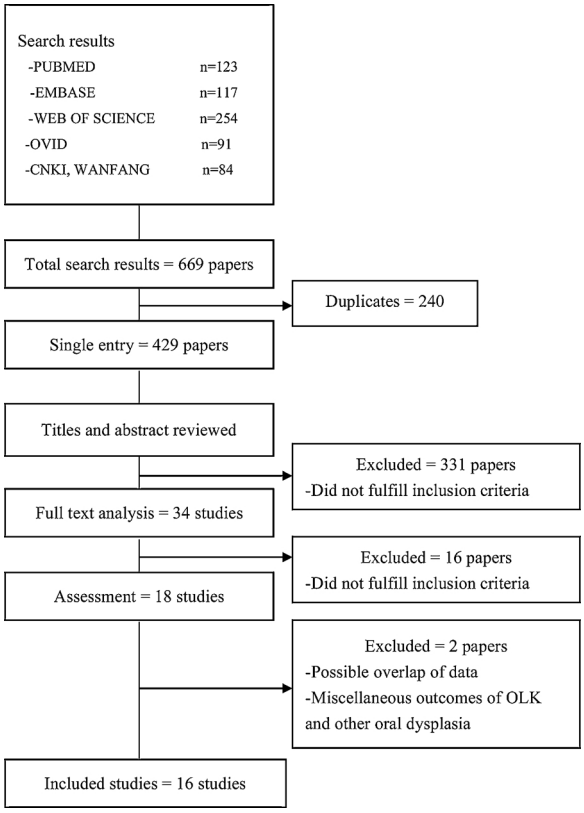

Fig. 1. Literature search and selection according to the PRISMA guidelines.

3. Results

3.1. Outcomes of the search and selection process

A total of 429 unique citations was identified after literature search, of which 34 papers were selected for full-text reading. After evaluation using the eligibility criteria, 18 studies were further excluded. One study was excluded due to miscellaneous outcomes of OLK and other oral dysplasia. [20] One study was excluded because it exposed possible overlap of data with another three included studies of the same authors [21]. None of the literatures in Chinese met the inclusion criteria. After the final stage of selection, 16 studies were included and processed for data extraction. Fig. 1 shows the study identification flow chart.

3.2. General characteristics of included studies

These articles were published between the year 1993 and 2016. All the studies were clinical studies without comparing PDT with other modalities except for two studies that compared PDT with cryotherapy [22] and retinoic acid [23] respectively. No randomized controlled trial has been reported. The included studies were conducted in 7 countries. A total of 352 patients was included in this review, of which 190 were men, 67 were women, and gender of the remainder was not reported. The reported age of patients ranged from 20 to 79 years.

Fouteen studies reported the site of lesions, which included, buccal and labial mucosa, tongue, palate, gingiva, floor of the mouth, buccogingival sulcus, retro molar area, and alveolar ridge. Patients from 13 studies were clinically and histopathologically diagnosed as oral leukoplakia, including 11 patients with "field cancerization" in oral cavity, who all have correlative area of OLK, from the study of Grant WE et al.

Table 1
General characteristics of the studies included.

Authors and year Of publication	Patients	Age range	Gender (female)	OLK LESIONS Site	follow up	Study outcome	Recurrence (%)
Wong SJ et al. (2013) [38]	11	48–74	5	T,L, alveolar ridge	3 months	NR: 11	Not reported
Pietruska M et al. (2014) [31]	23(44 lesions)	21–79	16	B,L,G,T	Not reported	CR : 12 lesions, PR : 22 lesions, NR : 10 lesions	Not reported
Kawczyk-Krupka A et al. (2012) [22]	48	32–75	20	B,G,L	1–119 months	CR: 35, PR: 11, NR: 2	27.1
Chen HM et al. (2004) [26]	36	Not reported	Not reported	Not reported	Not reported	Group 1:CR:3 PR:9 NR:12 Group 2:CR:4 PR:8	Not reported
Sieroń A et al. (2003) [25]	12	32–70	Not reported	B,G, Mandibular, L, B-G sulcus	4-34 months	CR:10, NR:2	8.3
Gaimari G et al. (2016) [34]	5	45–84	4	B,L,P, retro-molar	Not reported	CR:3, PR:2	60
Grant WE et al. (1993) [24]	11	Not reported	Not reported	B,T,L	3–19 months	CR:10, PR:1	18.1
Tsai JC et al. (2004) [39]	24	Not reported	Not reported	T,AND SO ON	6 months.	CR:3, PR:9, NR:12	0
Prasanna SW et al. (2015) [30]	10(13 lesions)	20–70	2	B,T,P	3 months	CR:1 lesion, PR:7 lesions, NR:5 lesions	30.8
Chen HM et al. (2005) [16]	24	30–73	2	B,L,T,Lower, Alveolar	3–16 months	CR:8, PR:16, NR:0	8.3
Chen HM et al. (2007) [35]	97	26–77	7	B,T, alveolar, G,L,P	3–36 months	Group 1:CR:5, PR:33, NR:27 Group 2:CR:11 PR:21	Group 1:1.5 Group 2:6.25
Kübler A et al. (1998) [17]	12	Not reported	1	B,B-G sulcus, floor of mouth	6–16 months	CR:5, PR:4, NR:3	0
Selvam NP et al. (2015) [36]	4	35–49	0	B,G,T	1 year	CR:1, PR:2, NR:1	0
Shafirstein G et al. (2011) [40]	23	37–79	10	T,B,G, floor of mouth, retro-molar	90-day	CR:8, PR:11, NR:4	4.3
Sieroń A et al. (2001) [41]	5	Not reported	Not reported	Not reported	6 months.	CR:4	20
Maloth, K. N et al. (2016) [23]	7(12 lesions)	39.17 ± 14.75	Not reported	B,T,G	Not reported	CR:2 PR:8 NR:2	Not reported

OLK: oral leukoplakia; PDT: photodynamic therapy; NR: no response; PR: partial response; CR: complete response; T: tongue; L: lips; B: buccal; G: gingiva; B–G sulcus: bucco-gingival sulcus; P: palate.

[24]. The remaining patients were only diagnosed clinically without confirmation by pathological examination. In all studies, follow-up period ranged from 1 month to 119 months.

All included studies used PDT solely without combination with other therapies for the management of oral leukoplakia (Table 1).

3.3. PDT related parameters of included studies

Eleven studies used light emitting diode (LED) or dye lasers as light source, while metal halide lamp, Xenon lamp, or Diode lasers were used in the other studies. The wavelengths ranged between 420 nm and 660 nm, with the majority between 630 nm and 635 nm. Energy fluence, power density, and duration of irradiation ranged between 2 and 200 joules per square centimeters (J/cm^2), 100 and 500 mW per square centimetre (mW/cm^2), and 60 and 1000 s (s) respectively, among which most researchers chose 100 J/ cm^2, 100 mW/cm^2, and 1000s as their parameters. Laser power output was reported by one study, which were 100 mW (milli-watts).

In thirteen studies, aminolevulinic acid (ALA) (10–20%) was used as photosensitizer (PS), while the other three studies used methylene blue, chlorin-e6, and photofrin respectively. Fifteen studies reported the frequency of PDT application, including one-time, once every two weeks, once a week, and twice a week. In studies using topical application of PS, pre-activation time ranged from 5 min to 5 h, when it was 48 h in one study using intravenous administration (Table 2).

3.4. Quality of the clinical studies

In the analysis of methodological quality, scores ranged from 8 to 19 points. The main shortcomings consisted of lack of randomization of the samples, blinding confounders, and sample size calculation.

3.5. Outcomes of included studies

The outcomes in all studies were categorized as complete response (CR), partial response (PR), and no response (NR).

With the exception of one study that all 11 patients showed no response to PDT, complete response were reported in 7.7%–90.9% of lesions, while 0–66.7% of lesions showed partial response to PDT. In the remaining fifteen studies, 0–59% showed no response to PDT. On the whole, the rates of complete and partial response were 32.9% and 43.2%, and the sum was 76.1%. Eleven studies reported the recurrence rate in oral leukoplakia patients treated with PDT ranging between 0 and 60%, and mostly below 20%.

4. Discussion

In this study, we reviewed relevant literature to the efficacy of PDT in the treatment of OLK. All included studies used PDT as therapeutic measure without combination with other measures, in which PDT proved to have some effect in the treatment of OLK. The sum of complete response rate and partial response rate was 76.1% after counting up all the included studies, which showed a high effective rate in general.

In the research of Sieroń A et al., 10 out of 12 achieved complete response, with only one recurrence during the six-month follow-up period. [25] And another group reported 8 complete response, 16 partial response, and 0 no response [16]. Grant WE et al. applied photofrin as photosensitizer to OLK lesions with the result that 10 out of 11 patients showed complete response. Three months later three clinically normal regenerated mucosa was biopsied, two of which even regained histologically normal epithelium [24]. In fact, the majority of the included studies demonstrated their no response rate less than 30%.

Kawczyk-Krupka A et al. compared cryotherapy with photodynamic therapy in the treatment of OLK, with a result of no significant difference in outcomes. Furthermore, PDT instead of cryotherapy enabled the treatment of multifocal lesions in one session. [22] Maloth K N et al. used retinoic acid as a control strategy to attest the efficacy of PDT, following a significant outcome ($P = 0.007$) to demonstrate PDT as a feasible alternative to conventional therapy of OLK [23].

From the included studies, advantages of PDT as a non-invasive therapy deserve more attention in clinical research and application.

We observed that the treatment frequency may influence the efficacy of PDT. Chen HM et al. mentioned in two studies [16,26] that OLK

Table 2
Parameters of photodynamic therapy in the included studies.

Authors	Photosensitizer	Concentration of PS	Light Source	Wavelength (nm)	Power density (mW/cm2)	Energy fluence (J/cm2)	Duration of irradiation(second)	frequency
Wong SJ et al. [38]	ALA	Not reported	Dye laser	585	Not reported	2 or 4	Not reported	one time
Pietruska M et al. [31]	Chlorine-e6	20%	Diode laser	660	Not reported	90	Not reported	once every two weeks
Kawczyk-Krupka A et al. [22]	ALA	20%/10%	Diode Laser or Dye laser	630–635	Not reported	100	900	once every two weeks
Chen HM et al. [26]	ALA	Not reported	LED	635 ± 10	100	100	1000	Group 1:once a week; Group 2:twice a week
Sieroń A et al. [25]	ALA	10%	Dye laser	635	150	100	900	once every two weeks
Gaimari G et al. [34]	ALA	20%	Diode laser	635	100	100	1000	twice a week
Grant WE et al. [24]	Photofrin	2 mg/kg	Dye laser	630	below 150	50–100	Not reported	one time
Tsai JC et al. [39]	ALA	20%	LED	635 ± 5	100	100	Not reported	Once a week
Prasanna SW et al. [30]	methylene blue	5%	Metal halide lamp	630 ± 10	Not reported	120	Not reported	twice a week
Chen HM et al. [16]	ALA	20%	LED	635 ± 5	100	100	1000	twice a week
Chen HM et al. [35]	ALA	20%	LED	635 ± 5	100	100	1000	Group 1:once a week Group 2:twice a week
Kübler A et al. [17]	ALA	20%	Dye laser	630	100	100	1000	one time
Selvam NP et al. [36]	ALA	10%	Xenon lamp	630 ± 5	Not reported	100	1000	Once a week
Shafirstein G et al. [40]	ALA	20%	Dye laser	585	Not reported	6 to 8	60–180	Not reported
Sieroń A et al. [41]	ALA	10%	Dye laser	635	Not reported	200	Not reported	Once or twice a week
Maloth, K. N et al. (2016) [23]	ALA	5%	LED	420	> 500	Not reported	600	One time

PS: photosensitizer; ALA: aminolevulinic acid; LED: light emitting diode.

lesions treated twice a week had a significantly better clinical outcome than OLK lesions treated once a week. The reason was stated that OLK lesions turned ulcerated 2–3 days after aminolevulinic acid-photodynamic therapy (ALA-PDT) and reepithelization occurred 5–6 days after PDT. Therefore the next PDT performed 4 days after the prior PDT may undermine the adjacent residual pathological epithelial cells, prevent the regrowth of the lesion, and ultimately lead to a significant reduction of the lesion's size [16].

Photosensitizer (PS) plays an important role in photodynamic therapy. Among all included studies, thirteen used aminolevulinic acid (ALA) as PS. In fact, ALA is not in itself a photosensitizer, but serves as a precursor of the photosensitizer, protoporphyrin IX (PpIX), which is the target of the light applied. [27] Exogenous ALA administration inhibits the first step of porphyrin biosynthesis and leads to the intracellular accumulation of PpIX. The thirteen studies all chose topical administration for the reason that systemic application to patients has side effects of naupathia, emesis, and elevation of bilirubin/liver enzymes in blood level [28]. ALA is rapidly cleared from tissues and bodies, and skin photosensitivity lasts less than 48 h [29]. Consequently, patients do not have to take any precaution against light and sun exposure after the first 48 h.

Prasanna SW et al. first used methylene blue in the management of OLK, achieving complete response for 1 lesion and partial response for 7 lesions of the 13 treated lesions. Four lesions of partial response recurred in three months. [30] Pietruska M et al. applied PDT to OLK lesions with the use of Chlorine-e6 as PS. Twelve (27.27%) lesions achieved complete response and twenty-two (50%) partial response [31]. Grant WE et al. [24] was the only team using Photofrin as PS intravenously. All the patients included in their study had "field cancerization" occurring in the oral cavity and associated areas of leukoplakia. Ten of eleven patients showed complete response to PDT. Photofrin has been proven to be an effective treatment modality for oral carcinoma, [32,33] and its efficacy in the treatment of OLK needs more research to explore.

From the above, ALA is commonly used as photosensitizer in OLK therapy and seems to be a good photosensitizer with higher efficacy and shorter time of photosensitivity.

Five studies applied illumination through a 1000-second course, which was divided into five periods of 180 s and one period of 100 s with five periods of 3-minute rest. [16,17,26,30,34–36] An efficient PDT needs sufficient and continuous supply of new PpIX and oxygen, while the 3-minute stops are supposed to wait for tissues to regenerate new PpIX and to acquire new oxygen. This pattern seems to be accepted extensively and makes sense in theory.

As for pre-activation time, Chen HM et al. [16] set it as 1.5 h through a beforehand kinetics study. The other studies mostly followed the former references, whereas Selvam NP et al. [36] suggested determining the peak accumulation for each individual before the start of therapy because of the difference in demographic profile of the patients and variable salivary flow rate.

The efficacy of PDT appears to be related to pathological diagnosis of OLK lesions. Oral verrucous leukoplakia (OVL), as an infrequent pathological type of OLK with high potential of neoplastic progression, showed a more effective result after PDT comparing with homogeneous types of OLK. It was explained that the irregularity of OVL made the gel difficult to be removed by salivary flow. [34] On the other hand, comparing with other types of OLK, OVL contained more areas of less differentiated oral squamous cell carcinoma with more active proliferation [37], which may lead to the better efficacy of PDT in OVL, because PDT takes effect through the oxidative damage to pre-malignant and malignant cells.

Chen HM et al. found that OLK lesions with mild or moderate dysplasia showed a better response than those without dysplasia after topical ALA-PDT treatment due to wide intercellular spaces of the dysplastic epithelium, which resulted in less keratotic epithelial surface as well as thinner and more permeable epithelium in dysplastic oral lesions. [35] Prasanna SW et al. used methylene blue (MB) as PS and made a suggestion that their MB-PDT protocol of OLK may be effective in the management of mild and smaller lesions. [30]

Only two research discussed the relevance between efficacy of PDT and lesion location. Pietruska M et al. inferred that PDT was more effective in lesions on the cheeks and lips comparing to those on tongues and gums. [31] Chen HM et al. analyzed the correlation between lesion location and therapeutic effect, with the result of no significant difference in different oral mucosal sites after PDT [35].

Smokers, as a high risk population of OLK, were included in seven studies [16,17,22,25,31,35,36]. However, no significant difference was reported in the efficacy of PDT between smokers and non-smokers, and

the difference of recurrence was not mentioned. It cannot be ignored that the sample size was not large enough to make a definite conclusion.

A plenty of literature demonstrated that the advantages of PDT as a non-surgical therapy are safe, non-invasive, and repeatable. Although side effects were reported occasionally, they seemed to be relatively mild and infrequent, including pain, burning sensation, tickling, and pricking, appearing during or after illumination. The severity of the above symptoms correlated with concentration of photosensitizer used, duration of irradiation, parameters of the light source, saliva flow of patients, application of local anesthetic or painkiller, and so on. Besides, post-PDT desquamation, edema, and ulceration were observed in several patients, which usually subsided without any measure. A participant in Wong SJ's study was reported to experience transient grade 3 transaminase elevation, as a known side effect of ALA [38]. In comparison with cryotherapy, Kawczyk-Krupka A et al. found that incidence of pain and adverse events was significantly lower in the PDT group [22].

However, the presence of patients with no response to PDT and recurrence demonstrated the limitations of this therapy. The situation where no patient showed response to PDT in the study of Wong SJ et al. [38] may be attributed to the low energy fluence as 2–4 J/cm^2, because the common parameter is around 100 J/cm^2. In addition, the reason may include the limited penetration depth of light source, large size of lesions, and incomplete courses of treatment.

Chen HM et al. [35] mentioned that some partial or no response OLK lesions receiving further treatment still failed to achieve a complete response. Chen suggested that those lesions showing partial or no response after eight treatments were probably resistant to further treatment with the PDT protocol, which required a new treatment modality.

In all above included studies, parameters of PDT had no unified standard. On the basis of the existing experience, ALA-PDT with LED to illuminate by the 1000-second course, executed twice a week, seems to be an effective pattern with less side effect, especially in the management of mild and moderate lesions. However, due to low-quality clinic test and potential publication bias, the extant evidence is not enough to make a definite conclusion.

5. Conclusion

As a non-surgical treatment, PDT seems to be a useful therapeutic strategy in the management of oral leukoplakia. Apart from patients who completely recovered with PDT, the reduction of lesion size is also of great significance for follow-up treatment or resection. It is still a long way to go to improve the effect of PDT in clinical application. Further RCTs with long follow-up period, standardized PDT parameters, and comparing efficacy of PDT with various therapies are expected to acquire definite conclusions.

Conflicts of interest

The authors have no conflict of interest to declare.

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