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Short Communication

Evaluating photodynamic therapy for oral precancerous lesions: Highlighting outcome measure of malignant transformation

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Abstract The main outcome measure assessed in previous studies on photodynamic therapy (PDT) for oral precancerous lesions (OPL) is clinical response based on the alteration in lesion size after treatment. However, the primary and secondary outcome measures of the interventions for OPL should be malignant transformation and recurrence. Thus, the objective of this short communication is to summarize the evidence on PDT in preventing the recurrence and malignant transformation of OPL. There were 16 eligible studies which addressed the issue of OPL patients who received PDT with recurrence outcome, and the pooled recurrence rate (95% confidence interval) was analyzed to be 20.1% (16.2–24.6%). Notably, only 1 study reported that 7.5% of malignant transformation rate for OPL received PDT. These should be interpreted with caution due to low-level evidence, such as differences in study design, clinical and pathological features of patients enrolled, limited sample size, short follow-up time. Given few evaluated the effect of PDT on malignant transformation, we highlight that this

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primary outcome measure of OPL needs to be investigated in further well-designed longitudinal studies with adequate follow-up periods.

Introduction

Oral precancerous lesions (OPL), mainly being oral leukoplakia and erythroplakia, are the best-known precursors of oral squamous cell carcinomas (OSCC). The presence and degree of epithelial dysplasia in a biopsy remains the most important determinant for malignant transformation risk in an individual patient with OPL.[1] Given that they often are asymptomatic lesions, the primary outcome measure of all the interventions for OPL is to prevent the malignant transformation,[1] so as to reduce the cancer morbidity and mortality and to reduce burden on healthcare expenditures. It is challenging to manage the OPL progression to OSCC which is a multistep malignant process, although various nonsurgical and surgical treatments have been reported.[2] According to a Cochrane updated systematic review, there was no evidence of an effective treatment to prevent the malignant transformation of oral leukoplakia.[2]

Photodynamic therapy (PDT) is a minimally invasive treatment that uses exogenous light with a specific wavelength and photosensitizers to create molecular oxygen, which causes the death of tissue cells by necrosis, apoptosis, or autophagia.[3] In the recent updated systematic review and meta-analysis, the efficacies of PDT in the treatment of both oral leukoplakia and all oral potentially malignant disorders (including oral leukoplakia, erythroplakia, lichen planus, verrucous hyperplasia, actinic cheilitis) patients were systematically assessed.[3,4] Notably, clinical response (complete-, partial-, or no response) was the main outcome measure assessed in all the studies, recurrence was the secondary outcome measure assessed in a portion of the previous studies.[3,4] However, the effect of PDT on the primary outcome of OPL malignant transformation was not systematically evaluated.

In such a context, malignant transformation and recurrence are the primary and secondary outcomes of OPL management. Thus, the objective of this short communication is to summarize the evidence on PDT in preventing the recurrence and malignant transformation of OPL patients and analyze collectively in detail as a comprehensive resource for clinicians and investigators.

Materials and methods

A systematic literature search regarding the papers on surgery and OPL from PubMed and Web of Science databases was conducted on 30 Aug 2023. Medical subject term "photodynamic" in title/abstract and "oral precancerous lesions" and its synonyms in title/abstract were used, according to the search strategy described in supplementary Table S1. Inclusion criteria was the articles which addressed the issue of OPL patients with the outcome of the recurrence or malignant transformation who received PDT.[5–20] Exclusion criteria were case reports, literature reviews, experimental studies, and papers that did not report the patients' outcome. The cases of oral leukoplakia and erythroplakia with/without dysplasia were included and those of other oral potentially malignant disorders such as lichen planus and actinic cheilitis were excluded. There was no restriction to language and year of publication, and an additional query was identified from cross-referencing. Titles and abstracts or full texts of the articles were screened and re-evaluated to confirm the eligible papers. Data search and extraction were undertaken independently by two investigators (W.L. and X.Z.), and any disagreement was resolved in a consensus symposium. Bibliographical characteristics of the eligible articles were reviewed and recorded the following information: authorship, publication year, country/region of origin, study design, number of subjects, dysplasia degree, follow-up times, and main results. Descriptive statistics and associations were calculated for these characteristics.

Results

Photodynamic therapy and the recurrence of OPL

As presented in Table 1, there were 16 eligible studies which addressed the issue of OPL patients who received PDT with recurrence outcome. A total of 534 OPL patients with/without dysplasia were identified from 11 retrospective, 4 prospective studies, and 1 phase I trial. These studies enrolled OPL patients with various grade of dysplasia and conducted different follow-up times (mean, 3—131.8 months). Of 354 patients with complete response (CR) after treatment with PDT, recurrence was observed in 71 patients, and then the pooled recurrence rate (95% confidence interval [CI]) was 20.1% (16.2—24.6%). In the recent systematic review and meta-analysis, the pooled recurrence rate (95%CI) of oral leukoplakia patients received PDT was reported to be 13% (8—18%);[3] the pooled recurrence rate (95%CI) of oral leukoplakia and erythroplakia received PDT was reported to be 22.3% (16.1—29.9%).[4] Besides, we recently reported the pooled recurrence rate (95%CI) of OPL patients received scalpel surgery and laser therapy was 29.5% (26.3—33.0%) and 32.2% (26.1—38.9%), respectively.[1]

Photodynamic therapy and malignant transformation of OPL

There was only 1 eligible study which addressed the issue of OPL patients who received PDT with the outcome of

Table 1 Characteristics of studies on photodynamic therapy (PDT) for OPL patients with the outcome of the recurrence or malignant transformation.

Author (year)	Location	Study design	No. Of OPL	Photosensitizer	Light tool of PDT	Dysplasia degree	Mean follow-up (range, m)	Recurrence (n, %)	Malignant transformation (n, %)
Narahara et al. (2023)[5]	Japan	Retrospective	8	Porfimer sodium	Irradiation output was 4 mJ/pulse/cm^2 and repetition rate was 40 Hz with a 630 nm wavelength	Unclassified	131.8 ± 26.2	1/6 CR (16.7%)	NR
Han et al. (2019)[6]	China	Retrospective	29	20% ALA	Using a 632 nm laser at 500 mW/cm^2 power density at a dosage of 90–180 J/cm^2	12 mild, 7 HGD, 10 no	3	3/25 CR (12.0%)	NR
Ahn et al. (2016)[7]	United Kingdom	Phase I trial	26	60 mg/kg ALA	Subjects treated with a total fluence of 50, 100, 150 and 200 J/cm^2 using red light (629–635 nm)	26 severe/CIS	41.6 (3.2–59.4)	10 (38.5%)	NR
Selvam et al. (2015)[8]	India	Retrospective	5	Methylene blue	using metal halide lamp filtered at 630 ± 10 nm, with a light exposure dose of 120 J/cm^2 per sitting	Unclassified	12	0	NR
Ikeda et al. (2013)[9]	Japan	Retrospective	7	Porfimer sodium	Irradiation output was 4 mJ/pulse/cm^2 and repetition rate was 40 Hz with a 630 nm wavelength	5 moderate, 2 severe	24	1/7 CR (14.3%)	NR
Kawczyk-Krupka et al. (2012)[10]	Poland	Retrospective	48	20% or 10% ALA	Diomed 630 laser or argon-pumped dye laser (light exposure dose: 100 J/cm^2; wavelength: 635 nm)	5 mild, 43 non	4–34	13 (27.1%)	NR
Jerjes et al. (2011)[11]	United Kingdom	Prospective	147	60 mg/kg ALA	Light was delivered to the target tissue at 100 or 200 J/cm^2 per site used a single-channel 628 nm diode laser	19 mild, 33 moderate, 95 severe	87.6	17/119 CR (14.3%)	11 (7.5%)
Shafirstein et al. (2011)[12]	United States	Retrospective	18	5ALA	Emits light with a 585 nm wavelength in pulses of 1–5 ms at intervals of 1–3 s	Unclassified	12	1 (5.6%)	NR
Lin et al. (2010)[13]	Taiwan, China	Retrospective	40	20% ALA	Irradiated with a 635 nm laser light generated by the Art-laser Power-adjustable (from 0 to 1200 nm) diode laser (Fluence rate-100 nW/cm^2, light exposure dose, 100 J/cm^2)	12 mild, 18 moderate, 10 severe	18 (6–30)	8 (20.0%)	NR

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Location	Study design	No. Of OPL	Photosensitizer	Light tool of PDT	Dysplasia degree	Mean follow-up (range, m)	Recurrence (n, %)	Malignant transformation (n, %)
Yu et al. (2009)[14]	Taiwan, China	Prospective	20	20% ALA	Either an LED red light at 635 ± 5 nm or a 635 nm laser light (fluence rate, 100 nW/cm^2; light exposure dosage, 100 J/cm^2)	4 mild, 12 moderate, 4 severe	32 (16–76)	5/17 CR (29.4%)	NR
Rigual et al. (2009)[15]	United States	Prospective	9	Porfimer sodium	Light dose of 50 J/cm^2 for dysplasia and CIS and 75 J/cm^2 for carcinoma with a 630 nm wavelength	9 severe/CIS	15 (7–52)	3/9 CR (33.3%)	NR
Chen et al. (2007)[16]	Taiwan, China	Retrospective	103	20% ALA	LED red light at 635 ± 5 nm (fluence rate, 100 nW/cm^2; light exposure dosage, 100 J/cm^2)	15 mild, 13 HGD, 75 no	24.3 (3–36)	3/16 CR (18.8%)	NR
Chen et al. (2005)[17]	Taiwan, China	Retrospective	24	20% ALA	LED red light at 635 ± 5 nm (fluence rate, 100 nW/cm^2; light exposure dosage, 100 J/cm^2)	2 mild, 3 moderate, 9 no	10.3 (3–16)	2/8 CR (25.0%)	NR
Tsai et al. (2004)[18]	Taiwan, China	Retrospective	26	20% ALA	LED red light at 635 ± 5 nm (fluence rate, 100 nW/cm^2; light exposure dosage, 100 J/cm^2)	Unclassified	6	0	NR
Sieroń et al. (2003)[19]	Poland	Retrospective	12	10% ALA	Light from an argonpumped dye laser at 635 nm wavelength, delivering a total dose of 100 J/cm^2 per session	2 mild, 10 no	15.8 (3–34)	1/10 CR (10.0%)	NR
Fan et al. (1996)[20]	United Kingdom	Prospective	12	60 mg/kg ALA	Laser light at 628 nm (exposure dosage, 100 or 200 J/cm^2)	Unclassified	6–18	3/10 CR (30.0%)	NR

ALA, 5-aminolevulinic acid; CIS, carcinoma in situ; CR, complete response; HGD, high-grade (moderate/severe) dysplasia; LED, light emitting diode; NR, not reported; OPL, oral precancerous lesions.

malignant transformation (Table 1). This was a prospective study enrolled 147 OPL patients with 19 mild, 33 moderate, 95 severe dysplasia. Within the mean follow-up of 87.6 months, malignant transformation was observed in 11 (7.5%) patients in the study by Jerjes et al.[11] The effect of PDT on the primary outcome of OPL malignant transformation was not evaluated in the previous review articles.[3,4] Besides, we recently reported the pooled malignant transformation rate (95%CI) of OPL patients received scalpel surgery, laser therapy, and clinical observation was 8.9% (7.3—10.9%), 6.0% (3.5—10.1%), and 10.2% (8.6—12.1%), respectively.[1]

Discussion

Hitherto, clinical response (complete-, partial-, or no response) based on the alteration in lesion size after treatment was the main outcome measure assessed in the previous studies on PDT for OPL.[5-20] The pooled CR rate (95%CI) of PDT was reported to be 50% (33—66%) and 47% (41—53%) for oral leukoplakia and OPL (containing oral leukoplakia and erythroplakia), respectively.[3,4] Although the clinical response-based efficacy evaluation is intuitive and simple to use in clinical practice, it still has some limitations. Response to PDT varied depending on the number of factors, such as type of lesion, photosensitizers and its penetration and administration, frequency and duration of PDT. Partial response which represents more than 20—30% reduction in lesion size varies in different studies. More importantly, the clearance of superficial lesion does not mean eradication of OPL due to the phenomenon of field cancerization.[21] In OPL patients, even the clinically normal appearing oral mucosa after therapy may contain histopathological or molecular aberrations, which might be the source leading to the recurrence or even malignant transformation. Therefore, in addition to clinical response, pathological examination is required to comprehensively evaluate the PDT efficacy on OPL and monitor the risk of recurrence and malignant transformation.

As for outcome measure of the recurrence, we pooled the recurrence rate (95%CI) of OPL received PDT being 20.1% (16.2—24.6%), in agreement with the rate (95%CI) of 22.3% (16.1—29.9%) systematically reviewed by Binnal et al.[4] Interestingly, the pooled rate of OPL received PDT was lower than the rates of that received scalpel surgery (29.5%; 95%CI, 26.3—33.0%) and laser therapy (32.2%; 95% CI, 26.1—38.9%).[1] This suggested that PDT might be superior to scalpel surgery and laser therapy in the control of OPL recurrence. As for effect of PDT on the outcome measure of malignant transformation, this aspect was sparsely investigated in the previous studies. Only 1 study reported that 7.5% of malignant transformation rate for OPL received PDT,[11] with no difference between the rates of that received scalpel surgery (8.9%; 95%CI, 7.3—10.9%) and laser therapy (6.0%; 95%CI, 3.5—10.1%).[1] Actually, it is important to note that the strength of these statistical data was low-level evidence, due to the significant publication bias observed in the previous studies. There were obvious limitations in the existing studies, such as differences in study design and purpose, clinical and pathological features of patients enrolled, limited sample size, short follow-up time, and ambiguous or no surgical margins used for outcome assessment, which inevitably lead to highly heterogeneous or even contradictory results. Hence, larger well-designed studies are needed to consolidate the current evidence.

Admittedly, PDT, laser therapy, and conventional surgery by scalpel are of distinct advantages and disadvantages.[1] As a minimally invasive, simple, affordable, and well-tolerated treatment, PDT presents advantages in less tissue distortion, achieving haemostasis, as well as absence of scars and minimal oral dysfunction. However, the critical disadvantage of PDT is that the tissue is evaporated leaving no sample available for further histopathological examination. These cause a problem that the ability to detect an occult primary in an area of carcinoma in situ or even micro-invasive carcinoma is lost, because this issue is further complicated by the fact that 5—10% of OPL contain micro-invasive carcinoma which was not initially revealed by an incisional biopsy but only afterwards on surgical excision.[1] These common errors may underestimate dysplasia severity or even contributory to missing a carcinoma. Moreover, the maximum penetration depth of the photosensitizer, e.g. aminolevulinic acid, in oral mucosa is about 2 mm.[3] Although PDT can accurately locate the target tissue, it is difficult to treat deep lesions due to the limitations of penetration depth. For instance, penetration of photosensitizer is often restricted due to hyperkeratosis and thickening of the epithelium as seen in oral verrucous leukoplakia. The effect of the application of photosensitizer for a longer duration and more session of PDT in the treatment needs to be explored.

Conclusively, considering its minimally invasive nature, PDT seems to be a promising treatment modality in the control of OPL recurrence; but the current evidence should be interpreted with caution due to low-level strength of evidence and small sample size. Given few evaluated the effect of PDT on malignant transformation, we highlight that this primary outcome measure of OPL needs to be investigated in further well-designed longitudinal studies with adequate follow-up periods.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2023.10.015.

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