Is topical photodynamic therapy with 5-ALA, using Tsai's protocol, useful in the healing of oral potentially malignant disorders? A systematic review of the literature

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Is Topical Photodynamic Therapy with 5-ALA, using Tsai's protocol, useful in the healing of oral potentially malignant disorders? A systematic review of the literature

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ABSTRACT

Aim The present review was performed in order to assess the effect of topical photodynamic therapy with 5-ALA in pre-malignant lesions, using the Tsai's protocol.
Material and methods Studies, using the Tsai's protocol with topical photodynamic therapy with 5-ALA, in oral potentially malignant disorders (oral leukoplakia, oral eryhtroplakia, oral verrucous leukoplakia, oral lichen planus) and with at least 5 months follow-up, were selected. The light source was: 635 nm laser light or LED red light at 635 nm. The main outcome measure was the healing of the potentially malignant disorders evaluated as Complete Response, Partial Response, No Response.
Results Of the 12 eligible studies, five studies were included. Seven studies were excluded because they did not followe the Tsai's protocol, 2 because the lesions were analyzed in other studies. The outcomes were: Oral Leucoplakia 7.7% complete response, 50.8% partial response, 41.5% no response; Oral Erythroplakia: 91,7% complete response, 8.3% partial response; Oral Verrucous Hyperplasia 100% complete response.
Conclusions Within the limitation of the present systematic review, the selected studies suggested that 5-ALA PDT, using the fractionated Tsai's protocol, had good results in the treatment of oral verrucous hyperplasia, less in erythroplakia and leukoplakia; this could be due to the different epithelial structure of the lesions. Further studies need to be conducted to confirm these data.

KEYWORDS: Laser, Malignant, Oral, Photodynamic therapy, Tsai's protocol.

INTRODUCTION

Oral potentially malignant disorders are a series of pathologies characterized by a risk of neoplastic degeneration superior than the normal mucosa. The most common are: leukoplakia, erythroplakia, oral verrucous hyperplasia and oral lichen planus (1). The treatment for premalignant lesions in the oral cavity includes: observation, laser ablation, surgical resection, topical application of vitamin A or beta carotene, photodynamic therapy (2-5). Photodynamic therapy (PDT) is a treatment that consists in the activation, by light, at a specific wave-lenght, of a photosensitizing agent in the presence of oxygen. The exposure of the photosensitizer to light results in the formation of oxygen molecules, causing localized photodamage and cell death. One advantage of PDT is that this technique can be applied repeatedly at the same site (6, 7). Several *in vitro* studies have demonstrated that PDT uses a cellular, vascular and immunological mechanism of destruction of the neoplastic tissue. *In vitro*, cell death occurs by a mithocondrial-dependent apoptosis (8-12). Usually the photosensitizer used for topical PDT on pre-malignant lesions is 5-aminolevulinic acid (5-ALA), which has been introduced for the therapy of cancer. It has a limited light penetration at 635 nm, so its use is restricted to superficial lesions (1-2 mm) (13). There are no evidence of the toxicity of 5-ALA before light exposure. After irradiation most patients report pruritus, prickling and burning sensation in the irradiated area (13).
The aim of this systematic review is to assess the role of topical photodynamic therapy with 5-ALA, with the fractionated Tsai's protocol, in the healing of oral potentially malignant disorders. This work has been performed according to the Preferred Reporting items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (14).

MATERIALS AND METHODS

This systematic review included RCTs, longitudinal studies, case series, case reports dealing with patients

First author Year	Manufacturer	Center Wavelenght	Average radiant power	Irradiance at target	Exposure duration	Energy density per point	Lesion
Lin 2010	Arts International Biotechnology Inc. Tapei Taiwan	635 nm	0-1200 mW	100mW/cm^2	fractionated protocol tot 1000 sec	100J/cm^2	40 OVH 40 OEL

TABLE 1 Summary of laser parameters and lesion treated.

First author Year	Center Wavelenght	Irradiance at target	Energy density per point	Exposure duration	Lesion
Yu 2009	635±5	100mW/cm^2	100 J/cm^2	multiple180 sec. irradiation several 180 sec rest tot 1000 sec	20 OEL
Yu 2008	635±5	100mW/cm^2	100 J/cm^2	multiple180 sec. irradiation several 180 sec rest tot 1000 sec	36 OVH
Chen 2007	635±5	100mW/cm^2	100 J/cm^2	multiple180 sec. irradiation several 180 sec rest tot 1000 sec	24 OVH 65 OEL
Chen 2004	635±5	100mW/cm^2	100 J/cm^2	multiple180 sec. irradiation several 180 sec rest tot 1000 sec	5 OVH

TABLE 2 Summary of LED red light parameters and lesions treated.

that had Topical-PDT for pre-malignant lesions, i.e. oral verrucous hyperplasia (OVH), oral leukoplakia (OL), oral erythroplakia (OEL), and oral lichen planus (OLP). Clinical diagnosis of the selected patients should be confirmed by histopathological examination of the biopsy specimens; smokers, areca chewers and drinkers were included.

The same type of intervention was considered as described: Topical photodynamic therapy should be applied with light source 635 nm laser light or led light at 635 nm, once a week, according to Tsai protocol (15): five 3-minute and one 100-second irradiations, separated by five 3-minute rests for a total of 1000 seconds (fluence rate, 100mW7cm^2; light exposure dose, 100 J/cm^2) (Table 1, 2), with 5-ALA (20% ALA gel form) as photosensitizer. Studies to be included had to have a minimum of 5-months follow-up.

All studies to be included had to report the following.

1) The healing of the lesions as:
   - Complete response (CR): complete healing of the lesion;
   - Partial response (PR): reduction in size of the lesion;
   - No response (NR): no change in size of the lesion.
2) Clinical features of the lesions (OL, OVH, OEL, OLP).

If possible the grade of dysplasia of the lesions (no dysplasia, mild dysplasia, moderate dysplasia, severe dysplasia, carcinoma *in situ*) had to be evaluated in connection with the healing of the lesion.

All studies with a different photosensitizer, different use of photosensitizer (e.g. intravenous, intra-muscle or per os) and different PDT protocol were excluded as studies not published in English. Review articles, experimental studies, commentaries, letters to the Editor and unpublished articles were excluded.

The outcome measure was:

- Healing of the lesion classified as:
  - Complete response (CR): complete healing of the lesion;
  - Partial response (PR): reduction in size of the lesion;
  - No response (NR): no change in size of the lesion.

The healing was analyzed according to the different premalignant lesions.

Hand searching was performed from 1998 to 2016:

- MEDLINE via OVID (December 1998-August 2016);
- EMBASE via OVID (December 1998-August 2016).

Key words used were: Photodynamic therapy AND/OR oral potentially malignant disorders, topical photodynamic therapy, photodynamic therapy with 5-ALA, oral potentially malignant disorders

The most recent electronic search was undertaken on 29/09/16.

Hand search was carried on the following journals: J Oral Pathol Med, Oral Oncology, Cancer, Lancet Lett, Lancet Oncol, J Dent Res, Head and Neck, Arch Oral Biol, Photochem Photobiol B, Photomed laser Surg, J Oral Pathol Med, Laser Surg Med, Int J Oral Maxillofac Surg, J Oral Pathol Med, Oral Oncol, Laser Surg Med, J Oral Pathol Med, Arch Otolaryngol Head Neck Surg, Annal Stomatol, Oral Oncol, Laser Surg Med, Photodiagnosis Photodyn Ther.

INCLUDED STUDIES			
Author/Year	Partecipants	Intervention	Outcome
Lin 2010	All patients affected by OVH (40 patients, 39 men and one woman, aged 42-74 years) or OEL(40 patients, 38 men and 2 women, aged 34-89 years). Pa-tients were treated in the Department oOf Oral and Maxillofacial Surgery, National Taiwan University Hospital (NTUH) from August 2006 to February 2010	Topical PDT with 5-ALA, according to Tsai's protocol, once a week. 635 nm laser light. Mean follow-up 20 months for OVH, 18 months for OEL	Healing of OVH and OEL characterized by complete response (CR), partial response (PR), no response (NR) Grade of dysplasia
Yu 2009	All patients affected by OEL. We selected only 20 patients tretated with LED light, because the other are included in further studies. Patients were treated in the Department of Oral and Maxillofacial Surgery, National Taiwan University Hospital (NTUH) from January 2002 to April 2009	Topical PDT with 5-ALA, according to Tsai's pro-tocol, once a week. 635 LED light. Mean follow-up 32 months	Healing of OEL characterized by complete response (CR), partial response (PR), no response (NR) Grade of dysplasia
Yu 2008	All patients affected by OVH (36 patients, 35 men and one women, aged 32-79 years). Patients were treated in the Department of Oral and Maxillofacial Sur-gery, National Taiwan University Hospital (NTUH) from July 2002 to December 2006	Topical PDT with 5-ALA, according to Tsai's pro-tocol, once a week. 635 LED light. Mean follow-up 26 months	Healing of OVH characterized by complete response (CR), partial response (PR), no response (NR) Grade of dysplasia
Chen 2007	All patients affected by OVH (24 male patients, aged 32-79 years), OL (65 patients, aged 26-77 years) and OEL (6 male patients). Patients were treated in the Department of Oral and Maxillofacial Surgery, National Taiwan University Hospital (NTUH) from November 2001 to December 2005	Topical PDT with 5-ALA, according to Tsai's pro-tocol, once a week. 635 LED light. Mean follow-up 22,2 months	Healing of OVH, OL, OEL characterized by complete response (CR), partial response (PR), no response (NR) Grade of dysplasia
Chen 2004	All patients affected by OVH (5 male patients, aged 37-64 years). Patients were treated in the Department of Oral and Maxillofacial Surgery, National Taiwan University Hospital (NTUH) from 2002 to 2003	Topical PDT with 5-ALA, according to Tsai's pro-tocol, once a week. 635 LED light. Mean folow-up 5.6 months	Healing of OVH characterized by complete response (CR), partial response (PR), no response (NR) Grade of dysplasia

EXCLUDED STUDIES	
Author/Year	Reason for exclusion
Maloth 2016	The light source was a light emitting diode with a different wavelength (420 nm)
Romeo 2014	Topical PDT performed twice a week
Sharfistein 2011	Use of a dye laser in pulse at 585 nm, at intervals of 1 to 3 seconds
Chen 2005	Topical PDT performed twice a week for OL and patients with OVH were enrolled in further studies
Sai 2004	Patients of this studies are enrolled in further studies
Sieron 2003	PDT protocol is not described
Kubler 1998	Topical PDT is performed without the fractionated protocol

TABLE 3 Included and excluded studies.

The references of the selected articles were analyzed to find other relevant studies.
The patient who had Topical-PDT for pre-malignant lesions (oral leukoplakia, oral erythroplakia, oral verrucous leukoplakia, oral lichen planus) was considered as unit of analysis.
The data were analyzed as percentage of the healing of the lesion evaluated as: CR, PR, NR in relation to the number of patient treated.

RESULTS

Of the 12 potentially eligible studies, seven studies had to be excluded (Kubler, 1998; Sieron, 2003; Tsai, 2004; Chen 2005; Sharfistein, 2011; Romeo, 2014; Maloth, 2016) (15-21) because: in 3 studies the author did not apply the fractionated protocol (Kubler, 1998; Sieron, 2003; Sharfistein, 2011); in 2 studies the lesions were included in further studies (Tsai, 2004; Chen, 2005); in one study topical PDT was applied twice a week (Romeo, 2014) and in one study the light source was a light emitting diode with a different wavelengh (420 nm) (Maloth, 2016). The five studies included were: Chen, 2004; Chen, 2007; Yu, 2008; Yu, 2009; Lin, 2010 (22-26) (Table 3).
The study of Chen (2007) and the study of Lin (2010) are repeated in the analysis because they treated two different types of lesions (Oral Erythroplakia and Oral Verrucous Hyperplasia).

1) Healing of Oral Leukoplakia (OL): 1 study (Chen 2007), 65 patients.
   - Chen (2007) studied 97 OL, of these we selected only 65 treated once a week. The mean follow-up was of 22.2 (range 3-34) months. The grade of dysplasia was not indicated. 5 lesions showed CR, 33 PR and 27 NR. The 5 OL required an average of 3.8 (range 1-7) treatments of ALA-PDT to achieve CR of the lesions. One of the five CR patients lesions recurred 6 months after the first PDT and finally was excised by surgery. The remaining four lesions with CR showed no recurrence after a follow-up period of 3-36 months (mean 24.3). Of the 33 PR patients, 8 received further treatment with topical ALA-PDT once a week, 2 received further treatment with topical ALA-PDT twice a week, 4 chose total excision of the lesion and the remaining 19 chose a follow-up schedule once a month. Of the 27 NR patients, 6 received further treatment with topical ALA-PDT once a week, 5 received further treatment with topical ALA-PDT twice a week, 10 chose total excision of the lesion and the remaining 6 chose the follow-up once a month.
2) Healing of Oral Erythroplakia (OEL): two studies (Yu 2009; Lin 2010), 60 patients.
   - Yu (2009) selected 46 patients with OEL and he treated 20 lesions with LED light and 26 lesions with laser light; in our review we selected only the 20 OEL lesions treated with LED light because the other lesions are included in another study (Lin, 2010). The mean follow-up was of 32 (range 16-76) months. Of the 20 lesions, 4 had mild dysplasia, 12 had moderate dysplasia, 3 had severe dysplasia and 1 was a carcinoma *in situ*. The lesions showed CR in 17 and PR in 3 cases. The 17 CR OEL lesions needed an average of 3.7 (range 2-7) treatments of ALA-PDT to achieve CR. After a follow-up period of 16-76 (mean 32) months, 5 (29%) of the 17 CR lesions recurred. The five lesions recurred 8-14 (mean 11) months after the last PDT treatment. The five recurrent lesions were treated by the same PDT protocol as before and showed complete regression after 2-4 (mean 2.8) treatments.
   - Lin (2010) selected 40 patients with OEL. The mean follow-up was of 18 (range 6-30) months. Twelve lesions had mild dysplasia, 18 had moderate dysplasia, seven had severe dysplasia and 3 were carcinoma *in situ*. The 40 OEL showed a CR in 38 and PR in two. The 38 CR OEL lesions required an average of 3.4 (range 2-6) treatments of ALA-PDT to achieve CR of the lesions. During the follow-up period eight (21%) of the 38 CR OEL lesions recurred. These eight OEL lesions recurred 6-14 (mean 9) months after the last PDT treatment. The eight OEL recurrent lesions were treated by the same PDT protocol as before and showed complete regression after 1-3 (mean 2) months.
3) Healing of Oral Verrucous Hyperplasia (OVH): 4 studies (Chen 2004; Chen 2007; Yu 2008; Lin 2010), 105 patients.
   - Chen (2004) studied the treatment of five patients. The mean follow-up was of 5,6 (range 3-11) months. Any lesions had dysplasia. An average of two treatments (range 1-3 treatments) of ALA-PDT were needed to achieve the complete regression of the lesion. No recurrence was found after a follow up period of 3-11 months (mean 5.6 months).
   - Chen (2007) studied 24 OVH. The mean follow-up was 15,2 (range 3-42) months.; 20 lesions had no dysplasia, 2 lesions had mild dysplasia, one had moderate dysplasia and one had severe dysplasia. All the 24 OVH lesions showed CR after an average of 3.5 (range, 1-6) treatments of ALA-PDT. No recurrence of the 24 OVH lesions was found after a follow-up period of 3-42 (mean 1.2) months.
   - Yu (2008) studied 36 OVH. The mean follow-up was 26 (range 6-56) months. Biopsy was not done in one patient because the lesion was too small; the other 35 lesions: 26 had no dysplasia, 2 mild dysplasia, 4 moderate dysplasia, 3 severe dysplasia. All the lesions showed CR after an average of

Author	Lesion	Grade of dyspla-sia	Patients	Response
Chen (2004)	OVH	No dysplasia	5	CR 5
Chen (2007)	OVH	20 no 2 mild 1 moderate 1 severe	24	CR 24
	OL	NA	65	CR 5 PR 33 NR 27
Yu (2008)	OVH	26 no 2 mild 4 moderate 3 severe	36	CR 36
Yu (2009)	OEL	4 mild 12 moderate 3 severe 1 ca in situ	20	CR 17 PR 3
Lin (2010)	OVH	25 no 9 mild 4 moderate 2 severe	40	CR 40
	OEL	12 mild 18 moderate 7 severe 3 ca in situ	40	CR 38 PR 2

TABLE 4 Healing of the lesions and histopathological datas (OVH = Oral verrucouse Hyperplasia, OL = Oral Leukoplakia, OEL = Oral Erytroplakia, CR = Complete Response, PR =Partial Response, NR = No Response).

3.8 (range 1-6) treatments of PDT. No recurrence of the 36 OVH lesions was found after a follow-up period of 6-56 (mean 26) months.

- Lin (2010) studied 40 OVH lesions. The mean follow-up 20 (range 8-37) months; 25 lesions had no dysplasia, 9 has mild dysplasia, 4 had moderate dysplasia and 2 had severe dysplasia. All 40 OVH lesions showed CR after an average of 3.6 (range 1-6) treatments of ALA-PDT. No recurrence of the 40 OVH lesions was found after a follow up period of 8-37 (mean 20) months.

Statistical analysis

1) Healing (Table 4-5).

- Oral Leukoplakia: one study, so meta-analysis could not be done. Total patients 65; CR was obtained in 5 patients (7.7%), PR in 33 patients (50.8%) and NR in 27 patients (41.5%).
- Oral Erythroplakia: Total patients 60 (2 studies); CR was obtained in 55 patients (91.7%); PR in 5 patients (8.3%); NR 0 patients.

Lesion	Author	Total number of lesions	Response
OL	Chen 2007	65	CR 5 (7,7%) PR 33 (50,8%) NR 27 (41,5%)
OEL	Yu 2009 Lin 2010	60	CR 55 (91,7%) PR 5 (8,3%)
OVH	Chen 2004 Chen 2007 Yu 2008 Lin 2010	105	CR 105 (100%)

TABLE 5 Healing of the lesions and clinical features.

- Oral Verrucous Hyperplasia: Total patients 105 (4 studies). CR was obtained in 105 patients (100%). The 100% CR was independent from the grade of dysplasia.

2) Mean follow-up.
   - Oral Leukoplakia: 22.2 (range 3-34) months (Chen, 2007).
   - Oral Erythroplakia: 32 (range 16-76) months (Yu, 2009); 18 (range 6-30) months (Lin, 2010).
   - OVH 5.6 (range 3-11) months (Chen, 2004); 15.2 (range 3-42) months (Chen; 2007); 26 (range 6-56) months (Yu, 2008); 20 (range 8-37) months (Lin, 2010).
3) Recurrence.
   - Oral Leukoplakia: 1 study of the 5 CR OL 1 recurred 6 months after the last treatment (20%).
   - Oral Erythroplakia: two studies Yu (2009), after a follow-up of 8-14 (mean 11) months, 5 of the 17 CR OEL lesions recurred (29%); Lin (2010), after a follow-up of 6-30 (mean 18) months, 8 of the 38 (21%) CR OEL lesions recurred.
   - Oral Verrucous Hyperplasia, four studies, no recurrence Chen (2004) after a follow up of 5.6 (range 3-11) months; Chen (2007) after a follow up of 15.2 (range 3-42) months; Yu (2008) after follow up of 26 (range 6-56); Lin (2010) after a follow up of 20 (range 8-37) months.

Number of treatments

- Oral Leukoplakia average of 3.8 treatments (range 1-7) to achieve CR of the lesions.
- Oral Erythroplakia Lin (2010) average of 3.4 treatments (range 2-6); Yu (2009) average of 3.7 treatments (range 2-7).
- Oral Verrucous Hyperplasia Lin (2010) average 3.6 treatments (range 1-6); Yu (2008) average treatment 3.8 (range 1-6); Chen (2007) average treatments 3.5 (range 1-6); Chen (2004) average treatments 2 (range 1-3).

DISCUSSION

The WHO Collaboration Centre well defined the pre-malignant lesions, describing them as "clinical presentations that may have a potential to become cancer" (1). Malignant transformation may occur in a limited, but not negligible, rate of patients, so early therapy is preferable to avoid further complications. One of the therapy proposed was topical photodynamic therapy.

The present review showed that topical photodynamic therapy with 5-ALA PDT applied once a week obtained resolution of the lesions treated in all the cases of Oral Verrucous Hyperplasia, in almost 90% of Oral Erytroplakia lesions and in less than 10% of Oral Leukoplakia. We found only one study that compared the healing of Oral lichen planus with PDT or with conventional therapies. We excluded this study because the LED light source applied was different from the one used in the Tsai protocol (21). No comparative studies about the treatment of OL, OEL and OVH with PDT versus conventional therapies were found, so it was not possible to determine which can be the best therapy for pre-malignant oral lesions. Even if Topical Photodynamic therapy seems promising, simple to use and with limited side effects, few studies were conducted on this topic. Topically PDT has a good response in the treatment of OVH, as reported in this review. If different studies use different protocols, they are difficult to analyze and it becomes difficult for the clinician to chose a specific treatment regimen. So we select the use of PDT applied once a week with LED light or laser light. According to the literature (25) the therapy could be conducted either with LED light or laser light. In fact, the total light dose is important for a successful PDT outcome, despite of the light source. At the end of the selection process, only 5 studies could be included out of twelve; five were excluded because they did not adhere to the chosen protocol.

The number of participants of each study was small and we didn't find any trial, for that reason a meta-analysis has been impossible to conduct.

From data analysis the healing of OVH showed to be better than the healing of OEL, while OL had scarse response to the therapy. This could be due to a different structure of the lesions, since OVH has a rough surface which is able to hold more drug. According to Yu (2008), OVH lesion provided a large area of good retention and absorption of ALA on the surface. For OVH lesions the grade of dysplasia did not influence the response to the therapy, but it was strictly connected with the mean number of treatments (24). We have to consider that this conclusion is based on only one study on OL with 65 lesions treated, while we have 2 studies (60 patients) and 4 studies (105 patients) on OEL and OVH respectively.

Another important aspect is the recurrence of the lesions. No recurrence was found in OVH, while in OL lesions 20% recurred at 6 months follow-up; in OEL lesions, according to Yu (2009) (25) 29% recurred after a follow-up period of 8-14 months and according to Lin (2010) (26) 21% after a follow-up of 6-30 months.

According to Lin 2010 (26), Yu 2008 (24), Yu 2009 (25) correlation analysis found that the mean treatment number of PDT to achieve a CR for OVH lesions and OEL lesions is strictly correlated to diameter, clinical appearence, color, epithelial dysplasia and surface keratine layer. In general, lesions with smaller size, pink to red color, epithelial dysplasia and thinner surface keratin layer had better PDT outcomes.

Another recent review analyzed the treatment of pre-malignant lesions with PDT (27). They concluded that in general PDT is effective in the management of premalignant lesions. Different therapies and different protocols were included so results ranged from 27-100% complete resolution, 5-50% partial resolution and 0-25% no resolutions of the lesions, with a recurrence rate of 36%. No comparative study was considered, so it was not possible to understand which the best treatment could be. Be-

sides, it is difficult to draw conclusions when different protocols are applied on few patients, so the present review was concentrated on a specific treatment protocol and comparison with the previous one was not possible. More studies are advisable comparing in a randomized way different protocols, so that the best treatment could be selected for the patient.

CONCLUSION

Within the limitation of the present systematic review the analysis of the clinical data of the selected studies suggests that 5-ALA PDT, using the fractionated Tsai's protocol, either with laser light or red LED light, is very effective in the treatment of the oral verrucous hyperplasia, less in erythroplakia and leukoplakia; this could be due to the different epithelial structure of the lesions. Further studies should be conducted to confirm this data and add more power to the findings.

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