Expert Consensus on 5-aminolevulinic Acid Photodynamic Therapy for Oral Potentially Malignant Disorders

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Society of Oral Medicine, Chinese Stomatological Association[1]

Photodynamic therapy (PDT) utilising 5-aminolevulinic acid (5-ALA) has emerged as a significant non-invasive treatment for oral potentially malignant disorders (OPMDs). PDT involves the use of a photosensitiser (5-ALA), light and oxygen to selectively target and destroy diseased tissues via photochemical reactions. This therapy has shown promising results in treating various OPMDs, such as oral leucoplakia, oral erythroplakia and oral lichen planus. This consensus document outlines the clinical application of 5-ALA-PDT, providing a comprehensive guide for oral mucosal specialists and stomatology departments. The consensus includes detailed recommendations on irradiation dose, irradiation time, light source selection, pre-treatment preparation, clinical diagnosis, treatment protocols, efficacy evaluation and management of post-treatment adverse events. The goal is to standardise 5-ALA-PDT procedures to improve clinical outcomes and provide a scientific basis for the treatment of OPMDs. By offering guidance on patient selection, lesion assessment and therapeutic strategies, this document aims to address current clinical challenges and enhance the effectiveness of PDT in managing oral mucosal diseases.

Keywords: *5-aminolevulinic acid, consensus, oral potentially malignant disorders, photodynamic therapy*
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Preface

This document was prepared in accordance with the GB/T 1.1-2020 Structure and Drafting Rules of Standardisation Documents. It was proposed by the Chinese Society of Oral Medicine and was under the jurisdiction of the Chinese Stomatological Association.

Photodynamic therapy (PDT) is an emerging and developing subject, and it is also an interdisciplinary subject involving a combination of pharmacy, optics, chemistry, metrology, cell and molecular biology, therapeutics and a variety of clinical topics. PDT emerged and developed gradually in the late 1970s, and is a combination therapy using photosensitiser and a light source, a new non-invasive treatment technology that selectively destroys diseased tissues by generating cytotoxic substances (such as singlet oxygen) through photochemical reactions with the participation of oxygen molecules in biological tissues. As the illumination of skin lesions is easy to achieve, the early application of PDT in dermatology is relatively active and has advanced to the field of tumour treatment. In recent years, oral mucosal scholars have gradually applied PDT to treat some oral mucosal diseases,[1,2] and achieved good results. For example, PDT can eradicate epithelial dysplasia of oral leucoplakia, oral erythroplakia and other oral potentially malignant disorders (OPMDs), achieve non-surgical remission of early oral squamous cell carcinoma or cases that are difficult to treat surgically, relieve long-term erosion of oral lichen planus, chronic discoid lupus erythematosus and other diseases and alleviate the restricted open-

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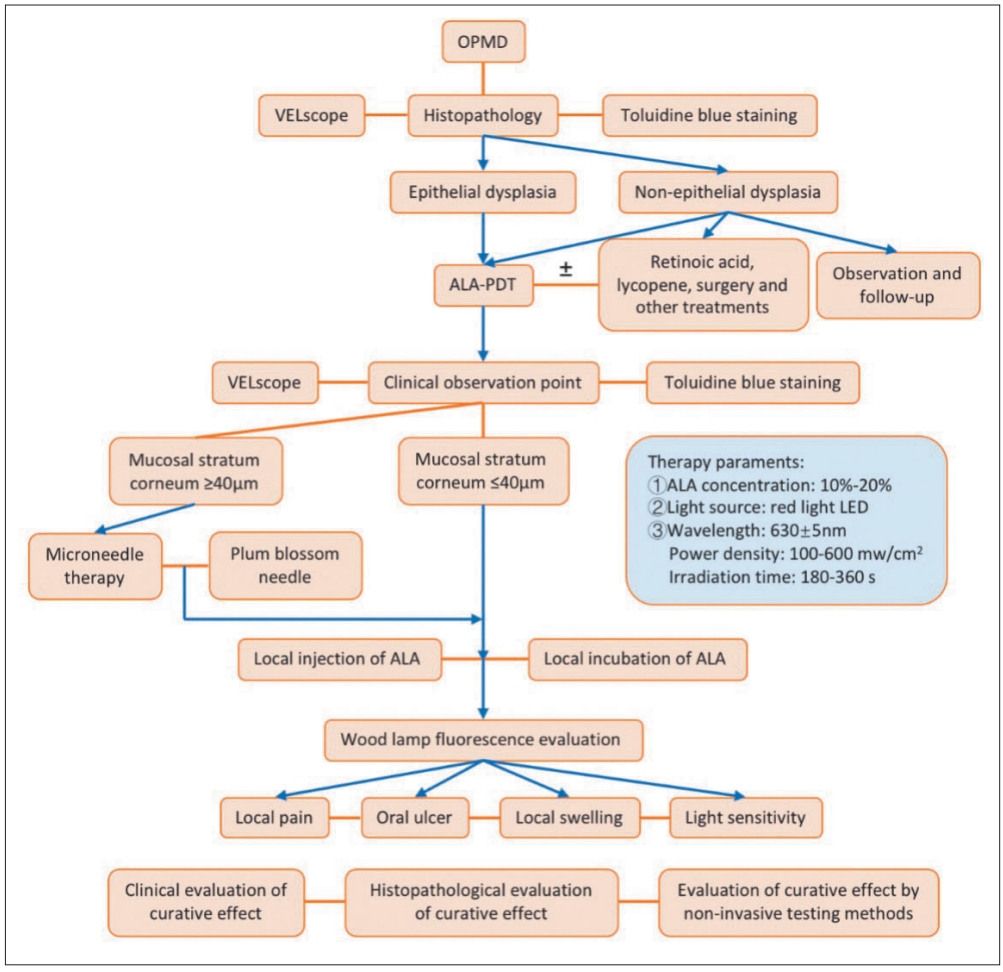

Fig 1 Flowchart of 5-aminolevulinic acid PDT for OPMDs.

ing and restore the elasticity of oral mucosa of the oral submucosal fibrosis.

This consensus aims to serve as a reference when dental practitioners choose PDT. It is hoped that clinical problems in the treatment of oral potentially malignant disorders at this stage will be solved, and a scientific basis for treatment will be provided.

Scope

This expert consensus proposes the irradiation dose, irradiation time, light source selection, pre-treatment preparation, oral clinical diagnosis and treatment recommended plan, evaluation plan of curative effect and post-treatment adverse event management recommendations of PDT in the diagnosis and treatment of OPMDs (Fig 1).

This expert consensus applies to all oral mucosal specialists and stomatology departments that carry out PDT.

Normative references

There are no normative references in this document.

Terms and definitions

The following terms and definitions are applicable to this document.

PDT

PDT is a new type of therapy that combines photosensitisers, light and oxygen molecules to selectively treat malignant (such as solid tumours and precancerous lesions)[3] and benign lesions (such as wet age-related macular degeneration) and infections through photodynamic reactions. PDT is an important field of international cutting-edge interdisciplinary "biomedical photonics". In recent years, both the basic research and clinical application of PDT have made great progress.

It has gradually become the fourth minimally invasive treatment for tumours after surgery, radiotherapy and chemotherapy, and has become the first choice for the treatment of some specific diseases, such as early-stage oral potentially malignant disorders or superficial lesions.

OPMDs

OPMDs are a group of diseases that occur on the oral mucosa and have the potential to develop into oral squamous cell carcinoma, including oral leucoplakia, oral erythroplakia, oral lichen planus, chronic discoid lupus erythematosus and oral submucous fibrosis.

5-Aminolevulinic acid (5-ALA)

5-Aminolevulinic acid (5-ALA) is the precursor of porphyrin compounds, an active substance that is ubiquitous in life. As the second-generation photosensitiser, 5-ALA shows superior PDT diagnosis and treatment capabilities.

Mechanism of PDT

PDT enables high concentrations of endogenous or exogenous photosensitive substances to accumulate in tumour target cells or diseased target tissues in a short period of time, and then irradiate them with a specific wavelength light source (visible, near-infrared or ultraviolet light). On the one hand, it stimulates photobiochemical changes to produce a large number of oxidation products in cells and uses its cytotoxic effect to kill tumour cells, which has strong targeting and causes less damage to normal tissues;[4] on the other hand, its physical processes can produce fluorescence and fluorescence spectroscopy can be used to locate and diagnose OPMDs.[5] Through a number of in vivo and in vitro studies, it has been confirmed that photodynamic therapy can inhibit the proliferation of cancer cells and induce their apoptosis.[6,7] Many pathways including NF-KB/JNK, ROS and MMP are involved in its regulation.[8-10]

Taking 5-ALA-PDT as an example, its biological effects can be roughly divided into three types of mechanisms, namely destroying blood vessels, killing tumour tissues and cells and inducing immune responses. When the photosensitiser is mainly retained in the blood vessel, the $^1O_2$ produced by the photochemical reaction can destroy the blood vessel, causing insufficient blood supply to the lesion, and indirectly causing cell death. When the photosensitiser reaches the cell, 5-ALA-PDT takes the cell as the therapeutic target, and $^1O_2$ may cause cell death, necrosis and autophagy. The death path of the cell mainly depends on the concentration and distribution of $^1O_2$ produced during the treatment. The non-specific emergency inflammatory response induced locally in the 5-ALA-PDT process and a series of immune responses in the later stage also have a continuous systemic effect on the suppression and destruction of tumours.

Irradiation dose and time of PDT

As a physical-chemical therapy, PDT effectively links and applies photosensitisers, light sources and oxygen through parameters that have important effects on photodynamic irradiation. The parameters of PDT dose monitoring mainly include irradiation dose (luminous flux density and irradiation time) and light distribution, the dose of photosensitiser and the concentration in the target tissue, the oxygen content in the tissue and the optical characteristic parameters of the tissue body. According to the Expert Consensus on the Clinical Application of Aminolevulinic Acid Photodynamic Therapy formulated in 2015, it is advisable to use the three elements of irradiation time, energy and power density for parameter calculation [irradiation time(s) = energy density(J/cm^2) / power density(W/cm^2)].[11] In 2016, the American Society of Dermatological Surgery (ASDS) proposed a new calculation formula: photon fluence = 4 × (power density × irradiation time) / (π × irradiation spot diameter^2).[12] Based on the past application of 5-ALA-PDT in OPMDs, the power density is 100-150 mW/cm^2, the irradiation time is 60 to 1000 seconds and the irradiation dose and time can be adjusted according to the area, depth and pathological type of the lesion.[13-15]

The area of the irradiation spot depends on the distance between the light source and the surface of the lesion, and its mathematical relationship has become an important factor affecting the 5-ALA-PDT-related parameters. A Wood lamp uses a high-pressure mercury lamp as the emission light source and emits light waves with a wavelength of 320 to 400 nm through a barium silicate filter containing 9% nickel oxide.[16] Illumination by the Wood lamp can induce fluorescence in the tissue, and the fluorescence intensity reflects the range of absorption of 5-ALA in the tissue, then the PDT spot area is determined to achieve precise positioning. Its output power is low, which will not affect the treatment effect.

Light source selection

PDT needs to select a light source with sufficient irradia-

tion depth and irradiate in the range of tissue that absorbs the photosensitiser to destroy the target area and minimise damage to the surrounding healthy tissue. At present, the commonly used light sources are semiconductor laser diodes, filter lamps and light-emitting diodes (LEDs).[17] Among these, the most commonly used for oral mucosal lesions are LEDs, which have the advantages of narrow spectrum and low cost, and their spectral parameters also support the suitability of LEDs for this application.[18] The wavelength of the light source ranges from 420 to 660 nm, and 630 ± 5 nm is widely used in the treatment of OPMDs.[19,20] Additionally, to avoid the thermal effect of light temperature on tissues and cells, the irradiance power density can also be controlled within 300 mW/cm^2.[6]

Oral clinical recommendations

5-ALA-PDT

At present, PDT technology is widely used in the diagnosis and treatment of oral mucosal diseases, and 5-ALA-PDT is a common method; however, due to the lack of randomised clinical controlled trials with large sample sizes and the inconsistent treatment procedures and related parameters, the promotion and application of this technology are limited.

The concentration of photosensitiser, incubation method, incubation time, range of the irradiation spot, distance between the light source and the surface of the lesion, light source dose intensity and irradiation time are all important factors affecting the treatment effect. The formulation of a strict clinical application process is conducive to standardising the application of PDT technology, and homogeneous standards can guarantee the value of high-quality clinical research in the future. The specific program recommendations are that the treatment procedure is divided into the administration of photosensitiser, pain relief and light irradiation.

Administration methods of photosensitiser: local incubation method and local injection method

Local incubation method of photosensitiser

Determine the irradiation range: An oral mucosa autofluorescence detector (VELscope), toluidine blue staining, Wood lamp and other oral mucosal examination techniques are used to locate the OPMD lesion area, then take pictures to guide the placement of photosensitisers.

Prepare 5-ALA solution: The 5-ALA solution is prepared with moisturising gel or sterile water for injection. The usual concentration is 20%, but it can be adjusted to 10% according to the patient's tolerance and local tissue response.

Select light source: Use a long-wavelength (630 ± 5 nm) red light LED therapy device for irradiation.[21]
Dosing schedule: Determine the number of irradiation spots according to the area of the lesion. Use sterile cotton swabs to make cotton pieces, one piece for each irradiation spot, each around 1cm^2 in size, then dip the prepared 5-ALA solution and cover the surface of the lesion (to completely cover the lesion and 0.3 to 0.5 cm around is appropriate). The cut rice paper (folded into three to four layers) and plastic wrap are successively used to cover the surface of the cotton piece dipped in 5-ALA solution, and finally secured with sterile gauze under light pressure for 2 hours.

Local injection of photosensitiser

The 5-ALA solution prepared with sterile water for injection is injected into the base of the lesion until the mucosa turns white.

Analgesia

Local injection anaesthesia

Local infiltration anaesthesia should be used as the effect of conduction block anaesthesia is poor or ineffective.

Local anaesthesia after incubating photosensitiser

Local infiltration aesthetic injection should be administered after 2 hours of incubation with photosensiser, and then light irradiation.

Local anaesthesia must be performed before injecting photosensitiser

Since the injection of photosensitiser will cause severe pain in the patient's irradiation area, the local aesthetic must be injected in advance, and the photosensitiser should be injected after it has taken effect.

Light irradiation

Irradiation parameters: light source wavelength is 630 ± 5 nm, power density is 150 to 300 mW/cm^2 and irradiation time is 180 to 360 seconds, irradiated in a dark environment. The recommended treatment interval is 7 to 14 days; three to four sessions of irradiation therapy constitutes one course of treatment, and whether to continue treatment is determined based on non-invasive examination. Some literature has also introduced the gargle and intravenous administration methods.[22] The authors believe the patient can only keep the mouthrinse in the oral cavity for a limited time, which cannot be compared to the effectiveness of local incubation for 2 hours. Furthermore, the effectiveness of the gargle method to penetrate into the tissue also cannot be compared with local injection. Its feasibility and effectiveness have yet to be verified. In addition, for safety reasons, intravenous administration is not recommended for outpatients.

Evaluation plan of curative effect

The current domestic PDT efficacy evaluation standards mainly follow the standards of the 1984 Beijing Hematoporphyrin Conference,[23] which are not completely applicable to 5-ALA-PDT. In addition, there are differences in the evaluation between oral mucosal diseases and solid tumours. Combined with the current status, the following evaluation criteria are recommended:

Histopathological evaluation of curative effect

Evaluation of biopsy or exfoliated cells at three points at the centre of the treatment spot and both ends of the long diameter. Those with negative results are defined as complete remission (CR), and those with one positive point are defined as partial remission (PR).

Evaluation of curative effect by non-invasive testing methods

Toluidine blue staining was used to assist subjective lesion evaluation to compare the changes in lesion range before and after treatment (in addition to surface area, the thickness of OPMD should also be compared and evaluated). A VELscope and Wood lamp were used to evaluate the changes in fluorescence intensity of lesions before and after PDT.

Clinical examination and evaluation of curative effect

In CR, all target lesions have disappeared, and in PR, compared with the baseline state, the size of the lesion is reduced by at least 30%, or has converted from a severe type to a milder type. Stable disease (SD) means there has been no change in the size and type of lesions, whereas progression disease (PD) means that the longest diameter of the target lesion has increased by at least 20% compared with the longest diameter of the smallest target lesion recorded after the start of treatment, or one or more new lesions have appeared.

Preparation before treatment

Indications

According to the authors' experience, the following diseases can be included in the indications: oral leucoplakia, oral erythroplakia, oral lichen planus and chronic discoid lupus erythematosus with intractable erosion, oral submucous fibrosis, verrucous hyperplasia or papilloma. With the continuous enrichment of clinical practice, it is believed that the indications will continue to expand.

Partial treatment

The efficacy of local 5-ALA-PDT in the treatment of OPMDs is affected by the thickness of the lesion and the degree of surface keratinisation. Yu et al[24] found that oral mucosal proliferative diseases with a diameter ≤ 1.5 cm, with histopathology indicating epithelial dysplasia and with mucosal stratum corneum ≤ 40 μm can achieve clinical cure over a shorter course of treatment than other types of OPMD after receiving PDT. Surface pretreatment of mucosal skin lesions can enhance the photodynamic effect of 5-ALA-PDT.[25,26]

At present, the most common pretreatment for skin and mucosal lesions before PDT is to use CO_2 laser to remove the thick stratum corneum on the lesion surface. A randomised clinical study evaluated the efficacy of CO_2 laser combined with 5-ALA-PDT and 88% of patients with grade 2-3 keratosis achieved complete remission after treatment.[27] However, a thermal agglutination zone will be generated in the tissue after laser irradiation, which may affect the diffusion and distribution of the photosensitiser in the tissue.[28]

As a physical therapy method, microneedle therapy can also be used in the pretreatment of OPMDs with

thick stratum corneum. The photosensitiser channel established by puncture accelerates the penetration of the drug to the base of the lesion. On this basis, Chinese scholars combine the plum blossom needle tapping method used in traditional medicine for the pretreatment of oral verrucous leucoplakia and have achieved good results. Additionally, this method does not increase the patient's pain or other adverse reactions, and the cost is low.[29,30]

Common adverse reactions and management after 5-ALA-PDT treatment of OPMDs

Local pain

Local pain occurs most frequently. Preventive local injection of lidocaine hydrochloride or articaine for analgesia before treatment and lidocaine spray can be given to relieve pain if symptoms occur after the operation. Before treatment, explain the possible symptoms the patient may experience and record the degree of pain using the visual analogue score (VAS) scale. Administer painkillers if necessary.

Some patients with OPMDs have local pain in the lesion before PDT and the original pain disappears after treatment, which indicates not only that there is no adverse reaction but also that the malignancy of the lesion has reduced or disappeared.

Oral ulcers

The frequency of ulcers is second only to pain. Strengthen the management of patients' oral hygiene and apply oral ulcer powder and other medicines locally and the ulcers can heal within 1 week.

Local swelling

Swelling is common, but it is relatively mild and often resolves on its own after 3 to 5 days. A local ice compress can be used.

Light sensitivity

Because of the local administration of photosensitisers, almost no photosensitivity reactions will be seen in oral PDT. Patients can be instructed to avoid light within 48 hours after treatment to avoid aggravating the photodynamic response caused by sunlight stimulating the residual photosensitiser.[31]

Summary

In short, PDT has developed rapidly in recent years and offers indisputable advantages in the treatment of oral mucosal diseases; however, its application time in stomatology is still short and it is still in the preliminary stage, meaning that many aspects need to be explored further. It is necessary to increase the sample size to observe the effectiveness and safety of PDT in the treatment of oral mucosal diseases, conduct long-term follow-up observations and form a standardised diagnosis and treatment process based on evidence-based medicine.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

This document was drafted by experts from Peking University School of Stomatology. The consensus experts were from Beijing Hospital, the Third Affiliated Hospital of Air Force Military Medical University, Guangxi Medical University College of Stomatology, Stomatological Hospital of Guizhou Medical University; Hospital of Stomatology, Jilin University, Qingdao Stomatological Hospital, Stomatological Hospital of Xiamen Medical College, Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine, the Affiliated Stomatology Hospital of Tongji University, Capital Medical University Beijing Stomatological Hospital, West China School of Stomatology Sichuan University, Tianjin Stomatological Hospital, Hospital of Stomatology Wuhan University, the Affiliated Stomatological Hospital of South-west Medical University, School of Stomatology, Zhejiang University School of Medicine, Affiliated Stomatological Hospital of China Medical University, Hunan Xiangya Hospital Stomatology of Central South University, Hospital of Stomatology, Sun Yat-sen University participated in the drafting.

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