

Photodynamic Therapy

Will it hit its stride anytime soon?

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Though photodynamic therapy (PDT) has been available in the United States since the late 1990s and many people were experimenting with its use before it received FDA approval in 2000, it has had a very slow adoption in this country. Physicians in the United States have one product that can do so many different things and potentially do them fairly well, but it doesn't seem to have really caught on yet. There have

atotic actinic keratoses (AKs) of the face and scalp using a 14- to 18-hour drug incubation period and a blue light source for 16 minutes and 40 seconds. All other uses and discussions of ALA-PDT are considered off-label.

What is Hampering the Widespread Use of PDT?

There are huge, potential advantages to using PDT — high cure rates, targeted treatments specific to the lesion, it's non-invasive, fast healing, provides excellent cosmetic results, multiple conditions can be treated at the same time, and it can be used with multiple indications. One of the difficulties, though, is that very few dermatologists are using this according to the FDA-approved guidelines. Mostly, it is being used off-label — from the indication to how we treat the skin, the incubation time, occlusion, non-occlusion, light exposure, wavelength time rate, etc. There are no set ways that it is being used, and that may contribute to why it hasn't been used on a wide-spread scale.

Other issues that may be hampering its wide-spread use are potential side effects, such as extended phototoxicity, the number of treatments that are really needed for the off-label indications and the lack of reimbursement for off-label uses. And, though we know that non-FDA approved uses are efficacious, more studies are needed. Also, there is a sparse avail-

What are the Controversies?

1. When will this therapy hit its stride?
2. Is the importance of the light source used underestimated?
3. What is inhibiting its wide-spread use?

been a number of studies published and some very good work that's been done to show what PDT can do, and every year there are review papers and consensus papers published to tell us how to use this therapy and what we should be treating with it, but currently the FDA approval is only very limited. In the United States, the only FDA clearance for 5-aminolevulinic acid (ALA) (Levulan Kerastick) is for the treatment of nonhyperker-

How Important is the Light Source?

By Daniel Barolet, M.D.

The challenge of selecting the ideal light source parameters for successful photodynamic therapy (PDT) remains underestimated. In the United States, the approved light source for 5-aminolevulinic acid (ALA)-PDT treatment is a non-thermal fluorescent blue light (BLU-U).

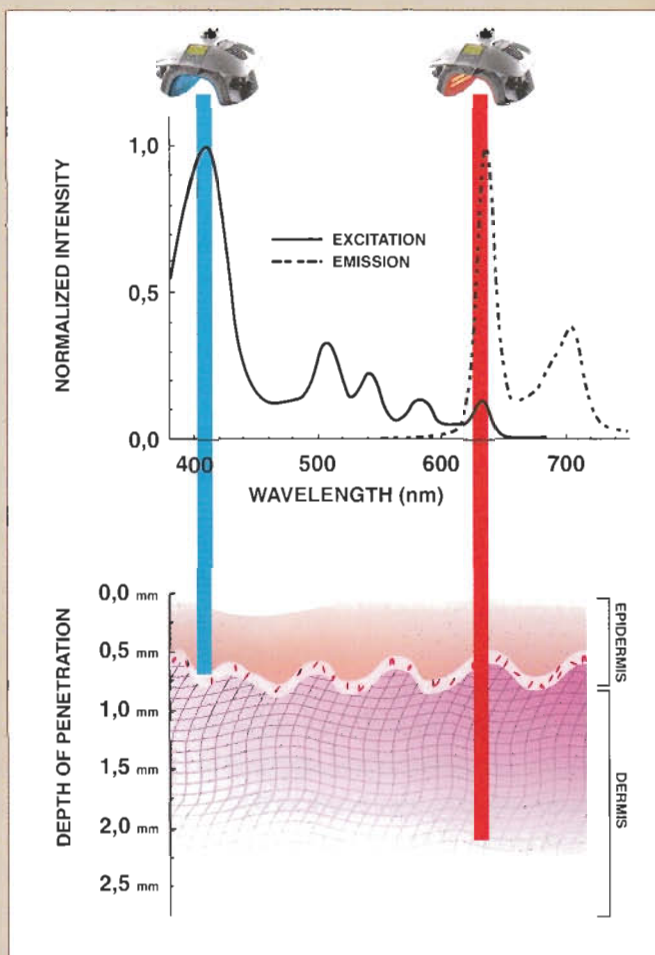
When compared to high-energy enablers, such as lasers or intense pulsed light (IPL) devices, I have found that high-end light emitting diode (LED) devices may be better able to meet the challenge and can be used as the light sources of choice for enhanced PDT. Clinical trials are needed and money needs to be invested to put in action some well-designed and well-controlled studies.

In the past, lasers and IPLs have been mostly used for PDT, mainly because they were available in doctor's offices. These devices may induce some peak power effects like tissue hypoxia, thermal diffusion in the dermis, photo bleaching of the photosensitizer before it gets photo-activated, and simultaneous micro-injury in the dermis, which sometimes is desirable when treating photodamage and trying to get rid of blood vessels and lentigines.

On the other hand, use of an LED source avoids thermal peak power effects on the photosensitizer. LEDs allow for progressive photoactivation of photosensitizers, can cover larger surfaces than lasers and are now available in multiple wavelengths that may meet the peak absorption peaks of protoporphyrin IX (PpIX). Red wavelengths (630 nm) can reach the sebaceous glands and blue light (405 nm) photobleaches any residual PpIX in the epidermis, thereby also reducing post-treatment photosensitivity. A dual-wavelength (red and blue) LED device optimizes PDT results by providing a superior activation of the photosensitizer deep at the target structure for maximized clinical effect and fewer side effects.

Irradiance is also something that's very important, and certain devices have optical positioning systems and aiming beams, which provide the right treatment distance between the light source and the surface of the face. For instance, if you move from 2.5 cm to 5 cm away from the skin surface, you may lose two-thirds of the irradiance or power density.

Also, finding a light source that allows for better drug penetration and enhances the efficacy of PDT is important. For example, the challenge for acne patients rests in reaching deeper in the skin, where the sebaceous glands are, to enhance clinical effect in the dermis, while triggering fewer side effects on the epidermis. LED sources can be used to stimulate a photosensitizer and high-power infrared LEDs can prepare the skin prior to treatment. A new pre-PDT method has been successfully used to presumably increase *in situ* conversion of 5-ALA to PpIX due to slight temperature elevation induced by radiant IR exposure. Ultimately, PDT efficacy is physically dependent on the photosensitizer reaching its targeted skin structure. ■



Fluorescence excitation and emission spectra of PpIX.



High-power LED device.

ability of new molecules and new photosensitizers. This may be because it's too costly and the approval process is a very long and tedious task. Also, the penetration of the photosensitizer can be a challenge. The stratum corneum is an excellent barrier.

Other cons to PDT treatment include photosensitivity for 48 hours and the need for multiple treatments.

Since some of the potential side effects of PDT may hamper its widespread use, it would benefit us to find protocols to lessen these effects. For example, pain is an issue in some patients and we are looking for an algorithm that may help reduce pain. We know that pain is more common in male patients than female patients and pain is more common in facial and scalp treatments than on the trunk. Actinic keratosis treatment results in more pain in our patients than basal cell carcinoma treatment, and sun-damaged skin areas on the face respond much more with respect to pain than the other skin sites.

Off-Label Indications

Anecdotally, PDT has shown promise as a treatment for diffuse actinic damage, particularly in transplant patients, for photorejuvenation and for acne (for which DUSA is starting a large clinical trial to help define treatment protocols). The most common off-label uses are for non-melanoma skin cancer, inflammatory acne, photorejuvenation, sebaceous hyperplasia, porokeratosis, and also sometimes only for oily skin. Work has also been done to show the positive effects of ALA-PDT on actinic cheilitis as well.

There have been studies in Europe to show that methyl aminolevulinic acid (MAL) (Metvix) with PDT treatment has resulted in longer duration to recurrence of AKs and non-melanoma skin cancer in immunocompromised patients than would be expected in this population. In Europe, there is also 5-year followup data available to show that MAL-PDT is effective for basal cell carcinoma.¹

European Experience with PDT

By Maurice Adatto, M.D.

In Europe, we use photodynamic therapy (PDT) for dermatological and mainly oncological purposes. We have very little experience in the cosmetic field of PDT.

We primarily use methyl aminolevulinic acid (MAL) (Metvix). The main difference between MAL and 20% 5-aminolevulinic acid (ALA) (Levulan Kerastick) is the acid group. This small change will change completely the behavior of the molecule. MAL penetrates much faster into the abnormal cells because it is non-polar and can diffuse into the cell and can also use the active transport of non-polar amino acids. Also, there is a much higher ratio of the product into tumor cells with MAL than with 5-ALA. Penetration of MAL is very selective into tumor cells and needs only 1 to 3 hours. Cells are quickly and precisely sensitized.

One large practical difference between MAL and ALA is cost. Metvix is still very expensive in Europe — the equivalent of \$385 for a very small 2-gram tube, which can't cover a large area. Levulan Kerastick, on the other hand, costs roughly \$110 for 1.5 ml, which allows for coverage of a much larger area. When you have small lesions to treat or a small number of lesions to treat, MAL is okay. If you have larger areas to cover, the cost becomes an issue, and ALA is a more cost-efficient option.

Because we are mainly treating some skin cancer, depth of penetration is crucial, so I prefer red light since it has been proven that red light penetrates the deepest. I use light sources with no emission of heat, spectrum around 630 nm and continuous wave because that is the way all the studies have been done to demonstrate the efficacy.

MAL-PDT with a 630-nm light source is ideal when selectivity and depth of penetration are appropriate. The gold standard of treatment for non-melanoma skin cancer is either surgery with Mohs micrographic surgery or radiotherapy, but when treating a difficult patient or difficult location, PDT is a very nice option. The indications in Europe for PDT are superficial basal cell carcinoma, superficial squamous cell carcinoma and nodular BCC.

ALA-PDT with a 630-nm light source is ideal when selectivity is less important, such as when treating a patient with diffused disease and multiple AKs on a large area need to be treated. ■

In the United States, some new anecdotal evidence regarding ALA-PDT also has shown longer duration to recurrence of AKs and longer duration to the development of non-melanoma skin cancer. There have been several studies to support this anecdotal evidence, as well.

There are huge, potential advantages to using PDT — high cure rates, targeted treatments specific to the lesion, it's non-invasive, fast healing, provides excellent cosmetic results, multiple conditions can be treated at the same time, and it can be used with multiple indications.

In the United States, one group² published 12-month data to show the development of actinic keratoses are delayed compared to what you would expect in this patient population. And, another group³ looked extensively at basal cell nevus syndrome patients and has shown that the development of basal cells are delayed after recurrent and numerous PDT treatments.

Over the last several years, it has been demonstrated that PDT is very effective for photorejuvenation — many of us have had experience seeing the photorejuvenation effects of PDT treatment in our practices.

In a recent report in the *Journal of Drugs in Dermatology*,⁴ a split-face trial demonstrated that using the Fraxel device before PDT treatments to increase the penetration of ALA and then following with ALA treatment increases efficacy.

As far as acne, clinical trials have been completed that have shown PDT treatments result in an

improvement in acne.⁵ Mark Nestor, M.D., has been able to show clinical results at 1- and 2-year and 5 years follow up, that patients with inflammatory acne respond to ALA-PDT treatment, though results have not been published.

The Future of PDT

In the future, combination therapies with PDT may enhance efficacy and lessen side effects. Pre-treatment, for example, with an erbium laser or a pre-treatment with a session of imiquimod could be possible. We also have penetration enhancers — ultrasound, electrophoresis, fractional lasers and more. Other ALA formulations, nano-colloids or patches are being developed. Penetration times can be varied, and also is a chance to reinforce PDT's effect with synergistic drugs or topical drugs, which can play an important role in the future.

Photodynamic therapy is close to hitting its stride. The commitment level needs to stay high from the pharmaceutical world. There is a need for continued funding and more research.

Clinicians will continue to use this therapy, especially as reimbursements for treatment increase. The availability of Metvix in the United States should add new indications and further research endeavors. The future for this PDT looks bright. ■

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