

# Phototherapy\*

## Fototerapia\*

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**Abstract:** Phototherapy has been used to treat a large variety of dermatoses since the past century. It is classified according to the type of irradiation (UVA or UVB).

Phototherapy is indicated for all types of inflammatory and chronic skin diseases, such as vitiligo, psoriasis, parapsoriasis, cutaneous T-cell lymphomas and chronic eczemas, with good therapeutic results. It can be used as monotherapy or associated with others drugs, such as retinoids, methotrexate and cyclosporine, aiming to reduce length of treatment and doses.

Like other treatments, phototherapy has some limitations - it requires specific equipment, patient's compliance, has restricted indications and leads to cumulative UV doses.

The therapy must be performed with strict follow-up to obtain effective therapeutic response and few adverse effects.

Keywords: Inflammation; Phototherapy; PUVA therapy; Ultraviolet rays

**Resumo:** Fototerapia é utilizada para tratar uma grande variedade de dermatoses. Desde o século passado a fototerapia tem sido utilizada em várias modalidades, com irradiação UVA ou UVB. Está indicada para todos os tipo de dermatoses inflamatórias e com período crônico de evolução, como vitiligo, psoríase, parapsoríase, linfomas cutâneos de células T, eczemas crônicos, demonstrando bons resultados terapêuticos.

Pode ser utilizada como monoterapia ou associada a outras drogas, como retinóides, metotrexate, ciclosporina, com objetivo de diminuir o tempo de tratamento e as doses das medicações mencionadas.

Como os demais tipos de tratamento, a fototerapia apresenta algumas limitações, como a necessidade de equipamentos específicos, a adesão do paciente, a possibilidade de indicação ao paciente e a dose cumulativa de irradiação UV.

A fototerapia deve ser conduzida com seguimento criterioso para a obtenção de resposta efetiva com poucos efeitos colaterais.

Palavras-chave: Fototerapia; Inflamação; Raios ultravioleta; Terapia PUVA

### INTRODUCTION

Phototherapy is a type of therapy used to treat several dermatoses. Its use dates back to Antiquity and is classified according to the type of radiation used (UVA or UVB), which varies depending on the wavelength.

This is a treatment option for various chronic skin diseases such as psoriasis, vitiligo, cutaneous T-cell lymphoma, parapsoriasis, and eczemas, among others, and produces very good results.

Additionally, phototherapy may be used in association with several systemic drugs, such as retinoids,

methotrexate and cyclosporin in order to attain rapid control of the dermatosis with smaller doses of medication.

As is true with any other curative option, phototherapy has limitations such as the use of specialized equipment, patient compliance with treatment, and clinical issues as the total cumulative UV radiation dose and its consequences.

The use of phototherapy requires caution and strict follow-up to achieve an effective therapeutic

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response and avoid undesirable side effects.

## BACKGROUND

The first descriptions on the use of phototherapy date back to 1400 and refer to the Hindu [practice and] use of medicinal plants associated with exposure to the sun for treating vitiligo.<sup>1</sup> However, it was only after 1903, when Niels Finsen was awarded the Nobel prize for his success in treating lupus vulgaris with UV radiation, that phototherapy began to be truly studied and practiced as a treatment for various skin diseases.

During the First World War (1914-1918), the treatment of traumatic ulcers with phototherapy and solar light began and produced good results.<sup>1</sup>

In 1925, Goeckerman introduced the combination of coal tar and ultraviolet radiation in treating psoriasis,<sup>2</sup> a regimen that was used for a long time.

In 1948, Moftly reported the effects obtained with 8-MOP in treating vitiligo, and was followed by Lerner, who showed the possibility of enhancing the effects of this substance by the use of UV radiation between 320-400 nm, constituting what is known as the PUVA treatment. In 1974, several authors (Parrish, Fitzpatrick, Tannenbaum et al.) reported on the beneficial effects of this type of therapy in psoriasis.<sup>3</sup> Since then, another series of diseases has been described as responsive to UV radiation as well.

The greatest leap forward was given with the discovery, in 1988,<sup>1</sup> that a small range of UVB radiation, between 311 and 313 nm, called narrowband UVB would be more efficacious than UVB in treating psoriasis.

## PHOTOBIOLOGY

Ultraviolet rays correspond to 5% of solar light on the Earth and represent a small part of the electromagnetic spectrum. Other regions of this spectrum include microwaves, radio waves, infrared radiation, visible light, X-rays, and gamma radiation.<sup>4</sup> The wavelength of each type of radiation is what defines its characteristics.

Ultraviolet rays are divided into UVA: 400-320 nanometers (nm), UVB: 320-290 nm and UVC: 290-200 nm. UVA is subdivided into UVA I (340-400 nm) and UVA II (320-340 nm), and the UVB range between 311 and 312 nm is called narrowband UVB.

UVA radiation reaches the epidermal and superficial and mid dermal skin layers and UVB reaches mainly the epidermis. Both UVB and UVA act on keratinocytes. UV light is absorbed by nucleotides and leads to the formation of DNA photoproducts, especially pyrimidine bases. This sets off photochemical reactions that result in biochemical changes in the tissues, such as induction of the activity of some

enzymes, cytokine secretion, and repair of structures.<sup>5</sup> All reactions depend on the wavelength employed.

The molecules in the skin that absorb light are called chromophores.<sup>5</sup> The most important chromophore is melanin that absorbs both UVA and UVB radiation. DNA is the most important chromophore for photobiological response in the UVB scale. Tryptophan, 7-dehydrocholesterol, urocanic acid, pyridoline (collagen), and desmosine (elastin) are also chromophores for UVB. NAD and FAD co-factors are chromophores for UVA. Not all chromophores are capable of initiating a photochemical reaction in the skin.

The main responses induced by ultraviolet radiation on the skin are:

### 1- Anti-inflammatory / immunosuppressant effect

a) Altering the production of cytokines such as Interleukin 10 (IL-10), interferon- $\gamma$  (INF- $\gamma$ ), interleukin 1 (IL-1) and tumoral necrosis factor (TNF- $\alpha$ ).

b) Inducing the production of prostaglandin E by keratinocytes, leading to a decrease of the molecular expression on the surface of antigen-presenting cells, and, consequently, diminishing activation of T lymphocytes.

c) Acting on keratinocyte surface receptors and antigen-presenting cells, altering the release of adhesion molecules (ICAM-1).

### 2- Antiproliferative effect

a) UVB and UVA lead to the formation of DNA photoproducts, causing a reduction in DNA synthesis and, consequently, a decrease in cellular proliferation.

b) Another mechanism by which UVB and UVA exert an antiproliferative effect is the induction of keratinocyte apoptosis.<sup>6,7</sup>

## TYPES OF PHOTOTHERAPY

### Phototherapy with UVB

UVB lamps emit wavelengths of 290 to 320 nm. There are two types of UVB lamps - one is broadband UVB, and the other, which emits 311 to 312 nm waves, is called narrowband UVB.

UVB generally is the first option before PUVA because of its smaller risk, no use of psoralens, and because it is more effective than PUVA in skin types I and II.<sup>8</sup> UVB is less effective in melanodermic patients.<sup>9</sup>

The patient's minimal erythematous dose (MED) should be established before treatment. (MED is the minimum amount of energy necessary to produce a uniform erythematous response in up to 24 hours). Treatment is initiated with 75 to 90% of this

dose, varying according to the patient phototype (Chart 1). Post-UVB erythema usually appears 12 hours after the session. The dosage is gradually increased in order to minimize burn reactions to the UV rays (Chart 2).

There are several treatment protocols using UVB, and the number of applications can vary from three to five times a week. Normally, two to three months of treatment are needed until a significant response is achieved. Maintenance with two to three times a month may help prolong the remission of the symptoms.<sup>9</sup>

### Phototherapy with PUVA

Treatment with PUVA is made associating a psoralen and radiation from UVA lamps that emit wavelengths between 320 and 400 nm.

Psoralen is the broad term used to describe furocoumarin compounds found in plants. When stimulated by UV rays, these substances bind to cellular DNA pyrimidine bases and set off photochemical reactions in the skin.<sup>5,10</sup>

In Dermatology, the most commonly used psoralens are 8-methoxypsoralen (8-MOP, methoxalen), 5-methoxypsoralen (5-MOP, bergapten) and 4,5,8-trimethoxypsoralen (4,5,8 TMP, trioxsalen).<sup>5</sup>

Oral psoralens are metabolized in the liver and maximum blood concentrations are reached within one to three hours. Drugs that activate cytochrome P450 enzymes accelerate and increase their metabolism.<sup>5</sup> Renal elimination occurs in 12-24 hours.<sup>5,10</sup>

The 8-MOP and 4,5,8 TMP psoralens may be used both systemically and topically, whereas 5-MOP is only used systemically.

Eight-methoxypsoralen [8-MOP] is normally used at a dose of 0.4 mg/kg of weight, one hour and a half before phototherapy when in liquid form or two to three hours before treatment if in crystalline form, and at the dose of 0.6 mg/kg of weight two hours before phototherapy when used as tablets.<sup>9</sup>

Topical PUVA is routinely used in an association of trioxalen with UVA light applied to the skin 30 min-

CHART 2: UVB radiation increment according to degree of erythema

Degree of erythema	Dose increment
0 (no erythema)	20%
1 (minimum erythema)	10%
2 (intense erythema)	Do not apply
3 (erythema and edema)	Do not apply
4 (erythema, edema and blisters)	Do not apply

Source: Zanolli MD, et al.<sup>42</sup>

utes before phototherapy. The dosage varies from 0.1%, where the skin is thinner, up to 1% in plantar areas, and PUVA is prepared in cream- or alcohol-based lotions.

For systemic PUVA, the initial UVA dose is usually based on the patient skin type and on the disease to be treated, and generally starts at 0.5 to 1 J/cm<sup>2</sup> (Chart 3).

With topical PUVA therapy, the initial UVA dose is between 0.12 and 0.5 J/cm<sup>2</sup>.

Considering that post-PUVA erythema may appear between 48 and 72 hours after the session, treatment could be given two to three times a week.<sup>10</sup>

Increase of irradiated light dose is determined by the intensity of erythema caused in the previous session, and its maximum value varies according to skin type and disease (Chart 4).

The absolute values needed to complete the total dose (in Joules/cm<sup>2</sup>) are more than one thousand times greater for UVA relative to UVB; this explains the need for using psoralens in order to facilitate UVA absorption and not prolong time of treatment for patients.<sup>10</sup>

### OTHER FORMS OF PHOTOTHERAPY

Extracorporeal photopheresis for cutaneous T-cell lymphomas<sup>11</sup> also used for severe atopic dermatitis<sup>1</sup> that is resistant to other treatments.<sup>12</sup> Following psoralen ingestion, the circulating mononuclear cells are submitted to PUVA by means of an extracorporeal exposure system and then returned to the patient.<sup>13</sup>

Phototherapy with UVA wavelengths between 340 and 400 nm (UVA-1) does not use a psoralen. The average initial dosage of UVA-1 is 50J/cm<sup>2</sup>. This method is primarily indicated for the treatment of atopic dermatitis. Some studies published report good results with doses that vary from 20 to 130J/cm<sup>2</sup>, using three to five applications a week, during 10 days for atopic dermatitis and 20 days for dyshidrosis. Since it is a form of therapy only recently introduced, its long-term effects are still unknown.

CHART 1: Initial UVB radiation dose

Skin type	mJ/cm <sup>2</sup>	75% of dose (mJ/cm <sup>2</sup> )
I	20 – 30	19
II	25 – 35	23
III	30 – 50	31
IV	45 – 60	37
V	60 – 100	50
VI	100 – 200	107

Source: Morison WL.<sup>10</sup>

**CHART 3: Skin types/ initial UVA dose**

Skin type	Characteristics	Initial radiation (Joules/cm <sup>2</sup> )
I	Always gets burned, never tans	0,5
II	Always gets burned, sometimes tans	1,0
III	Sometimes gets burned, always tans	1,5
IV	Never gets burned, always tans	2,0
V	Moderately pigmented	2,5
VI	Black	3,0

Source: Morison WL.<sup>10</sup>

Therefore, it is suggested that its use be limited to acute and severe exacerbation periods, with only one cycle a year and no more than 10 to 15 sessions.<sup>13</sup>

**PUVA immersion or "PUVA bath"**

This type of therapy was designed for cases with an indication for systemic PUVA treatment in an effort to reduce the dose of UVA exposure.<sup>14</sup> It is particularly useful for patients who receive other systemic medications<sup>14</sup> or are intolerant to psoralens.<sup>9</sup> The ocular and gastrointestinal side effects are minimal since there is no systemic photosensitization. Psoralen concentration on the skin is greater than with systemic PUVA therapy, hence providing less exposure to RUV.<sup>5</sup> A dilution of 8-MOP in warm water is used, immersing the area to be treated during 15 to 20 minutes before the UVA radiation. The 8-MOP concentration corresponds to 1 mg/l, obtained by diluting 20 ml of 0.5% 8-MOP in alcohol at 96° in 100 liters of water. Trioxsalen (4,5,8 TMP) may also be used, but in smaller doses.<sup>5</sup>

The dose of UVA is the same as that used for topical PUVA, with an initial dose of 0.12 - 0.5 J/cm.

**INDICATIONS FOR PHOTOTHERAPY**

Phototherapy is a treatment method that could be used in several skin diseases; its primary indications are inflammatory dermatoses and cutaneous T-cell lymphomas. The skin diseases include:

**Psoriasis**

Psoriasis is one of the main indications for phototherapy. All types of psoriasis could be treated with this method. The mechanism of action for phototherapy is antiproliferative, anti-inflammatory, and immunosuppressant activity.

Systemic photochemotherapy (systemic PUVA) is indicated in cases of extensive skin involvement or in individuals with thick skin lesions. It is also indicated in patients with type II skin or greater, according to Fitzpatrick's classification.

Topical photochemotherapy (topical PUVA) is indicated in localized lesions, such as palmoplantar psoriasis or scalp.

In light-skinned individuals with lesions bearing fine plaques of psoriasis, UVB radiation may be used for treatment.

Narrow-band UVB radiation is considered by several authors the first choice for psoriasis treatment.<sup>8,10,15</sup> It is safe and effective, and produces results comparable to those of systemic PUVA.

Combination treatments may be utilized in cases that are difficult to manage such as erythrodermic forms or clinical presentations that do not respond well to phototherapy alone.<sup>5,9</sup> Different medications are associated to the phototherapeutic treatment seeking to increase efficacy as well as to reduce treatment duration and the side effects of isolated treatments.<sup>5,10</sup> The goal of this combination is to expose the patient for the shortest time possible, both to the drug and to ultraviolet the radiation. As soon as control of the dermatosis is initiated, medication doses are progressively reduced, keeping phototherapy as maintenance. The most potent combination for the treatment of psoriasis is the use of Re-PUVA – systemic retinoids (etretinate or acitretin) with PUVA.<sup>5</sup> The dose varies from 0.5 to 1 mg/kg/day during a two to three week interval. PUVA is associated until lesions lighten in color, when the retinoid dose starts to be reduced.<sup>5</sup> This combination affords a rapid regression of the dermatosis and, according to some authors, diminishes the carcinogenic potential of PUVA.<sup>9</sup> Other combinations may be used, such as phototherapy

**CHART 4: UVA radiation increment according to degree of erythema**

Degree of erythema	Management
0 (no erythema)	Apply
1 (minimum erythema)	Apply
2 (intense erythema)	Do not apply
3 (erythema and edema)	Do not apply
4 (erythema, edema and blisters)	Do not apply

Source: Zanolli MD, et al.<sup>12</sup>

associated with methotrexate<sup>16</sup> or cyclosporin. Some disadvantages of these methods are synergism in immunosuppression, risk of skin cancer induction, and photosensitivity.<sup>2</sup>

Combinations of topical medications with PUVA help to cut the total duration of treatment.<sup>15</sup> Some drugs that may be used include anthralin, coal tar derivatives, vitamin D derivatives (calcipotriol, calcitriol), retinoids, and corticosteroids. The use of UVB radiation associated with topical corticosteroids has shown a reduction in remission time for the disease.

One can also associate keratolytics in areas of hyperkeratosis, as in the palmoplantar region, in order to improve the penetration of light.

UVB radiation associated with coal tar is known as the Goeckerman method; Ingram's method combines UVB with anthralin.<sup>2,15</sup>

Lubricants should be applied after the phototherapy sessions to avoid hindering the absorption of light.<sup>4</sup>

Sessions are carried out two or three times a week until total or almost complete control of the dermatosis is achieved. Then the number of sessions is reduced and this phase is called the maintenance treatment.

### **Vitiligo**

The primary treatment indication for vitiligo is photochemotherapy (PUVA). Similar to what happens in UVB radiation, UVA radiation stimulates melanogenesis and interferes in the inflammatory process of the dermatosis.<sup>17</sup> When there is an extensive involvement, systemic PUVA is used. In localized lesions or areas that are difficult to reach with radiation, topical PUVA is indicated. Narrowband UVB radiation treatment has proved to be effective and has provided satisfactory responses in patients with contraindications for PUVA.

The repigmentation pattern is less significant on the extremities. Lesions located on the hands, fingers, feet, and toes show an unsatisfactory response.<sup>10</sup>

Some authors describe better results after an association of PUVA and calcipotriol due to its effect on melanocytes and inflammatory mediators. Other authors associate UVB radiation with folic acid and vitamin B12 (cyanocobalamin) believing this causes quicker repigmentation. These methods need to be further studied.<sup>18</sup>

Sessions are held twice a week. Newer protocols call for only one session a week since this improves patient compliance and reduces side effects. The main disadvantage is prolonged treatment duration.

### **Atopic dermatitis**

Phototherapy is indicated for control of atopic

dermatitis in light of its anti-inflammatory and immunosuppressant mechanisms. Cytokines produced by T lymphocytes, which mediate the immune response for the development of eczematous lesions, are inhibited.<sup>13</sup>

Treatments with UVB and narrowband UVB show good results and are indicated for patients with chronic dermatosis and in maintenance therapy. Some authors consider narrowband UVB the treatment of choice for inducing a long-term improvement of atopic dermatitis besides being safe for use in children.<sup>13</sup>

Systemic PUVA is indicated during the acute phase of atopic dermatitis, in severe forms with extensive skin involvement. This type of therapy may be utilized during regression and removal of corticotherapy in corticoid-dependent patients.

Treatment with high doses of UVA-1 radiation using many applications over a short period may be an alternative to the use of corticosteroids and does not interfere in the child's development.<sup>13</sup>

Topical PUVA is indicated in localized eczematous lesions, such as those in palmoplantar areas.

Sessions are carried out two or three times a week, with a reduction in frequency after control of the clinical symptoms.

### **Cutaneous T-cell Lymphoma (CTCL)**

Phototherapy is indicated during the initial stages of the disease as monotherapy in order to avoid extracutaneous dissemination and determine longer periods of remission. It acts mainly on T lymphocytes as an antiproliferative agent.

In more advanced stages of lymphoma, isolated phototherapy shows partial results and a combination with other treatments is necessary. The medications usually associated are interferon- $\alpha$  or retinoids. This therapeutic approach seeks to improve the patient's quality of life and prolong survival.<sup>11,19</sup>

Systemic PUVA is the first choice, with three sessions a week. The average total time of treatment is three to six weeks, and maintenance treatment is always necessary. The number of sessions is small and can even occur every two or four weeks.

In tumoral lesions, the PUVA treatment has proved to be effective because of the epidermotropism of the infiltrate. The destruction of superficial cells favors a migration of the deeper infiltrate towards the surface, facilitating control of the tumor lesions.

Treatment with narrow-band UVB radiation shows advantages in comparison to PUVA because it presents a smaller risk of carcinogenesis and side effects and produces a good response. Some authors

suggest initiating treatment with this option, and, according to the patient clinical progress, substituting it for PUVA, if necessary.<sup>20</sup>

### Parapsoriasis

Phototherapy is indicated for all types of parapsoriasis and their clinical variations. The objective is to suppress the disease by the anti-inflammatory and immunosuppressant effects of this treatment, preventing the progression to cutaneous T-cell lymphoma.<sup>21</sup>

Some authors consider phototherapy with systemic PUVA a curative treatment for parapsoriasis. Narrow-band UVB has also proved to be effective in controlling the dermatosis. As is true in cutaneous T-cell lymphoma cases, treatment maintenance should be prolonged for sustained clinical remission.<sup>21</sup>

### Scleroderma

PUVA treatment is indicated both in generalized and localized forms of scleroderma, using systemic PUVA or topical PUVA, respectively.

Ultraviolet radiation induces the synthesis of collagenase. Phototherapy promotes the release of cytokines that induce formation of collagenase and inhibit collagen synthesis, in addition to its immunosuppressant effect.

According to some authors, phototherapy would be a valuable contribution to the few therapeutic options available for localized and systemic forms of scleroderma.<sup>22</sup>

### GVHD (Graft versus host disease)

The use of phototherapy is indicated in acute and chronic GVHD with its lichenoid and scleromatous forms. PUVA-type phototherapy was the first to be used for this disease,<sup>23</sup> in association with other conventionally used drugs. Recent studies have also shown good results of treatment of GVHD with narrow-band UVB.<sup>24</sup>

### Idiopathic photodermatoses (Polymorphic light eruption, Hydroa vacciniforme, Solar urticaria, Actinic prurigo, Chronic actinic dermatitis)

Phototherapy is indicated for individuals affected by these abnormalities with the purpose of increasing their tolerance to sunlight.

Treatment may be done in either one of two ways: using a light wavelength that induces dermatosis, in small doses, in order to desensitize the patient, or using a wavelength incapable of setting off skin condition as a therapeutic agent, thus increasing tolerance to light. Doses of PUVA or UVB are lower than those indicated for other dermatoses.<sup>25,26</sup>

### Other indications for phototherapy

Phototherapy is indicated for all inflammatory skin diseases. Dermatoses for which this treatment option has been used over the last few years include:

<sup>10,27-33</sup>

- Lichen planus
- Seborrheic dermatitis
- Chronic eczema
- Chronic and acute pityriasis lichenoides
- Pityriasis rosea
- Pruritus (autotoxic / HIV-related)
- Mastocytosis
- Granuloma annulare
- Grover's disease
- Subcorneal pustular dermatosis
- Chronic idiopathic urticaria
- Chronic progressive pigmented purpura
- Lipoid necrobiosis
- Erythropoietic protoporphyria
- Lymphomatoid papulosis
- Palmoplantar pustulosis
- Livedoid vasculitis

### PHOTOTHERAPY AND THE HUMAN IMMUNODEFICIENCY VIRUS (HIV)

The indication of phototherapy for patients with HIV causes some concerns. The fact that UV radiation alters cellular DNA could favor the inclusion of the viral gene into cellular DNA, inducing the proliferation of the HIV. Additionally, phototherapy is an immunosuppressant treatment. Nonetheless, the presence of HIV in the skin has not been demonstrated, and, according to some studies published, the immunosuppressant effect of phototherapy does not diminish the number of CD4<sup>+</sup> T-lymphocytes.<sup>34</sup> Phototherapy in HIV patients with pruritus and eosinophilic folliculitis<sup>35</sup> proved to be effective and did not lead to immunological changes in these patients.

Hence, phototherapy is safe in this group and it is recommended that HIV-positive patients who will undergo UVB or PUVA be monitored as to CD4 levels and viral load before, during, and for one month after the treatment.

In choosing treatment with ultraviolet radiation, one should consider the following issues:

- if the skin lesions are responsive to ultraviolet radiation;
- if the benefit obtained after phototherapy is sufficient to justify the possible potential risks;
- if the antiretroviral medications and other drugs the patient receives cause photosensitivity.<sup>4</sup>

### PHOTOTHERAPY AND OTHER ASSOCIATED TREATMENTS

Some studies published in medical literature demonstrated the use of an association of PUVA with systemic medications. In comparing the use of acitretin or PUVA alone and as an association, it was observed that combination therapy was more effective and limited the duration of treatment, frequency, and total cumulative dose of UVA radiation.<sup>15</sup> In general, etretinate is initiated two weeks before the etretinate-PUVA combination.<sup>2</sup>

Narrow-band UVB may be associated with other systemic treatments such as retinoids, anthralin, and calcipotriol.<sup>5,9</sup> With systemic retinoids, the carcinogenic potential of UVB can be reduced by decreasing the final total dose of UV radiation.<sup>5</sup> Dithranol and phototherapy are also described as options for treating psoriasis and offer a shorter remission time for this disease.<sup>15</sup> Coal tar associated with phototherapy has been known since Goerckerman,<sup>2</sup> but in comparison to monotherapy it does not seem to be much more effective.<sup>15</sup> Efficacy of treatments using topical corticoids with UVB radiation does not seem to be different when an emollient is used with UVB. Humectants utilized before exposure to UVB may diminish the quantity of light that penetrates the skin, hindering the efficacy of the treatment.<sup>9</sup>

#### LABORATORY TESTS AND CONTRAINDICATIONS FOR PHOTOTHERAPY

When initiating treatment with PUVA, it is wise to order some tests, such as AST/SGOT, ALT/SGPT, alkaline phosphatase, gamma-GT, urea and creatinine, anti-nuclear factor, and beta-HCG, besides an ophthalmological evaluation in order to proceed safely to treatment.

Phototherapy is contraindicated in patients with:<sup>36</sup>

- Xeroderma pigmentosum
- Albinism
- Photosensitive dermatoses, such as lupus erythematosus
- Pemphigus and bullous pemphigus
- Positive past and/or family history of skin cancer (melanoma and non-melanoma). Care should also be taken in patients previously treated with immunosuppressants because of the known role these medications play in enhancing the carcinogenic effects of phototherapy
- Previous use of arsenic or exposure to ionizing radiation
- Previous history of intense exposure to solar light
- Past history of cataracts or aphakia
- Hepatic or renal alterations
- Pacemaker (this contraindication is reported in several articles, but there is no explanation for it).

In pregnant women, the PUVA method is con-

traindicated in light of possible teratogenic effects of psoralen (C category), and in children, the use of PUVA is only allowed in specific situations.<sup>5</sup>

#### SIDE EFFECTS

The side effects are divided into acute and chronic.<sup>37</sup> Acute symptoms may be related to psoralens or to the ultraviolet light itself.

#### Acute symptoms:

1. gastrointestinal symptoms, such as nausea (that may be attenuated by ingestion of food before dosing medication), headaches, dizziness, insomnia and depression;
2. phototoxic effects: erythema, onycholysis, subungual hemorrhage;<sup>5</sup>
3. tachycardia, hypertrichosis, and herpes simplex.

#### Chronic symptoms:

1. carcinogenesis and photoaging;
2. cataracts;
3. xerosis;<sup>5</sup>
4. changes in skin pigmentation, lentigo formation.<sup>5</sup>

During exposure to UVA, the genital region and face should be protected. In men, an increase in cancer of the genital region was described.<sup>9,36</sup> Since the face is an area that already is exposed to light and therefore has a greater possibility of suffering solar damage it should be protected unless it is the area to be treated.

The presence of lentigos was also reported after treatment with PUVA and normally appears between six and 15 months after treatment is begun.<sup>38</sup>

The eyes should be protected with anti-UV safety eyeglasses because of the risk of developing cataracts; this care should extend throughout the entire day of the treatment session.<sup>5,36</sup>

Caution must be taken with medications already in use so that they do not interfere in the absorption of the psoralens, as happens with phenytoin that decreases its absorption, or medications that are known photosensitizers.<sup>36</sup>

#### PHOTOTHERAPY AND SKIN CANCER

In the early 20<sup>th</sup> century, as soon as UV rays began to be recognized as an effective therapeutic form for some skin diseases, the first reports appeared describing the harmful effects of sunlight as a cause for some skin disorders, such as xeroderma pigmentosum, hydroa vacciniforme, prurigo aestivalis, and some types of skin cancer. Paul German Unna was the first dermatologist to associate pro-

longed exposure to sunlight and the onset of skin lesions in sailors.<sup>3</sup>

Treatment with PUVA or UVB is considered carcinogenic since both act at the cellular DNA level and can cause mutations in the skin.

Several studies showed an induction of squamous cell cancer caused by phototherapy. Nevertheless, one must not overlook the fact that patients have a greater predisposition to cancer when they have been submitted to other immunosuppressant treatments such as methotrexate and cyclosporin. In these cases, it is difficult to quantify the influence of phototherapy in inducing skin cancer.<sup>39</sup>

Some studies have shown that PUVA is more carcinogenic than UVB radiation.<sup>5</sup> The fact that PUVA therapy is carcinogenic is linked to the UVA radiation, which when used alone can produce mutations in cells, and to psoralens, which could also show these effects.

The relative risk of squamous cell carcinoma in the skin is greater in patients exposed to high doses of UV radiation, defined as at least 200 sessions or 2000J/cm<sup>2</sup> of PUVA or 300 sessions with UVB,<sup>2,10</sup> and this risk remains elevated even during a decade after treatment discontinuation.<sup>40</sup> On the other hand, the risk of basal cell carcinoma does not increase.<sup>5</sup>

In a study published in 1990, the incidence of squamous cell carcinoma of the penis and scrotum was 286 times higher than expected for the general population in those patients who had been treated with PUVA.<sup>40</sup>

Cyclosporin and methotrexate have immunomodulatory properties and can result in more malignant skin lesions caused by UVB and PUVA.<sup>15</sup> The association of cyclosporin and PUVA may increase the risk of squamous cell carcinoma, but the combinations of UVB and cyclosporin and of methotrexate UVB and PUVA have not yet been well

evaluated.<sup>8</sup> Both combinations of PUVA + acitretin and UVB + acitretin produce good results, and the latter association may also reduce the risk for malignancies induced by phototherapy.<sup>15</sup>

Sunburn is caused by UVB rays that are absorbed by cellular DNA, causing chromosome damage; this is why it is considered the most important risk factor for development of melanomas.<sup>38</sup>

The role UVA plays in the pathogenesis of melanoma is controversial. The capacity of UVA radiation to produce cellular DNA damage was demonstrated many times by means of in vitro observations, photosensitivity reactions that result in the formation of oxidative substances that would lead to mutations and development of cancer, and laboratory demonstrations of immunosuppression in humans and animals.

The risk of melanoma in patients who receive UVB seems to be 2.5 to 7.5% higher than that of the general population, and patients treated with PUVA seem to have a risk five times greater for developing melanoma.<sup>38</sup>

Malignant melanoma induction by phototherapy has been reported.<sup>38</sup> The choice of more aggressive treatments with more than three sessions a week favors the appearance of malignant melanoma in patients with a predisposition for this, especially those who have been submitted to more than 250 phototherapy sessions.<sup>41</sup> In cases of prolonged treatments a periodic dermatologic exam is recommended,<sup>5</sup> and these patients should be taught to examine themselves regularly.<sup>10</sup>

These effects should not influence the choice of phototherapy for treating various dermatoses with precise indications.<sup>42</sup> Actually, there is no study proving an induction of melanoma or non-melanoma skin cancer related to other immunosuppressant treatments. From this point of view, phototherapy treatment is even safer than other therapeutic options since none of the others have yet been researched. □

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