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The dark side of the light: Phototherapy adverse effects

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Abstract Phototherapy is a valuable therapeutic tool in Dermatology, but there may be drawbacks. Acute and long-term adverse effects, of variable severity, include skin erythema, xerosis, pruritus, blistering, altered pigmentation, photoaging, and photocarcinogenesis. Despite concerns over the carcinogenic potential of ultraviolet radiation, most studies have not found an increased risk of non-melanoma or melanoma skin cancer in patients treated with ultraviolet B (broadband and narrowband) and ultraviolet A1 phototherapy. These are therefore considered reasonably safe treatment modalities concerning the development of skin neoplasms, although caution and further investigation are warranted. Photoprotective measures, such as avoidance of concurrent sunlight exposure and covering skin areas not afflicted with disease, or more modern strategies, including phytochemical antioxidants and exogenous DNA repair enzymes, can minimize the hazards of phototherapy. Patients submitted to phototherapeutic regimens should undergo complete, careful dermatologic examination regularly and lifelong.

Introduction

The development of artificial light sources has led to great advances in phototherapy during the last decades, allowing its common use for multiple conditions in Dermatology.[1] The beneficial effects in many inflammatory dermatoses and lymphoproliferative skin diseases are thought to result largely from the ability of ultraviolet radiation (UVR) to induce immunosuppression and alter cell proliferation; however, phototherapy also has some drawbacks. There is a wide spectrum of possible adverse effects of variable severity, the most worrisome being the potential of UVR to induce or stimulate skin carcinogenesis.

This concern is justified by the well-established epidemiologic link between solar UVR exposure and an increased risk of skin cancer, as well as by the evidence that UVR, by impairing immunologic mechanisms of tumor surveillance while disturbing DNA stability, can trigger skin carcinogenesis. However, the magnitude of the photocarcinogenic risk of phototherapy is not yet definitely established. We review the adverse effects of phototherapy, and particularly the state-of-the-art evidence about the development of skin malignant neoplasms in patients treated with this modality, and preventive strategies to minimize such potential risk.

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The bright side of the light: UVR as treatment

The use of artificial UVR for therapeutic purposes started with the combination of topical coal tar and subsequent ultraviolet (UV) irradiation by William Goeckerman (1884-1954) in 1925. The use of broadband ultraviolet B (BBUVB) radiation (280-315 nm) alone began in the 1970s; fluorescent lamps of BBUVB devices emit a wide range of wavelengths (approximately two thirds in the UVB range, the rest primarily in the ultraviolet A [UVA] range). Psoralen-UVA photochemotherapy (PUVA), combining oral or topical psoralens and subsequent UVA exposure, was initiated in the 1970s. Later, the potential of selectively using a subset of the UVB spectrum was explored. Fluorescent bulbs, emitting narrowband UVB (NBUVB) radiation at 311 - 313 nm, were a major advance, giving rise to a more effective and less harmful treatment. UVA1 (340-400 nm) phototherapy, a more recent and safer alternative to PUVA, uses longer wavelength UVR, which penetrates deeper and targets cells residing in or infiltrating the dermis.[2]

Phototherapy has revolutionized Dermatology and is of unquestionable value. In fact, because UVR suppresses the immune system in a more specific fashion, phototherapy can have fewer side effects than conventional, broader immunosuppressive drugs.[3]

The dark side of the light: adverse effects of phototherapy

The UVR used in phototherapy is nevertheless a double-edged sword, whose harmful potential has to be considered. Varying in severity, there are both short-term and long-term, wavelength-dependent adverse effects attributed to phototherapy (Table 1).

Short-term side effects of UVB phototherapy on skin include sunburnlike erythema (NBUVB being approximately 5-10 times less erythemogenic than BBUVB[4]), xerosis accompanied by pruritus, occasional blistering, and an increased frequency of recurrent herpes simplex viral infections.[1,5] The adverse effects of UVA1 are less severe than those of UVB,[1] with studies reporting a low frequency of side effects in UVA1-treated patients[2]; severe acute adverse effects of UVA1 phototherapy have not been reported, whereas common mild acute adverse effects include altered pigmentation (mostly hyperpigmentation), xerosis, and pruritus; although UVA1 is not highly erythemogenic, phototoxicity may occur, especially among individuals with lower skin phototypes.[2,6] PUVA is highly associated with these and other adverse effects, including enhanced systemic toxicity.

Table 1 Short- and long-term adverse effects of phototherapy

Short-term adverse effects	Long-term adverse effects
Skin	***Skin***
Erythema	Photoaging
Xerosis	Photocarcinogenesis
Pruritus	
Blistering	
Altered pigmentation (mostly hyperpigmentation)	
Herpes simplex infections (recurrence)	
Eye	***Eye***
Photoconjunctivitis	Cataractogenesis
Photokeratitis	

Long-term exposure to UVB, UVA1, or PUVA causes profound changes in the skin, including photoaging, cumulative actinic damage, and possibly photocarcinogenesis.[1,5] Skin carcinogenesis is the most feared potential adverse effect of phototherapy, especially in prolonged, repeated phototherapeutic regimens, due to the UVR capacity to disturb the DNA structure and impair tumor immunosurveillance mechanisms.

Phototherapy can also be ophthalmologically hazardous, potentially causing photoconjunctivitis and photokeratitis.[5] Unprotected eye exposure to UVB and deeper-penetrating UVA can even induce cataracts.[7]

Phototherapy and photocarcinogenesis: what is the evidence?

Although there is great concern among dermatologists and patients about the potential of UV phototherapy to induce or stimulate skin carcinogenesis, the actual magnitude of this risk has yet to be fully delineated. First, the design of most studies has been generally suboptimal: many are retrospective analyses with low sample sizes and short follow-up times. Second, there are several confounding factors to be taken into consideration: for instance, studies on phototherapy-associated carcinogenesis generally fail to precisely quantify solar exposure, which is particularly relevant considering that patients with phototherapy-responsive dermatoses might seek more natural sunlight; moreover, patients submitted to phototherapy have often undergone many other topical and, more importantly, systemic therapies, some of which have carcinogenic potential. In addition, the vast majority of data available on this topic have been obtained from psoriatic patients, because they represent the largest group receiving phototherapy. Finally, regular dermatologic follow-up of treated patients accounts for some diagnostic bias, because they are more likely to have skin cancers detected, excised, classified, and registered.

We review here the state-of-the-art evidence about the development of skin malignant neoplasms in patients treated with different phototherapy modalities.

PUVA therapy

Although a thorough discussion about PUVA is beyond the scope of this paper, it is important to mention that this form of photochemotherapy has been better studied than the remaining phototherapy modalities and proven to have a well-established role in human photocarcinogenesis. PUVA is associated with

an increased risk of skin cancer – non-melanoma skin cancer (NMSC) (particularly squamous cell carcinoma [SCC] and, to a lesser extent, basal cell carcinoma [BCC], as well as Merkel cell carcinoma) and melanoma –, also in non-exposed skin areas, with a clear dose–effect relationship.[8–18] About 15 years after the first treatment with PUVA, the risk of malignant melanoma increases, especially among patients receiving 250 or more treatments.[12] This effect is apparent even with low-dose exposures and may persist for many years after cessation of treatment.[8–18]

UVB phototherapy

The first published study on the rate of skin cancer in patients treated with UVB (Goeckerman therapy) appeared in 1980, where 305 patients with atopic dermatitis were followed up for 25 years, during which 11 were diagnosed with NMSC.[19] In 1981, a study on skin cancer incidence in psoriatic patients treated with tar and UVB phototherapy showed no increased risk, as only 19 patients out of 260 developed NMSC in up to 25 years.[20] In a retrospective analysis of a cohort of psoriatic patients, there was no additional increased risk for skin cancer in those treated with tar and UVB.[21] Another study, in which 85 psoriatic patients were extensively treated with UVB for up to 25 years, found no significant difference of prevalence of premalignant/malignant skin lesions in those patients (5.9%) from the control group (10.1%).[22] In a study of 2247 psoriatic patients for up to 15 years, there was an unexpected non-significant lower incidence of NMSC in those treated with UVB (1.2%), compared with control non-treated patients (1.8%).[23] A cohort study including 5687 psoriatic patients revealed a non-significant relative risk of 1.6 for the development of SCC with UVB treatment.[24] An important confounder of such studies assessing the photocarcinogenic risk of UVB phototherapy is that most patients received primarily other treatment modalities.

The American "PUVA Follow-up Study",[9–14,17,25–27] a 16-center prospective, long-term safety trial of PUVA therapy, analyzed the skin cancer incidence upon UVB phototherapy among 1380 psoriatic patients. In 1980, the first analysis of this cohort revealed an odds ratio of 4.7 for cumulative incidence of NMSC in patients with high UVB exposure[25]; however, in an updated corrected analysis the relationship between exposure to UVB phototherapy and NMSC risk was no longer apparent.[11] Later, high UVB exposure (≥ 300 treatments) was found to be associated with a modest but significant increase in SCC and BCC risk, with such skin tumors developing on anatomic sites typically exposed during UVB phototherapy (torso, buttocks, and legs) but not on chronically sun-exposed sites such as the head and neck[27]; this was most apparent among individuals with previous low PUVA exposure (< 100 treatments).[27] Nevertheless, no difference in the risk of NMSC was documented between patients moderately exposed to UVB (100-299 treatments) and those exposed to only 1-99 treatments.[27] Interestingly, an increase (relative risk of 4.6) was found in genital tumors in men from the PUVA cohort treated with high doses of UVB phototherapy.[10] However, it is important to note that all patients in these series of studies share the confounding factor of previous exposure to PUVA, which is firmly associated with an increased risk of skin cancer.

In a study of 496 psoriatic patients also previously treated with PUVA, 111 were treated with UVB as well; 11 cases of skin cancer occurred among the 385 patients not exposed to UVB, whereas only 2 were found in the UVB-treated, resulting in a non-significant relative risk (0.36) of NMSC after UVB therapy.[28]

In 2014, a cross-sectional study found 8 cases (4.9%) of histopathologically verified NMSC among 162 psoriatic patients treated with UVB, some of whom had previously received PUVA, among other treatments; the risk of skin cancer correlated with the number of UVB treatments, but the overall risk of malignancy in the UVB-treated patients was not greater than in the general control population.[29]

Among several reports, only three cases of melanoma were identified among approximately 1000 UVB-treated patients.[21,30] No study provided a relative risk for melanoma.[31]

Although UVB itself is a known carcinogen, worldwide data accumulated over recent decades suggest that the risk of non-genital skin cancer (melanoma or non-melanoma) is not significantly increased by UVB phototherapy. Even though high cumulative UVB exposure might confer a modest increase in NMSC risk, its carcinogenic potential is still significantly (about seven times) lower than that attributed to PUVA[27]; moreover, given the relatively small underlying tumor incidence on the anatomic sites preferentially affected by phototherapy, even an increased relative risk of NMSC in these sites does not translate into a substantially higher absolute incidence of tumors.[27] UVB phototherapy appears to have a reasonably positive safety profile, remaining a relatively low-risk treatment option for many dermatologic conditions.

NBUVB phototherapy

NBUVB is clinically more effective than BBUVB, requiring lower dosages to achieve therapeutic response, and is considered less carcinogenic.[1] Because it has only recently been introduced as a therapeutic tool, the long-term carcinogenic risk of NBUVB is, however, not yet firmly established.[18,31] There are conflicting data from murine studies,[32–36] and only a few studies in humans have considered its relative carcinogenicity.

Prospective studies in patients treated with NBUVB are lacking.[18] A systematic review[18] from 2012 identified only four retrospective studies[4,37–39] focusing on the potential carcinogenic risk of NBUVB used for psoriasis; none of them suggested an alarming increase in the risk of NMSC or melanoma. In a 2004 report about the incidence of skin tumors in 195 psoriatic patients receiving BBUVB or NBUVB, only 1 patient treated with NBUVB developed skin cancer (*in situ* melanoma), and this happened within the first year of phototherapy, most likely ruling out treatment-related photocarcinogenesis.[4] In 2005, another group saw no increased incidence

of SCC or malignant melanoma in 1908 patients treated with NBUVB, with 4 years of median follow-up and a median cumulative number of treatments of 23 (1-199)[37]; however, a small but significant increase of BCC was detected with NBUVB use (10 patients developed BCCs, whereas 4-7 were expected in the control population).[37] A 2006 report found that the skin cancer rate recorded among 484 patients treated with NBUVB for a variety of skin disorders (mostly psoriasis) was as expected in the general population.[38] Another group, aiming to define the long-term carcinogenic risk of NBUVB treatment in humans, studied 3867 patients for up to 22 years (24,753 person-years), with a median cumulative number of 29 treatments (352 patients received ≥ 100 treatments)[39]; their results, published in 2008, indicated no significant association between NBUVB treatment and BCC, SCC, or melanoma, with a modest greater incidence of BCCs among patients also treated with PUVA.[39]

If the carcinogenic risk of NBUVB were as great as that of other treatment modalities, such as PUVA, then an increased cancer incidence would have been expected to have been detected by now.[39] NBUVB is therefore considered a well-tolerated form of phototherapy so far, possibly even less carcinogenic than BBUVB.[1] Nevertheless, these reassuring results should be cautiously interpreted, because the slow evolution of skin cancers may result in a delayed incidence peak yet to be reached in the treated patients.[39] Also, relatively few patients have been exposed to high-NBUVB in the published studies.[39] Ongoing risk assessment is essential, and longer monitoring and treatment periods in larger, controlled prospective studies are needed for accurate assessment of the carcinogenic risk of NBUVB phototherapy.[18,31]

UVA1 phototherapy

UVA1 phototherapy has been found to be relatively free of side effects.[2] Since the widespread use of this modality began, no serious associated negative side effects in humans have been reported.[1] Nevertheless, concerns about the potential photocarcinogenic risk of UVA1 phototherapy (especially for the development of melanoma) still persist because thorough investigation on this topic has not been pursued.

There has been a single case report of melanoma developing in a patient with mastocytosis who received intense UVA1 treatment[40]; however, this patient had previously received PUVA bath therapy, so a definite link between melanoma and UVA1 phototherapy could not be established.[40] Two cases of Merkel cell carcinoma have also been reported in immunocompromised patients treated with high-dose UVA1.[41] The results of a European prospective longitudinal study, intending to monitor patients treated with UVA1 phototherapy for the development of skin cancer, are awaited.[1]

Considering this, UVA1 phototherapy is an option for several skin conditions, but cautious treatment regimens are recommended[1] because its true carcinogenic risk has not been determined. As for NBUVB, continuous risk assessment and further investigation are required.

Prevention

The acute and long-term side effects of phototherapy can be prevented, or at least minimized, by judiciously limiting and recording the UVR dose and the number of treatment sessions, adjusted accordingly to skin phototype (Table 2). However, because most dermatologic conditions requiring phototherapy are chronic, repeated sessions are generally necessary, leading to higher cumulative levels of UVR; consequently, the lifetime probability of adverse events, including mutagenic effects, can be higher. Findings from clinical research permit cautious optimism when pondering the skin cancer risk of phototherapy. In fact, unlike for PUVA, there is currently no clear recommendation on the number of sessions, after which phototherapy with UVB (BBUVB or NBUVB) and UVA1 must be discontinued to hedge their potential photocarcinogenic risk. Quantitative UV dosimeters for phototherapy (Table 2) would allow determination of the energy absorbed by the skin targets. Dermatologists could thus maximize the biologic therapeutic effects of UVR, while minimizing the hazardous consequences of overexposure; however, this is an underdeveloped area.[42]

Safety measures are recommended for photoprotection of patients undergoing phototherapy (Table 2)[5,6]:

1. The face, if not involved, should be protected either by sunscreen with sun protection factor (SPF) of 50+ or a cloth barrier.
2. The eyes should be protected by wearing UV-blocking goggles; patients with photoresponsive dermatoses involving the eyelids may use UV-blocking contact lenses instead; eyelids themselves block the majority of

Table 2 Preventive strategies against the potential adverse effects of phototherapy

General measures
Limiting UVR (cumulative) dose
Quantitative UV dosimeters
Avoidance of concurrent sunlight exposure
Regular complete dermatologic examination
UVR blockade
Facial protection (eg, SPF50+ sunscreen)
UV-blocking goggles or contact lenses
Genital shielding
Countering UV damage
Antioxidant agents (oral/topical)
Vitamin A, retinoids
COX-2 inhibitors, NSAIDs
PAF and 5-HT_{2A} receptor antagonists
Xenogenic DNA repair enzymes (T4N5, photolyase, OGG1)

5-HT, serotonin; *COX-2,* cyclooxygenase 2; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *OGG1,* 8-oxoguanine DNA glycosylase 1; *PAF,* platelet-activating factor; *SPF,* sun protection factor; *T4N5,* T4 endonuclease V; *UV,* ultraviolet; *UVR,* ultraviolet radiation.

radiation, but protection is recommended when possible because eyelid closure may be incomplete, or patients may inadvertently open their eyes during phothoterapy.[43]
3. If not afflicted, the genitalia should be shielded (by underwear, for instance).
4. Concurrent natural sun exposure should be avoided.

Importantly, patients should undergo a thorough dermatologic examination before starting phototherapy and be monitored regularly and lifelong for the development of significant actinic damage, premalignant lesions, and skin malignancies (Table 2). Follow-up care should be continued even after the eventual treatment discontinuation, because an increased cancer risk persisting afterward cannot be securely ruled out at this point. Educating patients to perform skin self-examination is also of great value.

UV-induced oxidative stress is a major contributor to photocarcinogenesis, conditioning skin cell mutagenesis, tissue remodeling, inflammation, and immunosuppression. As a result, photoprotective strategies using oral, or to a lesser extent topical, antioxidant agents, namely phytochemical derivatives, have gained increased attention for their potential anti-neoplastic properties (Table 2).[44–47] Such botanic antioxidants include polyphenols (flavonoids and non-flavonoids), non-phenolic derivatives, and whole plant extracts, which are present in various vegetables, fruits, beans, cereals, and beverages, such as tea, cocoa, and wine. These can also be found as concentrated dietary supplements and skin care products.[44–47]

Vitamin A and its derivatives are largely beneficial in preventing skin cancer (Table 2) because they promote differentiation, growth arrest, and apoptosis of epidermal keratinocytes.[31,45,48] Retinoids have actually been found effective in preventing NMSC in high-risk patients, namely those submitted to large doses of PUVA.[49] Associating these agents with phototherapy treatment regimens may have potential anti-cancer benefits in the long term. Topical retinoids should, however, be used cautiously because they may cause photosensitivity which is why these agents are commonly not used simultaneously.

The synthesis of cyclooxygenase 2 (COX-2), not constitutively expressed in normal epidermis, is markedly increased after UVR exposure.[48] This enzyme is required for the formation of prostaglandin E_2, which has been implicated in UV-induced tumor promotion and progression.[48] Considering this, COX-2 inhibitors (Table 2), such as celecoxib, have been used in animal models to prevent UV-induced skin cancers with success.[50–52] Epidemiologic evidence suggests that patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) on a regular basis have lower incidence of SCCs.[53]

The platelet-activating factor (PAF) and cis-urocanic acid (binding to the receptor 5-HT_{2A}) are also mediators of photoimmunosuppression and photocarcinogenesis. The preventive potential of PAF and 5-HT_{2A} receptor antagonists is being explored (Table 2),[54,55] with mice experiments indicating their ability to reverse photocarcinogenesis by accelerating UV-induced DNA damage repair by the nucleotide excision repair (NER) complex.[54]

Considering the key role of DNA repair systems in preventing photocarcinogenesis, three xenogenic DNA repair enzymes are therapeutic candidates for reversing UV-induced damage in human skin when applied topically in liposomal form (Table 2)[56]:

1. T4 endonuclease V (T4N5) is a bacterial enzyme that prevents mutations in UV-irradiated keratinocytes by removing cyclobutane pyrimidine dimers (CPDs); it has been found to reduce the incidence of actinic keratoses and BCCs in patients with NER defects.[57]
2. Photolyase, derived from a photosynthetic plant, has been proven effective in reverting DNA photoproducts (CPDs and 6-4 photoproducts) after UVB irradiation when given in exogenous preparations.[58]
3. Exogenous oxoguanine DNA glycosylase-1 (OGG1), the enzyme recognizing and initiating the repair of UV-induced DNA oxidative damage (8-oxoG), has produced reductions in skin tumor size and malignant transformation rates in UV-irradiated mice.[59]

These promising results suggest that the use of skin care products containing such enzymes may be of interest in the reversal of photodamage and for skin cancer prevention in patients treated with phototherapy.

Conclusions and perspectives

The use of UV light in Dermatology is a double-edged sword, having both therapeutic and harmful effects, the most feared being photocarcinogenesis. Although both UVB and UVA are established skin carcinogens and are associated with the development of skin neoplasms in humans, current phototherapy protocols have not been found to be significantly associated with an increased risk of skin cancer. Unlike for PUVA, the best available evidence regarding the carcinogenic risk of phototherapy is reassuring, especially when considering the increasingly used selective spectra (NBUVB and UVA1). Phototherapy is currently cautiously assumed to be a reasonably safe treatment option, provided that photoprotective measures and regular, lifelong clinical vigilance are guaranteed.

Ongoing risk assessment is required, and the need for further investigation cannot be overemphasized. Larger, controlled prospective studies, with longer follow-up and treatment periods, would not only enlighten us about the true carcinogenic risk of phototherapy but also improve educated risk–benefit clinical decision making.

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