Targeted phototherapy

Fototerapia celowana

Zonun Sanga

Department of Skin and VD, RNT Medical College, Udaipur, India

ABSTRACT

Conventional phototherapy uses a whole body cabinet or body part machines for the hand, foot or scalp. It has many disadvantages, due to which new phototherapy techniques have been developed. These new techniques are called targeted phototherapy. They include excimer laser, the intense pulse light (IPL) system, photodynamic therapy, and an ultraviolet (UV) light source with a sophisticated delivery system which is easy to operate by hand. The mechanisms of action of targeted phototherapy systems are similar to those in conventional UVB/UVA therapy. They have many advantages including lower risk of side effects, avoidance of exposure of unnecessary sites, faster response, and shorter duration of treatment. But they also have disadvantages such as high costs and inability to use them for extensive areas. This review article discusses targeted phototherapy, its mechanisms of action, and advantages and disadvantages in comparison to conventional phototherapy.

STRESZCZENIE

INTRODUCTION

Phototherapy is a therapeutic strategy in dermatology for treating several skin diseases. Conventional phototherapy uses a whole body cabinet or body part machine such as hand, foot or scalp machines [1, 2]. It includes broadband ultraviolet B (UVB) therapy, ultraviolet A (UVA) therapy, SUP or selective ultraviolet phototherapy (310–318) therapy, narrowband UVB (311 nm), and ultraviolet A1 (UVA1) therapy. Phototherapy is used for a wide variety of skin diseases. There has been considerable progress in cellular and cutaneous photobiology leading to improved understanding of different photodermatoses and their treatment. However, the developments in phototherapy have been comparatively slow, as reflected in a recent publication stating that “developments in phototherapy have not kept pace with scientific progress, as has been the case with radiotherapy” [3].

Conventional phototherapy has many disadvantages including exposing uninvolved areas, a slow delivery system and lengthy treatment sessions, multiple and frequent visits to the clinic, difficulty in treating certain areas (such as genitalia, oral mucosa, ear, etc.), difficulty in treating children who may feel intimidated by the large machines, and the large office space required to house the bulky machines [4]. Due to these disadvantages of conventional phototherapy, a new phototherapy technique was developed to overcome these problems. This technique was called targeted phototherapy and is also known as concentrated phototherapy, focused phototherapy, microphototherapy and localized phototherapy. This review mainly focuses on this newer technique called targeted phototherapy.

Targeted phototherapy is defined as a therapeutic method using a device that delivers laser light or ultraviolet light spectrum of a specific wavelength focused on specific body areas or lesions. This definition includes different technologies used, such as excimer laser, intense pulse light system (IPL), photodynamic therapy, and ultraviolet (UV) light source with a sophisticated delivery system which is easy to operate by hand [3].

MECHANISM OF ACTION

Most phototherapy devices (laser or non-laser type) emit radiation in the UVB range, with peak emission in the narrowband wavelength (around 308–311 nm), while some light-based nonlaser machines emit UVA radiation also. Hence mechanisms of action of targeted phototherapy systems are similar to those in conventional UVB/UVA therapy [2, 5–8]. Ultraviolet light has a spectrum which is divided into 3 parts according to their wavelengths, namely UVC with the shortest wavelength (200–290 nm), UVB with the intermediate wavelength (290–320 nm) and UVA with the longest wavelength (320–400 nm). Ultraviolet A is then divided into UVA1 (340–400 nm) and UVA2 (320–340 nm) [9, 10]. The light sources include broadband UVB (BB-UVB) with a wavelength of 290–320 nm and a peak at 313 nm, narrowband UVB (NB-UVB) with a wavelength of 311–313 nm, UVA (320–400 nm, peak at 355 nm), and UVA1 (340–400 nm, peak at 365 nm). Excimer laser, which emits monochromatic UV light, has various wavelength ranges depending on the molecules used. Especially in the field of dermatology, XeCl laser with a wavelength of 308 nm is used. Various mechanisms have been found, and it was proposed that phototherapy can give either a systemic or a local effect. Ultraviolet B rays have shorter wavelengths, so they do not penetrate as deeply as UVA rays do, but UVB rays have more energy. Ultraviolet B phototherapy’s primary effect is on the function of keratinocytes and Langerhans cells. The effectiveness of UVB therapy in psoriasis depends especially on its antiproliferative effects. The decrease of pruritus after treatment with both BB-UVB and NB-UVB is caused by cell mast apoptosis [11]. In the use of targeted BBUVB phototherapy, NBUVB and excimer laser, T cell apoptosis was found [12–14]. The apoptosis mechanism may be caused by the damage of the epidermis and dermis cells, which are susceptible to UV light exposure. Ultraviolet B rays cause DNA damage and formation of pyrimidine dimmers [15]. In addition to T cell apoptosis, UVB radiation triggers changes in cytokine production, local immunosuppression and stimulation of melanocyte-stimulating hormone (MSH), and increases migration, proliferation of melanocytes and melanogenesis [16, 17]. A two-step effect of NB-UVB has been proposed – both of them may occur simultaneously though. Firstly, there is immunomodulation (local as well as systemic), leading to downregulation of the immune attack against melanocytes. Subsequently, the melanocytes are stimulated to migrate to the epidermis and synthesize melanin [18]. NB-UVB phototherapy increases synthesis of interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α) and leukotriene-4 (LTC-4), and these cytokines induce melanocyte mitogenesis, melanogenesis and melanocyte migration. However, the roles of IL-1 and TNF-α in melanogenesis are controversial and contradictory, as has been observed in some studies. It was proposed that TNF-α inhibits the expression and activity of tyrosinase, the key enzyme in melanin synthesis. This inhibition of melanogenesis induced by TNF-α is secondary to activation of nuclear-factor κB [19]. Interleukin-1 stimulates synthesis of endothelin-1, which is mi-
togenic and melanogenic. The contradiction is that IL-1β has been found to reduce proliferation of melanocytes and melanogenesis, while IL-1β reduces melanocyte tyrosinase activity without any effect on proliferation [20]. It was also observed that the increase of expression of endothelin-1, IL-1 and tyrosinase in human keratinocytes in vivo and in vitro after UVB irradiation suggested the possible mechanism of repigmentation [21]. Release of prostaglandins (PGE₂ and PGF₂) is another mechanism of action of phototherapy [22]. Prostaglandin E₂ is synthesized in the skin and regulates melanocyte and Langerhans cell function, and promotes melanocyte mitogenesis [23]. Ultraviolet A has a longer wavelength, so it can reach the dermis and have an effect on fibroblasts, dermal dendritic cells, endothelial cells, T lymphocytes in the dermis and granulocytes. In atopic dermatitis, UVA is shown to cause apoptosis of T helper cells in the skin with eczema lesions through the FAS/FAS ligand system [24]. In addition, UVA and UVA1 irradiation may also reduce histamine release by basophils and mast cells [25]. The combination of UVA and psoralen (PUVA) has a more complex mechanism. Psoralen undergoes intercalation in the double-stranded DNA. Ultraviolet A exposure causes the formation of a 3,4 or 4',5' cyclobutane monoaduct with pyrimidine bases on a single photon absorption. The double helix DNA then undergoes a crosslinking process when the second light photon is absorbed by 2 monoaducts forming a bifunctional adduct. DNA replication is inhibited by the cross-linking, resulting in cell cycle disruption and decreased epidermal proliferation. Once psoralen is excited by the photons, it can react with oxygen molecules to form reactive oxygen species (ROS), which can cause mitochondrial dysfunction and apoptosis of Langerhans cells, keratinocytes and lymphocytes. Both UVA and UVB cause decreased expression of intercellular adhesion molecule 1 (ICAM-1) and increased levels of immunosuppressive cis-urocanic acid that can depress the cellular immune response and inhibit Langerhans cell activities [26]. Although the mechanism of action of targeted phototherapy is similar to the mechanism of action of conventional UVB/PUVA phototherapy, it is thought to be more aggressive because the dose given can be higher than the erythemogenic dose, which results in greater efficacy due to its ability to deliver the energy to the deeper dermis layer [27–33].

**ADVANTAGES OF TARGETED PHOTOTHERAPY OVER CONVENTIONAL PHOTOTHERAPY**

Several advantages have been claimed for targeted phototherapy: exposure of involved areas only and sparing of uninvolved areas, thus minimizing acute side effects such as erythema and long-term risk of skin cancer over unaffected skin; quick delivery of energy and thereby shortened duration of treatment; delivery of higher doses (super-erythemogenic doses) of energy because uninvolved areas are not exposed; these higher doses of energy can be delivered selectively to the lesions, thereby enhancing efficacy and achieving a faster response; shortening of the duration of treatment, leading to less frequent visits to the clinic, which is more convenient for the patient; the maneuverable hand piece allows treatment of difficult areas such as scalp, nose, genitals, oral mucosa, ear, etc; easy administration for children as delivery is hand-held, and it also occupies less space [30].

**DISADVANTAGES OF TARGETED PHOTOTHERAPY OVER CONVENTIONAL PHOTOTHERAPY**

Targeted phototherapy devices have certain disadvantages: They are more expensive. Also, they are not adequate to treat extensive areas in view of the cost of treatment and time involved in treatment. They are not recommended for use if lesions cover more than 10% of the body area [30, 31].

**CONVENTIONAL PHOTOTHERAPY**

In one study, after treating vitiligo with NB-UVB administered as monotherapy 3 times a week [34], 5 of the 7 patients achieved more than 75% repigmentation with a mean of 19 treatments, whereas the remaining 2 patients had 50% and 40% repigmentation after 46 and 48 treatments respectively. In another study, higher success rates were observed with NB-UVB (63%) than with oral PUVA (51%) [35]. As in the western population, NB-UVB phototherapy produces a cosmetically good color match in Indian patients [36]. Its distinct advantages over PUVA include the lack of psoralen-related side effects and precautions, cosmetically better color match, and its safety in children. However, the relative stability of NB-UVB-induced repigmentation over PUVA, its maximum safe duration and cumulative dose allowed still remain to be determined.

The NB-UVB lamp was developed as a “new” UVB phototherapy source with an emission spectrum within the therapeutic waveband for psoriasis phototherapy. NB-UVB phototherapy has a higher ratio of therapeutic to erythemogenic activity, resulting in increased efficacy, reduced incidence of burning and longer remission. Results from two therapeutic action spectroscopy studies indicated that wavelengths of the range 295–320 nm are effective in...
clearing psoriasis, whereas shorter wavelengths are more erythemogenic, and wavelengths longer than 320 are less therapeutic [37, 38]. Subsequent clinical studies have tended to report significantly greater improvement of psoriasis with NB-UVB including reduced incidence of burning episodes, increased efficacy and longer remission when compared with broad band sources [39]. When NB-UVB phototherapy and PUVA were compared, there was little overall difference in efficacy [40, 41].

Prophylactic low dose NB-UVB has been found to be useful in various predominantly UVA induced photosensitivity disorders such as polymorphic light eruption, actinic prurigo, hydroa vacciniforme and cutaneous porphyrias by providing a ‘hardening photoprotective’ effect. A typical course involves 10–15 treatments given in early spring [42]. We have also observed a beneficial role of NB-UVB in patients with airborne contact dermatitis to Parthenium hysterophorus, a frustrating problem for both the patient and the physician [43].

NEWER/TARGETED PHOTOTHERAPY

Excimer laser/excimer light (308 nm)

The various uses of excimer laser include palmo-plantar pustular psoriasis, plaque-type psoriasis, nail psoriasis, chronic atopic dermatitis of the hands, non-atopic dermatitis of the hands and alopecia areata. The common side-effects include intense erythema and, more rarely, blisters, but these are usually well tolerated [32].

Nisticò et al. [32] described different applications of monochromatic excimer light in skin diseases in 152 patients with stable and localized plaque psoriasis, 47 with palmoplantar psoriasis, 7 with palmoplantar pustulosis, 32 with vitiligo, 11 with prurigo nodularis, 9 with mycosis fungoides stage I a, 8 with alopecia, 5 with localized scleroderma, 5 with genital lichen sclerosus, and 3 with granuloma annulare. The treatment produced complete remission in more than 50% of patients with plaque psoriasis and palmoplantar dermatoses, respectively, complete remission in all patients affected by mycosis fungoides, excellent repigmentation in one third of vitiligo patients, hair regrowth in three patients with alopecia areata, an overall improvement in prurigo nodularis, a partial remission in patients affected by localized scleroderma, and a complete remission in most of the patients with genital lichen sclerosus and granuloma annulare [33].

Dualight

Previously called Theralight TM, Inc., it emits both UVA radiation in the range 330–380 nm and UVB in the range 290–330 nm with a peak at 303 nm [5]. The system has a 2-meter long fiber-optic delivery system, with a spot size of 4 cm². UVA intensity is 10–550 mW/cm² for a 3.63-cm² exit aperture, while UVB intensity is 50–250 mW/cm² for a 3.63-cm² exit aperture.

B clear targeted photoclearing system

The B clear system is mercury-based noncoherent UVB radiation with a therapeutic wavelength of 290 nm to 320 nm and pulse width of 0.5 s to 2.0 s. Fluence ranges from 50 to 800 mJ/cm² in increments of 10 mJ/cm². Its disadvantage is that only the UVB range is available, unlike Dualight, which delivers both UVA and UVB ranges [2, 44].

Photodynamic therapy

Photodynamic therapy (PDT) involves the use of photochemical reactions mediated through the interaction of photosensitizing agents, light, and oxygen for the treatment of malignant or benign diseases. Photodynamic therapy is a 2-step procedure. In the first step, the photosensitizer is administered to the patient by one of several routes (e.g., topical, oral, intravenous), and it is allowed to be taken up by the target cells. The second step involves the activation of the photosensitizer in the presence of oxygen with a specific wavelength of light directed toward the target tissue. Then there occurs a sunburn reaction, which usually heals within 4–8 weeks. Because the photosensitizer is preferentially absorbed by hyper-proliferative tissue and the light source is directly targeted at the lesional tissue, photodynamic therapy achieves dual selectivity, minimizing damage to adjacent healthy structures. The photosensitizers are aminolevulinic acid (ALA) and methyl aminolevulinate (MAL), porphyrin sodium (Photofrin), benzoporphyrin derivative monoacid ring A, tin ethyl etiopurpurin, and lutetium texaphyrin [45–48].

Light at a wavelength corresponding to a peak of the porphyrin excitation spectrum in tissues is used. The Soret band (approximately 405–420 nm) is the most important excitation peak for protoporphyrin IX and is included in the spectral output of the US Food and Drug Administration (FDA)-approved Blu-U device, which is used with ALA. Another peak in the excitation spectrum for porphyrins includes red light at approximately 635 nm, which is targeted by different devices, including those approved to be used with MAL [34, 36–38].

Light sources used in PDT include laser and non-laser light. Laser light has the advantages of being [45]: monochromatic (exactly one color/wavelength that corresponds to the peak absorption of the photosensitizing agent); coherent (able to focus light waves
at a specific site); intense (high irradiance allowing for shorter treatment times).

The only FDA-approved indication for ALA photodynamic therapy and MAL photodynamic therapy in dermatology is currently the treatment of actinic keratoses (AKs). Common off-label uses include the treatment of BCC, photaging, acne vulgaris, and Bowen disease [49–51].

Side effects of PDT are due to hypersensitivity to light of treated areas. The photosensitivity usually lasts about 24 h (depending on the specific agent). Side effects may include [45]: burning/stinging sensation; swelling and redness; crusting; pruritus; peeling and blisters; skin infections.

The treated area should be protected from light exposure using a dressing. A local anesthetic such as lignocaine (lidocaine) spray may be applied to the treatment area before or during stage 2 of the procedure to help relieve pain [51].

The author’s experience is that although excimer light is effective for treatment of stable localized vitiligo and psoriasis, its efficacy is limited for treatment of alopecia areata.

References

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