Introduction

Photodynamic therapy (PDT) \(^{1,2}\) is a novel non-invasive cancer therapy, in which photosensitive substances are selectively accumulated in target cells, followed by generation of active cytotoxic oxygen by excitation light and destruction of the target cells. In 1990, Kennedy and co-workers \(^{3}\) introduced the photosensitizing prodrug: 5-aminolevulinic acid (ALA) as a new photosensitizing agent. ALA itself is not a photosensitizer, but it takes advantage of the intrinsic cellular hem biosynthetic pathway to produce photoactive porphyrins. Using a series of enzymatic reactions between the mitochondria and the cytosol, exogenously administered ALA is ultimately converted to fluorescent protoporphyrin (Pp) IX endogenously in tumor tissues. \(^{4,5}\)

Topical PDT is an accepted treatment for non-
melanoma skin cancers especially superficial lesions. PDT using ALA or its methyl ester (MAL) is a very effective method to treat actinic keratoses (AKs) and Bowen’s disease (BD). 2-4,5

Guidelines for topical PDT were established by the British Photodermatology Group in 2008. 2) Multicenter randomized controlled studies have now demonstrated a high efficacy of PDT for AKs and BD. MAL-PDT cleared 69% of predominantly thin and moderate thickness actinic keratoses of the face or scalp after a single treatment, 6) increasing to 89-91% clearance when two treatments were performed 7 days apart. 7,8) Topical ALA-PDT cleared, on average, 86-93% of lesions of Bowen’s disease after one or two treatments. 4) Regarding treatment efficacy, no significant difference in lesional response was found between ALA-PDT and MAL-PDT. 9)

However, skin pigmentation affects light penetration in PDT and higher light doses and longer irradiation times are required for darker skin. It seemed possible, therefore, that topical PDT would be less effective in brown-skinned individuals including Japanese patients than in white Caucasians.

Itoh et al. demonstrated for the first time that three to six treatments with 50-250J/cm 2 of PDT were needed to achieve a cure rate of 82% for facial AK in Japanese patients. 10) We reported earlier on a pilot study to assess the efficacy of PDT in 30 Japanese patients with AKs using our protocol. 11)

We have here attempted to establish a standard treatment modality for ALA-PDT in Japanese patients in order to evaluate and improve the effects of PDT in the treatment of AKs and BD.

PDT has been used for the treatment of extramammary Paget’s disease and mycosis fungoides, Kaposi’s sarcoma, and actinic cheilitis. PDT cannot be recommended for the treatment of squamous cell carcinomas. 5) Malignant melanoma and other pigmented tumors are resistant to PDT because of absorption of light by melanin.

ALA has the ability to penetrate sebaceous glands as well as skin tumors. Topical ALA application to skin induces an accumulation of PpIX not only in epidermis but also in its adnexa including hair follicles and sebaceous glands.

PDT is used for the stimulation of immunomodulatory effects, 12) such as induction of transcription factors, especially AP-1 and NFκB. These act on cytokine formation in keratinocytes, inflammatory cells in the epidermis and dermis, and stimulation of collagen synthesis. Reactive oxygen species destroy the bacterial sheath and also lead to oxidation of bacterial lipids and amino acids.

Therefore, a therapeutic benefit of PDT is evident in inflammatory and other dermatoses such as acne vulgaris, alopecia, psoriasis, sarcoidosis, localized scleroderma, sebaceous hyperplasia, verruca vulgaris, leishmaniasis, wound healing and photorejuvenation.

Patients and methods

Patients

All patients were Japanese and were diagnosed in our outpatient clinic of the Department of Dermatology, Aichi Medical University Hospital in Japan, between 2005 and 2009. All patients had at least one primary AK or BD diagnosed histologically. A total of 152 lesions of AKs and 48 lesions of BD were treated with ALA-PDT using our protocol. The mean age of patients with AKs was 76.7 years (range, 48-95 years), and for those with BD, it was 76.2 years (range, 41-92 years). The sex distribution was 39 males and 47 females in the AK group, and 24 males and 19 females in the BD group. The average diameter of lesions was 11.7mm (range 9.9-12.1mm) for AKs, and 18.2mm (range16.1-20.2mm) for BD. Lesions were located at different sites of the body. The most commonly treated lesions were located on the face of AK patients, and on the extremities of those with BD (Table 1).

We have treated other skin tumors and non-oncological diseases with ALA-PDT in Japanese patients.

Informed consent concerning the objectives, technical details and side effects of PDT was obtained from all patients.

Methods

Surface scales or crusts on the skin lesions were removed three times by tape stripping, and a 20% oil-in-water emulsion (Japanese Pharmacopoeia, Merck Hiei Ltd. Osaka, Japan) of ALA (Sigma, St Lois, MO, U.S.A.) was then applied to the lesions, which were occlusively dressed with a cling film and covered with aluminum foil for light protection. About 4 hours after application of ALA, lesions were treated in three sessions one week apart with 50J/cm²•100mW/cm² for a total dose of 150J/cm 2 irradiation for AKs, and 100J/cm²•100mW/cm² for a total dose of 300J/cm² irradiation for BD, using a pulsed (10 nsec) excimer-dye laser (PDT EDL-1, Hamamatsu Photonics K.K., Hamamatsu, Japan) emitting 630 nm laser light with a spot of about 10mm in diameter. For larger lesions,
lesions were irradiated in several spots without inter-
vening spaces.

The single irradiation doses of 50J/cm² for AK, and 100J/cm² for BD were chosen for ALA-PDT based on the following findings. For AK, we measured the fluorescence intensity of ALA-induced PpIX based on the ratio of R(636nm, PpIX fluorescence)/G(500nm, autologous fluorescence) at the surface of the lesions, using a laser spectrometer (VLD-V1 version 2; M&M Co. Tokyo, Japan; excitation 405nm, peak emission 635nm) before irradiation and just after 25 and 50J/cm² irradiation respectively. PpIX was almost consumed just after exposure to the 50J/cm² irradiation dose with an excimer-dye laser 4h after ALA application. For BD, we similarly measured R/G before and after irradiation with 50 and 100J/cm². PpIX was almost consumed after exposure to the 100J/cm² irradiation dose.

The procedure of three irradiation treatment ses-
sions was chosen for ALA-PDT based on the following findings. We have evaluated the effectiveness of one, two or three treatments 2-3 weeks apart of ALA-PDT for AKs and BD between 2002-2005. We achieved com-

Table 1: Results of ALA-PDT for actinic keratoses and Bowen’s disease with a follow-up of 12 month

<table>
<thead>
<tr>
<th>Actinic keratoses</th>
<th>Bowen’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. lesions</td>
<td>152</td>
</tr>
<tr>
<td>No. patients</td>
<td>86</td>
</tr>
<tr>
<td>Sex No. M/F</td>
<td>39/47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age, mean (range) y.</th>
<th>76.7 (48-95)</th>
<th>76.2 (41-92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>75.8 (48-94)</td>
<td>72.1 (41-83)</td>
</tr>
<tr>
<td>Female</td>
<td>77.5 (48-95)</td>
<td>81.3 (65-92)</td>
</tr>
<tr>
<td>Total range</td>
<td>76.7 (48-95)</td>
<td>76.2 (41-92)</td>
</tr>
</tbody>
</table>

| Average size of lesion (mm) | 11.7 (9.9x12.1) | 18.2 (16.1x20.2) |
| (Min-Max)                  | 2-50            | 2-60            |

| Histologically proven     | 152/152 (100%) | 48/48 (100%)   |
| Pre-PDT                   | 147/152 (98%)  | 45/48 (98%)    |
| Post-PDT (1M)             |               |               |

| Complete response (CR)    | 124/152 (81.6%) | 36/48 (75.0%) |
| Overall lesions           |               |               |
| Face/Scalp                | 109/125 (87.2%) | 4/7 (57.1%)   |
| Trunk                     | 19/27 (70.3%)  | 8/9 (88.9%)   |
| Extremity                 | 24/32 (75.0%)  |               |

| Partial response (PR)     | 9/152 (5.9%)   | 8/48 (18.8%)  |
| No-response (NR)          | 18/152 (11.8%) | 3/48 (6.3%)   |
| Missing                   | 1/152 (0.7%)   | 1/48 (2.1%)   |

| Recurrence rate in 12 months | 14/152 (9.2%) | 12/48 (25.0%) |
|                            |               |               |

TOPOICAL PDT OF SKIN DISEASES IN JAPAN
plete response (CR) rates of 70.4% (50/71 lesions) with one, 72.2% (39/54 lesions) with two, and 81.4% (35/43 lesions) with three treatment sessions for AK, and 50.0% (10/20 lesions) with one, 68.7% (11/16 lesions) with two, and 69.2% (9/13 lesions) with three treatment sessions for BD. Further, we chose a one-week interval between irradiations, since we observed the disappearance of AK tumor cells and regenerative thickening of the epidermis histologically at one week after ALA-PDT.13)

One month after the final treatment with ALA-PDT, treated lesions were evaluated by clinical inspection and biopsies of all lesions were taken. Complete clinically improved eruption together with histological disappearance of atypical cells was evaluated as a complete response (CR). Complete either clinical or histological remission was evaluated as a partial response (PR), no complete clinical or histological remission was considered as a no-response (NR). The patients were followed-up every 3 months up to 12 months.

Results

Analysis of our treated patients is shown in Table 1. We treated a total of 152 AK lesions and 48 BD lesions with ALA-PDT. One month after treatment, an overall complete response rate of 81.6% (124/152 lesions) was observed for AK (Fig. 1). With respect to locations, the CR rate was 87.2% (109/125 lesions) on the face/scalp and 70.3% (19/27 lesions) for other lesions. For BD, an overall CR rate of 75.0% (36/48 lesions) was observed (Fig. 2). The CR rates on the trunk, extremities and face/scalp were 88.9% (8/9 lesions), 75.0% (24/32 lesions), and 57.1% (4/7 lesions) respectively. The recurrence rates after 12 months were 9.2% (14/152 lesions) for AKs, and 25.0% (12/48 lesions) for BD. These cases were retreated and 64.2% (9/14 lesions) of AKs, and 41.6% (5/12 lesions) of BD lesions responded.

We have earlier reported on a case of actinic cheilitis 14) and on patients with extramammary Paget’s disease 15,16) treated with PDT, with satisfactory outcome in both clinical and pathological aspects. For mycosis fungoides of patch and plaque lesions, regression of eruption and histological disappearance of atypical lymphocytes in the lesions were achieved with PDT.17) For the treatment of cutaneous sarcoidosis, ALA-PDT was useful with excellent cosmetic results (Fig. 3).18) We treated a case of recurrent sarcoïd flexor tenosynovitis of the hand with PDT using ALA injected into the tendon sheath, which resulted in reduction of the lesional swelling with no recurrence. 19) For recalcitrant warts, PDT provided beneficial results (Fig. 4).20) We have described cases of toenail onychomycosis that were successfully treated with PDT (Fig. 5). 21) Also, we have treated cases of sebaceous hyperplasia, pustulosis palmoplantaris, lichen sclerosus et atrophicus, cutaneous pseudolymphoma 22) and Bowenoid papulosis.

Regarding the safety of ALA-PDT, erythema just after the treatment and subsequent pigmentation were seen in all patients. The pigmentation disappeared at the latest in 3 months. No scar was seen 12 months after treatment. All patients complained of some pain of various degrees at the time of ALA-PDT, but none of them required local anesthesia during the subsequent treatment.

Discussion

We aimed at establishing a protocol for ALA-PDT in the treatment of AKs and BD in Japanese patients. We treated a total of 152 AK lesions, and 48 BD lesions with ALA-PDT. Overall complete response rates of 81.6% and 75.0% were observed for AK and BD respectively. Especially high complete response rates of 87.2% and 88.9% were observed for AKs located on the face/scalp, and BD lesions on the trunk respectively. The present study showed high clearance rates equivalent to those of white Caucasians, especially for AKs on the face/scalp, and BD on the trunk.

Our protocol with three treatment sessions 1 week apart — each of 50J/cm2 irradiation for AK, and 100J/cm2 for a total of 150J/cm2 irradiation for BD — was very successful in the treatment of Japanese patients.

However the recurrence rates were 9.2% for AK and 25.0% for BD after 12 months of follow-up. Larger lesions (diameter ≥ 20mm) had lower complete response rates than smaller lesions. 23) For larger lesions, the procedure required considerable time and skill of the operator.

We observed that multiple low-dose exposures to ALA-PDT increased the expression of thioredoxin, a common antioxidant that suppressed apoptosis and facilitated the growth of cultured tumor cells.24) We tried to administer sufficiently high-doses of ALA-PDT at short intervals to induce cell death.

In order to obtain even greater efficacy of ALA-PDT, we investigated the synergistic effects with combinations of COX-2 selective inhibitor 25) or etretinate 26) which have anti-cancer effects, and calcipotriol 27) which regulates the proliferation and differentiation of
Fig. 1: Case of actinic keratosis. (a) Actinic keratosis on the face prior to PDT. (b) The lesion had disappeared 12 months after three treatments (50J/cm² irradiation for a total dose of 150J/cm²) with ALA-PDT one week apart.

Fig. 2: Case of Bowen’s disease. (a) Bowen’s disease lesion on the finger prior to PDT. (b) The lesion had disappeared 12 months after three treatments (100J/cm² irradiation for a total dose of 300J/cm²) with ALA-PDT one week apart.

Fig. 3: Case of sarcoidosis (a) Sarcoidosis on the face prior to PDT. (b) At 10 months after PDT, improvements were seen in the eruptions, and disappearance of epithelioid cell granuloma was also confirmed histologically.
Fig. 4: Case of recalcitrant warts
(a) Recalcitrant warts on the fingers prior to PDT.
(b) At 4 months after PDT, the warts had disappeared.

Fig. 5: Case of toenail onychomycosis
(a) Fungal infection of the nail prior to PDT.
(b) At 4 months after PDT, toenail onychomycosis was successfully improved.
keratinocytes.

Nonlaser light sources, which are now becoming popular in topical PDT have the advantages over lasers of being inexpensive, stable, easy to operate, requiring little maintenance, and providing wide-area illumination fields. A retrospective comparison of laser and filtered broadband sources suggested equivalent efficacy in topical PDT. Lasers and non-laser light sources emitting 630nm light have been used in PDT and usually show similar efficacies.

ALA-PDT is a convenient, non-invasive dermatological treatment with excellent cosmetic outcomes without surgical scars or discoloration. PDT has both cytotoxic and immunomodulatory effects. PDT has a future in dermatology, developing into a useful complement to the established therapeutic management of skin tumors and non-oncological diseases.

References


