Novel Photodynamic Therapy Does Not Prevent New Skin Cancers—Randomized Controlled Trial

Anthony J. Dixon, PhD, MBBS,* Stuart J. Anderson, MBBS,† Jason D. Mazzurco, DO, MS,‡ and Howard K. Steinman, MD§

OBJECTIVES To determine whether field photodynamic therapy (PDT) of actinic keratoses using a novel preparation of 5-aminolevulonic acid (novel ALA) results in fewer subsequent invasive skin cancers developing on the face of individuals with previous facial cutaneous malignancy in a prospective randomized controlled trial.

METHODS AND MATERIALS Intervention patients received two treatments of novel ALA 2 weeks apart. Controls were observed. Patients were followed up with biopsy of any suspicious lesions for 3 years.

RESULTS The trial was suspended early because of problems with trial governance and the reporting of severe adverse events. Sixty-four patients who were recruited at that time at one center were monitored. Their average age was 71, and 57% were male. Patients were randomized to intervention (n = 34) or observation (n = 29). Over the subsequent 3 years, 13 intervention patients (38%) developed 30 new cutaneous malignancies in the field treated, and 11 control patients (38%) developed 22 new malignancies. Some intervention patients experienced prolonged adverse events, including permanent scarring.

CONCLUSION Novel ALA made no difference in the likelihood of new malignancies developing. The risks without benefit of this novel ALA are troubling. Lack of efficacy and safety of novel ALA cannot be extrapolated to other PDT products.

Family interests of author AD have shares in the sponsoring company. This holding has and is being managed independently with all profits (if any) directed to independent medical research and all other authors have indicated no significant interest with commercial supporters.

Photodynamic therapy (PDT) has become an established option in the management of actinic keratoses (AKs), with many studies demonstrating a reduction in lesion count after treatment.[1–6] Efficacy in individuals with transplantation has also been demonstrated.[7]

Experience with PDT to manage skin disease pertains predominantly to two active ingredients, methyl aminolevulinate (MAL) and 5-aminolevulinate (ALA). These similar ingredients are intracellularly converted to protoporphyrin IX, which is light sensitive and essential to the mechanism of action. The product is applied to the affected skin, followed by an incubation period, and then a light source is applied. Active ALA has been demonstrated to be more effective than vehicle control.[8] The active ingredient can be illuminated using proprietary lights. Illumination has also proved effective with daylight to activate MAL[9,10] and other light sources.[11–14]

The research supporting usage of topical PDT treatment to manage AKs pertains essentially to

*Department of Cutaneous Oncology, Australasian College of Cutaneous Oncology, Belmont, Victoria, Australia; †Maffra Medical Group, Maffra, Victoria, Australia; ‡Division of Dermatology, Department of Internal Medicine, College of Osteopathic Medicine, Michigan State University, Ypsilanti, Michigan; §Department of Dermatology, College of Medicine, Texas A&M Health Science Center, Temple, Texas

ISSN: 1076-0512 • Dermatol Surg 2014;40:412–419 • DOI: 10.1111/dsu.12462

MAL (Metvix and Metvixia; Galderma, Lausanne, Switzerland) and ALA (Levulan; DUSA, Wilmington, MA). The two products appear to have broadly similar efficacy.[3,15,16] Other PDT preparations have been studied infrequently.[17,18] The Australian Therapeutic Goods Administration (TGA) has approved Metvix cream. The TGA is the Australian equivalent to the U.S. Food and Drug Administration (FDA). The FDA has approved Levulan (US-ALA) and Metvixia (US-MAL). US-MAL is available in a cream form and was not yet approved for use in the United States at the time of the study. US-ALA has a complex and expensive delivery system that involves two breakable chambers containing the active ingredients that are crushed in a tube to allow the ingredients to mix immediately before application.

In 2008, Allmedic Pty Ltd (Taren Point, NSW, Australia) advised that they were marketing and selling a novel preparation of ALA along with a lower-intensity light specifically for the management of AKs. Unlike with Levulan, the sponsor claimed that this delivery system was premixed and simple, with a long shelf life.

Most studies of PDT for AKs have assessed outcomes in terms of a reduction in lesion count or cosmetic appearance.[19,20] It is unclear whether a reduction in lesion count leads to a reduction in invasive skin malignancies. In general, the prevention of new skin cancers has not been evaluated, although de Graaf demonstrated in a randomized controlled trial that PDT did not prevent subsequent squamous cell carcinomas (SCCs) in transplantation patients.[21] Apalla demonstrated that PDT delayed the return of actinic damage in a 12-month follow-up study.[22] A delay in the return of AKs may not translate into fewer subsequent malignancies.

Methods

The product sponsor, who provided the commercially available ALA preparation and light source, approved a prospective randomized controlled trial protocol. The study was designed as a postmarketing study to investigate the incidence of new skin cancers after treatment with the trial of ALA.

The protocol received approval from the Bond University Human Research Ethics Committee in accordance with the TGA Clinical Trial Notification (CTN) Scheme. The trial was registered (12609000025235) on the Australian New Zealand Clinical Trials Registry, where full methodology details are available. The primary trial sponsor was Allmedic Pty Ltd.

In January 2009, the trial started recruitment at multiple treatment centers in Australia. Patients were randomized into two groups: management with trial ALA or observation. Randomization involved the treatment centers submitting an online form to a site interstate. A random number generator applied a code to each patient. The code determined randomization status and results were e-mailed to the trial center.

Inclusion Criteria

Patients who had one or more histologically proven invasive facial skin cancers that had been surgically removed with proven histologic clearance were offered enrollment in this trial. Degree of background facial actinic damage was not a criterion for enrollment. The risk factor for future face skin cancers common to all trial participants was previous skin cancer on the face rather than a specific level of actinic damage. Minors and those unwilling or unable to understand and consent to the protocol were excluded. Immunosuppressed patients were also excluded.

The intervention protocol involved two PDT treatments 14 days apart. Patients were provided with a 10% alpha hydroxy acid solution to reduce thickened hyperkeratoses that was to be used twice daily for 2 weeks before PDT. A test dose of trial ALA (20% ALA solution) was applied to a small area of

skin off the face. If there was no apparent short-term adverse reaction at the test site, the trial ALA was applied to the whole face (except for eyelids and near mucosal surfaces), followed by a 5-hour incubation period during which exposure of light to the face was avoided. The border of the face was defined as the hairline superiorly, anterior to the tragus laterally, and the lower margin of the mandible inferiorly.

The patient was then exposed to a 30-minute illumination with the PDT light source provided by the sponsor (blue LED light at 465 nm, 48 J/cm^2 for 20 minutes and then red LED light at 625 nm, 64 J/cm^2 for 10 minutes). The sponsor advised that the efficacy and safety of their trial ALA had been optimized with this light source. They advised that a combination of blue and red lights was designed to allow for two levels of penetration of the skin. Incubation involved the liquid being massaged into each side of face to provide a thin, uniform cover. Before illumination, the face was washed with warm water and dried. During illumination, the eyes and eyelids of the patient were shielded from the light source. Each patient had an attendant present at all times during illumination. A fan to reduce burning sensation was provided as required. The treatment was paused if the patient requested and discontinued if the patient found it to be intolerable.

After treatment, the patient was given extensive advice regarding minimizing sun exposure and analgesia. They were encouraged to remain indoors in a darkened room for the initial day and were provided with a sunscreen to apply when outside before and after treatment. All patients had scheduled appointments every 6 months for at least 2 years after randomization. Patients were advised to request additional appointments if they had concerns requiring attention. At follow-up, any face lesion suspected of being malignant was biopsied. All lesions were photographed. Any lesion that proved malignant on biopsy was then widely excised with clear histologic margins confirmed. Only new skin cancers within the area of face treated, as defined, were included in the trial data.

Assessors were not blinded. The medical staff who implemented the PDT were also the staff who monitored the patients. Intervention patients were to be offered the option of undergoing PDT free of charge once the trial was completed.

Statistical Analysis

Primary analysis was conducted on an intention-to-treat (ITT) basis, and a per-protocol analysis was conducted for sensitivity. Patient characteristics and differences between groups were assessed using analysis of variance using a Tukey post hoc analysis, the Kruskal–Wallis H test, and the chi-square test as appropriate. All critical outcome incidences were analyzed using the chi-square test, and PDT intervention was compared with control using two-by-two tables.

Results

Shortly after study-patient treatment was commenced, several problems were encountered regarding trial governance. The trial was suspended in March 2009 after discussions with investigators and the ethics committee, and the sponsor formally stopped it in June 2009. Although the initial protocol planned for recruitment of 500 patients, no further recruitment occurred after trial suspension. Nearly half of all recruited patients had been recruited at one trial center, with 63 patients recruited before suspension of the trial. Thirty-four of these patients were randomized to intervention, and 29 were control patients. After suspension of the multicenter trial, 63 patients were monitored for the development of new cancers on the face. Six patients treated with PDT developed severe and prolonged pain. After treatment, their pain continued for up to 5 weeks and longer. Permanent scarring was reported in three treated patients. The adverse effects that these patients described—including pain, extreme photosensitivity, severe crusting, blistering,

and peeling—were more severe and prolonged than in any cases treated with the US-ALA in the experience of two of the authors (JM and HS). Seven intervention patients declined to have PDT (and did not develop any further skin cancers on the face). The trial safety committee was conscious of the promise made to observation patients that they would be offered PDT once the trial was complete. As such, observation patients were offered PDT after trial suspension and were counseled regarding the troubling adverse events observed. Seven control patients chose to have PDT following suspension of the trial. One of these patients suffered severe and prolonged pain following PDT. He later developed an invasive SCC on the face.

The average age of the 63 patients was 71, with no significant difference between intervention (average 70) and control (average 72) patients.

Of the recruited patients, 57% were male, with no significant difference in sex between intervention (56% male) and patients (58% male) control. None of the patients had previously been treated with PDT. There was no statistically significant difference in numbers of past skin cancers or background face actinic damage between intervention and control patients. Two patients had diabetes, one in each arm of the trial. All patients signed an ethics committee—approved written consent form before their involvement in the trial (Figure 1).

Patients were followed for an average of 34 months. The longest follow-up period was 38 months, and the shortest was 13 months. Two patients were lost to follow-up. Three patients died from unrelated events during the follow-up period but were followed for periods of 13, 18, and 24 months. Two other patients (both intervention) were not followed

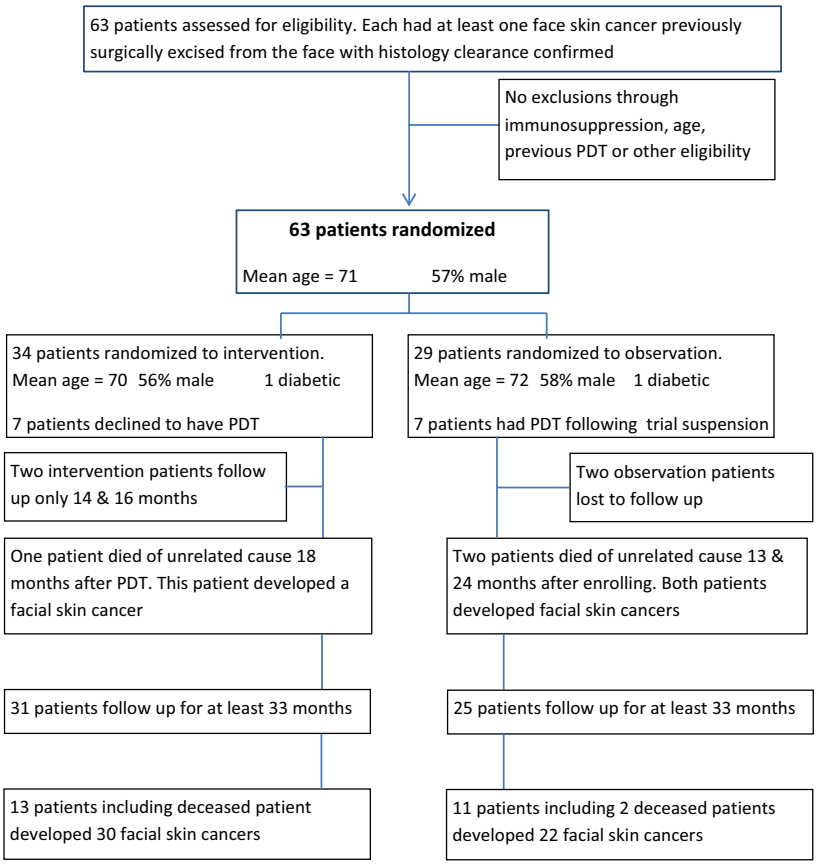

Figure 1. Patient flow diagram.

for at least 33 months. These two patients were followed for 14 and 16 months and then were lost to follow-up.

Fifty-two new cutaneous malignancies developed on the faces of 24 trial patients (38%). One control patient reported three face malignancies treated elsewhere, but the details could not be obtained. The remaining 49 malignancies reported in trial patients were all managed at the trial center. All 49 tumors were treated with surgical excision, and clear margins were obtained in each case. All patients in both arms of the trial who had had three or more skin cancers on the face before enrollment developed more face skin cancers during the trial period.

Two melanoma in situ of lentigo maligna type (MIS) developed in a single intervention patient and were documented, photographed, and managed at 12-month review (Figure 2). The remaining tumors consisted of 26 SCCs, including three SCC in situ. There were 21 basal cell carcinomas (BCCs), one of which was a superficial BCC. The remaining BCCs were of the nodular or infiltrating type.

Intervention Patients

Using ITT analysis, 13 of the 34 intervention patients (38%) developed 30 new malignancies on the face (2 MIS, 13 SCC, 15 BCC).

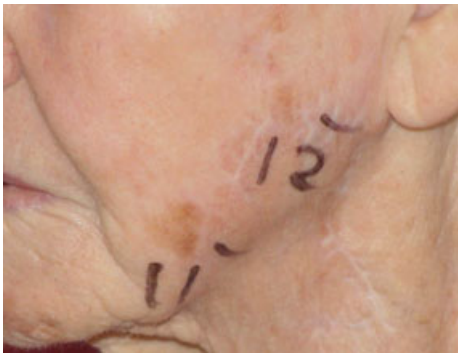

Figure 2. Photograph of the lower left cheek and mandible region of an intervention patient 12 months after photodynamic therapy. Two foci of melanoma in situ were identified. Each was subsequently surgically excised with clear margins.

Observation Patients

Using ITT analysis, 11 of the 29 observation patients (38%) developed 22 new malignancies (13 SCC, 6 BCC). There were also three reported malignancies treated elsewhere.

There was no significant difference between study groups in numbers of patients who developed new malignancies (relative risk (RR) = 1.00, 95% confidence interval (CI) = 0.52–1.94, p = .98). There was also no significant difference between intervention and observation patients in tumor burden in terms of total numbers of new cancers developed (p = .71).

Per-protocol Outcomes

Of the 34 patients who were treated with PDT (including seven patients randomized to observation), 31 malignancies developed on 14 patients (41%). This is similar to the 29 patients who did not have PDT (including seven patients randomized to intervention). In this group, 21 new malignancies were recorded in 10 patients (34%) (RR = 1.20, 95%
CI = 0.60–2.5, p = .58).

To determine whether there was early improvement after PDT that dissipated over 3 years, a Kaplan–Meier curve was developed to compare face cancer free survival over time (Figure 3). At no stage after trial enrollment were there significantly fewer skin cancers in the PDT group.

Although the trial was stopped early, the data collected did not indicate that PDT therapy reduced the risk of developing malignancy after therapy.

Discussion

Substantial improvements in AK count and cosmetic appearance have repeatedly been reported to occur after PDT to the face,[4,8,17,23] although this may not translate into a reduction in the future risk of developing new cutaneous malignancies.

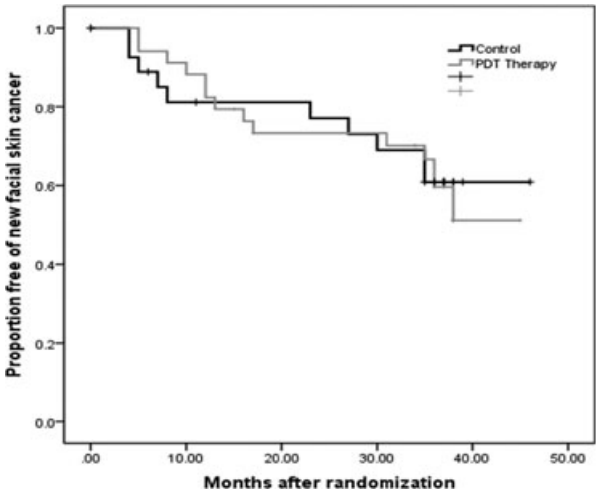

Figure 3. Kaplan–Meier curve. Face tumor–free survival in patients treated with photodynamic therapy versus control group.

A reduction in new malignancies was not found when organ transplant recipients received PDT in a randomized controlled trial.[21]

Our data suggest that the broader community may not experience a reduction in cancer risk when the face is treated with this trial PDT. Even the promise of cosmetic improvement with this product is questionable because outcomes that include scarring cannot be regarded as acceptable. These outcomes cannot be extrapolated to other formulations of PDT, especially because other preparations have not resulted in the adverse events noted with this product. We are unaware of any previous reports of permanent scarring after the use of other PDT products.

Investigating doctors were advised that the study product that the sponsoring company provided and that Australian doctors used commercially was an established and approved ALA-PDT therapy. This trial was an aftermarket study to investigate the potential for reduction in new skin cancers. When the severe adverse events were reported, the sponsoring company was asked to provide further details of the efficacy and safety of their novel ALA. No data were supplied, and the sponsor has declined to communicate further with the investigators. A literature search in February 2013 failed to identify any published data, including efficacy and safety data, on this novel ALA. It is not known whether the sponsor had data that they did not release for commercial in-confidence reasons. We were unable to identify this novel product as being approved for marketing by the TGA. The TGA regulates products that claim a therapeutic benefit. If a company makes no direct therapeutic claims regarding its products, then it need not seek TGA approval. There is the potential for "independent experts" to promote therapeutic benefits of a product without the company directly making such claims. We were unable to identify any other regulatory approval of this novel ALA product. We recommend that investigators seek confirmation of regulatory approval of products before subjecting them to clinical trials of this type. In retrospect, we wish we had done so. The adverse events recorded in this trial were reported to the TGA. Despite this, the product was still being offered for sale in May 2013.

The novel ALA used in this trial has resulted in greater adverse events than the ALA products that the FDA has approved. Bioequivalence cannot be presumed. This may be because of different delivery system whereby the manufacturer performs final mixing of the ingredients rather than the physician just before application. The known stability risks of ALA may be stretched with this production process.

The apparent ineffective outcomes with regard to preventing new skin cancers demonstrated in our study with this ALA may not reflect the potential for other PDT treatments to reduce cancer risk. There is inadequate evidence of this product's safety and efficacy in the public domain. After trial closure, the trial safety committee was aware of their responsibilities to continue to monitor patients. The safety committee also needed to ensure any safety and efficacy concerns that might continue to occur with these former trial patients was recorded and made available in the public domain.

The planned protocol was to include 500 patients and was powered on such a basis. Because the trial was suspended early, the numbers recruited were less than intended, and the power of our data is therefore limited. A larger study would be required to confirm these findings.

Conclusion

This novel PDT therapy raises several safety concerns. It has not provided any suggestion of a reduction in the future cutaneous malignancy risk on trial patients. Adverse events that treated patients reported were at times more prolonged and severe than previously reported with PDT to the face. Permanent scarring has occurred.

The adverse events, together with questionable efficacy in reducing the future burden of skin cancer, raises questions as to why people would be offered this product. We are concerned that Australians and New Zealanders may be exposed to potential harm from a product not adequately evaluated and regulated, and we believe the product should be withdrawn until such time as these safety concerns are addressed.

The lack of efficacy and prominent adverse events reported with this product should not be extrapolated to other rigorously tested and approved PDT products, but the efficacy of other PDT therapy in reducing subsequent cancer risk is not established; and therefore, the risk-to-benefit ratio needs to be evaluated carefully before any PDT therapy is used for cancer prevention. Cancer risk reduction cannot be presumed when any PDT is used to manage actinic damage to the face.

References

1. Kurwa HA, Yong-Gee SA, Seed PT, Markey AC, et al. A randomized paired comparison of photodynamic therapy and topical 5-fluorouracil in the treatment of actinic keratoses. J Am Acad Dermatol 1999;41:414–8.
2. Touma D, Yaar M, Whitehead S, Konnikov N, et al. A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage. Arch Dermatol 2004;140:33–40.
3. Gold MH, Bradshaw VL, Boring MM, Bridges TM, et al. Split-face comparison of photodynamic therapy with 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone for photodamage. Dermatol Surg 2006;32:795–801.
4. Tschen EH, Wong DS, Pariser DM, Dunlap FE, et al. Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up. Br J Dermatol 2006;155:1262–9.
5. Braathen LR, Morton CA, Basset-Seguin N, Bissonnette R, et al. Photodynamic therapy for skin field cancerization: an international consensus. International Society for Photodynamic Therapy in Dermatology. J Eur Acad Dermatol Venereol 2012;26:1063–6.
6. Hadley J, Tristani-Firouzi P, Hull C, Florell S, et al. Results of an investigator-initiated single-blind split-face comparison of photodynamic therapy and 5% imiquimod cream for the treatment of actinic keratoses. Dermatol Surg 2012;38:722–7.
7. Dragieva G, Prinz BM, Hafner J, Dummer R, et al. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. Br J Dermatol 2004;151:196–200.
8. Taub AF, Garretson CB. A randomized, blinded, bilateral intraindividual, vehicle-controlled trial of the use of photodynamic therapy with 5-aminolevulinic acid and blue light for the treatment of actinic keratoses of the upper extremities. J Drugs Dermatol 2011;10:1049–56.
9. Wiegell SR, Fabricius S, Gniadecka M, Stender IM, et al. Daylight-mediated photodynamic therapy of moderate to thick actinic keratoses of the face and scalp: a randomized multicentre study. Br J Dermatol 2012;166:1327–32.
10. Wiegell SR, Fabricius S, Stender IM, Berne B, et al. A randomized, multicentre study of directed daylight exposure times of 11/2 vs. 21/2 h in daylight-mediated photodynamic therapy with methyl aminolaevulinate in patients with multiple thin actinic keratoses of the face and scalp. Br J Dermatol 2011;164:1083–90.
11. Radakovic-Fijan S, Blecha-Thalhammer U, Kittler H, Hönigsmann H, et al. Efficacy of 3 different light doses in the treatment of actinic keratosis with 5-aminolevulinic acid photodynamic therapy: a randomized, observer-blinded, intrapatient, comparison study. J Am Acad Dermatol 2005;53:823–7.
12. Babilas P, Kohl E, Maisch T, Bäcker H, et al. In vitro and in vivo comparison of two different light sources for topical photodynamic therapy. Br J Dermatol 2006;154:712–8.
13. Babilas P, Knobler R, Hummel S, Gottschaller C, et al. Variable pulsed light is less painful than light-emitting diodes for topical photodynamic therapy of actinic keratosis: a prospective randomized controlled trial. Br J Dermatol 2007;157:111–7.
14. Kim BS, Kim JY, Song CH, Kim HY, et al. Light-emitting diode laser versus pulsed dye laser-assisted photodynamic therapy in the treatment of actinic keratosis and Bowen's disease. Dermatol Surg 2012;38:151–3.

15. Kuijpers DI, Thissen MR, Thissen CA, Neumann MH. Similar effectiveness of methyl aminolevulinate and 5-aminolevulinate in topical photodynamic therapy for nodular basal cell carcinoma. J Drugs Dermatol 2006;5:642–5.

16. Moloney FJ, Collins P. Randomized, double-blind, prospective study to compare topical 5-aminolaevulinic acid methylester with topical 5-aminolaevulinic acid photodynamic therapy for extensive scalp actinic keratosis. Br J Dermatol 2007;157:87–91.

17. Hauschild A, Popp G, Stockfleth E, Meyer KG, et al. Effective photodynamic therapy of actinic keratoses on the head and face with a novel, self-adhesive 5-aminolaevulinic acid patch. Exp Dermatol 2009;18:116–21.

18. Dirschka T, Radny P, Dominicus R, Mensing H, et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a multicentre, randomized, observer-blind phase III study in comparison with a registered methyl-5-aminolaevulinate cream and placebo. Br J Dermatol 2012;166:137–46.

19. Sotiriou E, Apalla Z, Chovarda E, Goussi C, et al. Single vs. fractionated photodynamic therapy for face and scalp actinic keratoses: a randomized, intraindividual comparison trial with 12-month follow-up. J Eur Acad Dermatol Venereol 2012;26:36–40.

20. Wiegell SR, Fabricius S, Gniadecka M, Stender IM, et al. Daylight-mediated photodynamic therapy of moderate to thick actinic keratoses of the face and scalp—a randomized multicentre study. Br J Dermatol 2012;166(6):1327–32.

21. de Graaf YG, Kennedy C, Wolterbeek R, Collen AF, et al. Photodynamic therapy does not prevent cutaneous squamous-cell carcinoma in organ-transplant recipients: results of a randomized-controlled trial. J Invest Dermatol 2006;126:569–74.

22. Apalla Z, Sotiriou E, Chovarda E, Lefaki I, et al. Skin cancer: preventive photodynamic therapy in patients with face and scalp cancerization. A randomized placebo-controlled study. Br J Dermatol 2010;162:171–5.

23. Kleinpenning MM, van de Kerkhof PC, Gerritsen RM. The clinical efficacy of topical methyl-aminolevulinate photodynamic therapy in moderate to severe actinic keratoses of the face and scalp. J Dermatolog Treat 2010;21:252–7.

Address correspondence and reprint requests to: Anthony J. Dixon, PhD, MBBS, FACRRM, Cutaneous Oncology, Australasian College of Cutaneous Oncology, 66 Roslyn Rd, Belmont, Vic. 3216, Australia, or
e-mail: Anthony@acco.org.au