Polypodium Leucotomos Supplementation in the Treatment of Scalp Actinic Keratosis: Could It Improve the Efficacy of Photodynamic Therapy?

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BACKGROUND Actinic keratoses (AKs) are a common premalignant skin condition. Many treatments are available for AKs. Photodynamic therapy (PDT) is one of the most effective treatments. However, major concerns exist on the possibility of PDT-induced DNA-mutagenesis/immunosuppression, leading to AKs recurrence/treatment failure. An extract (PLE) from the fern polypodium leucotomos reduces UV-induced immunosuppression and mutagenesis.

OBJECTIVE To assess the ability of PLE to enhance the efficacy of PDT treatment, reducing AKs recurrence on the scalp.

MATERIALS AND METHODS Thirty-four bald patients presenting at least two AKs on the scalp were alternatively assigned to two groups. Both groups underwent two PDT-sessions one-week apart. The first group began oral PLE supplementation one week after the last PDT session. Evaluation of the effect of PLE supplementation was performed by direct inspection of the bald areas, lesions count, and photodynamic diagnosis assessment at 2 and 6 months.

RESULTS Both groups were homogeneous in terms of skin phototype and previous UV exposure. Mean age was 75.7 ± 7.8 years and 76.5 ± 5.5 years, respectively. Both treatment modalities were successful in reducing AKs number ($p < .001$). However, PLE supplementation increased clearance rate compared with PDT alone ($p = .040$).

CONCLUSION Polypodium leucotomos improves PDT clearance and decreases AK recurrence rate at 6 months, suggesting its use as a complementary agent in the treatment of field cancerization.

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Actinic keratoses (AKs) are the most common form of premalignant skin condition in fair skinned population.[1,2] Actinic keratosis prevalence increases in elderly people living in geographic areas bearing high exposure to UV radiation, in skin Fitzpatrick phototypes ≤2. Actinic keratosis occurs in the context of a field of UV-damaged skin defined as skin field of cancerization. The risk of developing a squamous cell carcinoma (SCC) within this area is estimated to be 65% to 97% over the years.[3]

Various treatment modalities are available. They include surgery, cryotherapy, laser therapy, topical treatment with 3% diclofenac, 2.5% hyaluronic acid, topical immunotherapy with imiquimod, topical treatment with 5-fluorouracil, and photodynamic therapy (PDT). More recent treatment modalities include topical application of ingenol mebutate. Photodynamic therapy is regarded as a very well-tolerated and effective treatment for AK and is highly recommended by evidence-based clinical studies.[4,5]

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Nonmelanoma skin cancer (NMSC) clearance rate varies from 50% to 84% depending on lesion size and PDT treatment modalities.[6] Photodynamic therapy-driven AK clearance rate ranges from 60% to 90%, with a recurrence rate of 20% at 12 months[7]; clearance rate is lower in immunosuppressed patients. This evidence suggests an important role of UV immunosuppression[8] in the development of field cancerization and raises some concerns regarding its use as a primary treatment. In this regard, recent published data suggest that PDT itself may induce immunosuppression and mutagenesis potentially leading to recurrence.[9] Moreover, the immunosuppressive activity of PDT has been also sustained as one of the action mechanisms for its use in different inflammatory skin conditions.[10]

Polypodium leucotomos (PL) is a tropical fern that has long been used for the treatment of inflammatory disorders in folk medicine.[11] An extract of PL (PLE) is endowed with potent antioxidant activity, reducing reactive oxygen species (ROS) in UV-exposed skin. PLE also exhibits DNA repairing features[12] and can counteract UV-induced immunosuppression[13] and reduces cyclobutane pyrimidine dimers formation.[14]

The aim of this study was to assess the efficacy of PLE supplementation in reducing the recurrence of AK on the scalp of older individuals after standard PDT treatment.

Methods

Patients were enrolled in the Dermatologic Clinic of G. d'Annunzio University of Chieti from January 2012 to June 2012 and from September 2012 to June 2013. This enrolling scheme aimed to avoid bias because of summer sun exposure. All patients were male and older than 18 years. Each patient presented with at least 2 visible AKs on the scalp and a Hamilton–Norwood baldness scale ≥IV. All enrolled patients were eligible for PDT therapy.

Exclusion criteria were female gender, age younger than 18 years, known allergy to porphyrins and their derivatives, presence of autoimmune disease or other immunosuppressive conditions, current use of potentially phototoxic or photoallergic topical or systemic medications, and skin phototype >3.

Scalp was photographed and assessed for AK presence using photodynamic diagnosis. Actinic keratoses were counted and their diameter was measured.

All patients underwent two sessions of methyl aminolevulinate (MAL) PDT one week apart. Treatment consisted of lesions curettage, 16% MAL cream (Metvix, Lausanne, Switzerland) occlusive application for 3 hours, and subsequent irradiation with an LED lamp (635 nm, Aktilite CL128 lamp; Galderma; Photocure ASA, Oslo, Norway) with a total energy of 37 J/cm^2 in 8 minutes.

One week after the last PDT session, patients were randomly assigned to one of the two treatment groups. The first group underwent oral PLE supplementation (provided by Industrial Farmaceutica Cantabria—IFC Group, Madrid, Spain) at a dose of 960 mg per day for 1 month and then 480 mg per day for 5 months. The second group was followed for the same period without supplementation.

Patients from both groups were instructed to use a sun blocker with an SPF ≥50 daily every 2 hours during sun exposure periods. Patients were evaluated before the first treatment (T0—enrolment), 2 months later (T1), and 6 months since the enrolment (T2).

Clinical, dermoscopic, and fluorescent images were recorded using a FotoFinder Dermoscope and Medicam 800HD (FotoFinder Systems GmbH, Bad Birnbach, Germany).

All the patients were treated with commonly available therapies following the principles of the 1975 Declaration of Helsinki.

Statistical Analysis

All quantitative variables were reported as mean and standard deviation or median and interquartile range in the tables and figures. The results were reported separately for each of two groups (PDT + PLE and PDT). To detect departures from normality distribution, Shapiro–Wilk test was performed. Because the

distribution of the data was not normal, statistical significance was assessed using the Mann–Whitney *U* test for quantitative variables between the two groups (PDT + PLE vs PDT), whereas chi-squared test was applied for qualitative variables.

Friedman test was performed to evaluate statistical significant differences between the baseline and 2- and 6-month post-treatment data of each study group. Wilcoxon *U* test was applied to evaluate the post hoc difference between time points.

All statistical analyses were conducted using SPSS software 11.0 (SPSS Inc., Chicago, IL). A post hoc power analysis demonstrated that a sample size of 17 subjects may provide sufficient statistical power to evaluate a difference between groups in variation of scalp AK of 5 ± 3.0 with an alpha error of 0.05. This evaluation was performed using the "sample size" function of R 3.0.2 open source software.

Results

From January 2012 to September 2013, 40 patients with scalp AKs were enrolled in the study. Six patients missed at least one of the appointments and were excluded for the study: 3 belonged to the PDT plus PLE group and 3 in the PDT only group. Finally, 34 patients fulfilled all criteria and attended all follow-up visits. Seventeen patients underwent treatment with PDT alone (2 treatments 1 week apart), and 17 were treated with standard PDT and subsequent supplementation with PLE.

The mean age of the 2 groups was 75.7 ± 7.8 years and 76.5 ± 5.5 years, respectively. The majority of patients presented a Fitzpatrick phototype II. The 2 groups were also homogeneous for age, phototype, outdoor habits, AKs numbers, and size (Table 1).

Both treatment modalities were successful in reducing AKs number at the 2 follow-up time points (Figure 1, $p < .05$). However, at the 6-month follow-up, PDT treatment + PLE supplementation displayed a better clearance rate compared with PDT alone (Table 2, $p = .040$). At T1, both groups presented a statistical significant reduction of AKs count, whereas only the group with PLE supplementation gained a statistically significant improvement of AKs count at T2 (Figure 1 and Table 2).

None of the patients included in either group showed evidence of progression to SCC. No major side effects were recorded in either group.

TABLE 1. Baseline Characteristics of 34 Patients

Variable	*PDT + PLE Group (n = 17)*	*PDT Group (n = 17)*	*p*
Age, mean ± SD, yr	76.5 ± 5.5	75.7 ± 7.8	.812*
Phototype, *n* (%)			.497†
I	6 (35.3)	3 (17.6)	
II	9 (52.9)	11 (64.8)	
III	2 (11.8)	3 (17.6)	
Outdoor working, *n* (%)			.724†
Yes	11 (64.7)	10 (58.8)	
No	6 (35.3)	7 (41.2)	
Baseline scalp AK			
Median (interquartile range)	8.0 (5–10)	7 (4–9.5)	.139*
Aks' dimension, *n* (%)			1.000†
<1 cm	4 (23.5)	4 (23.5)	
≥1 cm	8 (47.1)	8 (47.1)	
Unknown	5 (29.4)	5 (29.4)	

*Mann–Whitney *U* test, PDT + PLE group versus PDT group.
†Chi-Squared test, PDT + PLE group versus PDT group.

TABLE 2. Median and Interquartile Range of Scalp AK at Baseline and 6 Months After Treatment for Each Group

	Scalp AK		
Group	*Baseline (T0)*	*6 months (T2)*	*Δ (T2–T0)*
PDT + PLE	8 (7–10)	1 (1–3)	−8 (−9 to −5)
PDT	7 (4–9.5)	2 (1–4.5)	−3 (−6.5 to −1.5)
*p**	.139	.409	.040

*Mann–Whitney *U* test, PDT + PLE group versus PDT group.

Conclusion

Photodynamic therapy is a well-established treatment for scalp AK, with a variable clearance rate.[5] Photodynamic therapy failure rate and neoplasm recurrence may be the result of various factors. Among them, immunosuppression[15] and DNA damage,[16,17] two of the most important mechanisms of NMSC induction, may be favored by PDT treatment itself.

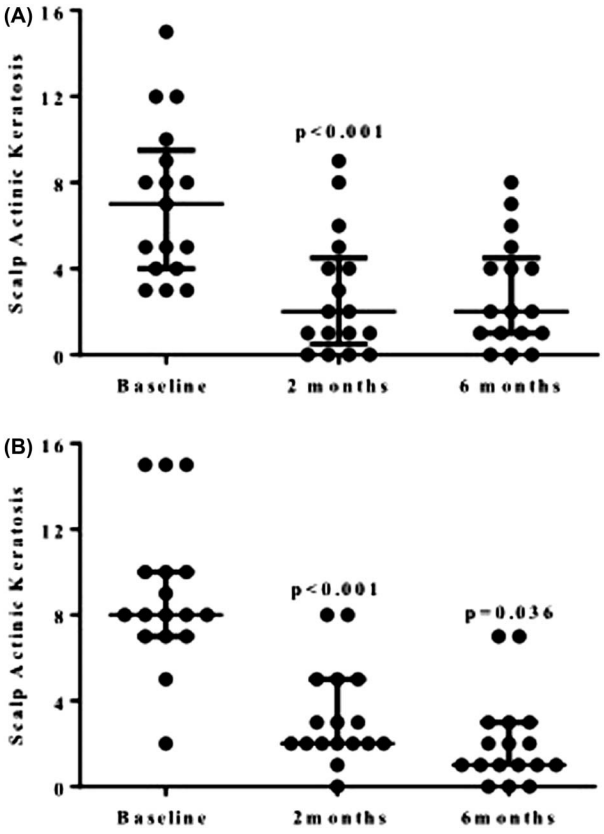

Figure 1. Median and interquartile range of scalp AK at baseline, 2, and 6 months in the PDT group (A) and in the PDT + PLE group (B). $p < .001$ Friedman test for each group; *p* value in figure are relative to Wilcoxon *U* test versus previous time point.

The results show that PDT is an effective tool for treating scalp's AK. PLE supplementation seems to improve long-term PDT clearance rate. At the 6-month follow-up time points, PLE supplementation induced a statistically significant reduction of AK compared with the 2-month follow-up consultation.

The authors think that PDT may act synergistically with UV to promote recurrence after scalp AK treatment. These data could explain the reported tumor resistance and recurrence rates after PDT treatment, ranging from 10% to 45%.[18] Light fluence seems to be one of the major determinants of PDT-induced immunosuppression. Part of this mechanism likely involves oxidative DNA photolesions.[19] For this reason, several studies have tested different compounds to reduce PDT-induced immunosuppression. In this regard, nicotinamide was able to reduce immunosuppression in human skin not only after UV irradiation but also after PDT treatment.[20]

Oral administration of PLE has been shown to prevent UV-induced photoaging and photocarcinogenesis, and to revert UV-induced immunosuppression.[12,13,21] The authors used these data to formulate the hypothesis that PLE supplementation could improve the efficacy of PDT treatment. The data show that PLE supplementation after PDT treatment reduces the recurrence of AK in high-risk individuals.

Although PLE could work as an antioxidant, the evidence supports that this activity has not interfered with PDT, which relies on oxidative stress as a mechanism. To further prevent such possibility, PLE supplementation has been started one week after PDT treatment. These observations postulate the use of PLE as an

adjuvant after PDT treatment; however, more studies are needed to fully elucidate potential interactions between PLE and PDT.

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