Objective: To report the use of wide-area 5-aminolevulinic acid photodynamic therapy to treat numerous basal cell carcinomas (BCCs) and basaloid follicular hamartomas (BFHs).

Design: Report of cases.

Setting: Roswell Park Cancer Institute.

Patients: Three children with BCCs and BFHs involving 12% to 25% of their body surface areas.

Interventions: Twenty percent 5-aminolevulinic acid was applied to up to 22% of the body surface for 24 hours under occlusion. A dye laser and a lamp illuminated fields up to 7 cm and 16 cm in diameter, respectively; up to 36 fields were treated per session.


Results: Morbidity was minimal, with selective phototoxicity and rapid healing. After 4 to 7 sessions, with individual areas receiving 1 to 3 treatments, the patients had 85% to 98% overall clearance and excellent cosmetic outcomes without scarring. For laser treatments, a sigmoidal light dose–response relationship predicted more than 85% initial response rates for light doses 150 J/cm² or more. Responses were durable up to 6 years.

Conclusion: 5-Aminolevulinic acid photodynamic therapy is safe, well tolerated, and effective for extensive areas of diffuse BCCs and BFHs and appears to be the treatment of choice in children.

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The nevoid basal cell carcinoma syndrome (NBCCS), an autosomal dominant disorder in which those affected lack 1 functional copy of the patched suppressor gene (PTCH) that negatively regulates the hedgehog signaling pathway, results in multiple congenital abnormalities, increased risk of medulloblastoma, and early development of multiple basal cell carcinomas (BCCs). Recent studies in mouse models suggest that hedgehog pathway activation is sufficient for development of BCCs and that a lower level of hedgehog pathway activation can lead to the formation of multiple basaloid follicular hamartomas (BFHs). The phenotypic expression of NBCCS is variable, but some individuals develop extensive BCCs in childhood. As expected, patients with NBCCS who receive curative radiation therapy for childhood medulloblastoma have accelerated development of BCCs within radiation fields. Management of these diffuse carcinomas is challenging, since they may extend over large surface areas. Conventional therapies can have high morbidity, and multiple surgical or ablative procedures may cause scarring and disfigurement.

Topical 5-aminolevulinic acid photodynamic therapy (ALA-PDT) is a relatively new treatment modality effective for localized BCCs and other superficial nonmelanoma skin cancers. The application of ALA leads to transient, preferential production of the endogenous photosensitizer protoporphyrin IX (PpIX) within carcinomas, with minimal photosensitizer in the dermis and connective tissues. Subsequent light activation generates cytotoxic reactive oxygen species. Potentially, ALA-PDT should be suitable for treating large fields of BCCs, since it causes little dermal damage and heals rapidly with minimal scarring. We report the first use, to our knowledge, of topical ALA-PDT to successfully treat extensive areas of BCCs and BFHs in children, with individual treatments covering as much as 20% of the body surface area (BSA). The responses, which
suggest a Hill curve light dose-response relationship for laser irradiation, have provided durable relief that extends more than 6 years in one patient.

**METHODS**

**PATIENTS**

The patients were 3 successive children with NBCCS who had diffuse popular or nodular BCCs that involved 12% to 25% of their BSA and who were referred to Roswell Park Cancer Institute between 1995 and 2001 from Tennessee, Michigan, and Canada, respectively. Patient 1 was a 6-year-old girl who presented with medulloblastoma at age 4 years that was treated with surgery and ionizing radiation therapy to the skull and the anterior and posterior aspects of the spine. Approximately 8 months after completing radiation therapy, she began developing extensive plaques of BCCs throughout the radiation fields on her torso. She was referred to our institution after unsuccessful attempts to treat the carcinomas with laser ablation and limited surgical procedures. At the time of referral she had a broad, dense band of thousands of 1- to 3-mm-diameter BCCs along the anterior and posterior aspects of the spinal axis from the neck to the pubis and upper gluteal cleft, respectively, involving approximately 25% of her BSA (Figure 1A). She had symptomatic radiation dermatitis in the areas of the pubis and the sacrum-gluteal cleft. The scalp appeared clear at this time. There was no family history of NBCCS.

Patient 2 was a 10-year-old boy who had more than 300 1- to 3-mm-diameter, nodular, moderately brown, pigmented BCCs predominantly located on the neck, shoulders, upper chest, and back; many appeared as pedunculated papules (Figure 2A). He had no history of radiation therapy. He also had several thousand 0.5- to 1.2-mm-diameter, translucent and flesh-colored papules (Figure 2C), which were histologically BFHs (Figure 2E). He had no family history of NBCCS or BFHs, and he had no signs of hypotrichosis or hypohydrosis. The lack of family history; sparing of the face, scalp, and ears; and absence of hypotrichosis or hypohydrosis differentiated him from those with the generalized BFH syndrome or other previously described syndromes with diffuse BFHs.

Patient 3 was a 17-year-old boy successfully treated for childhood medulloblastoma with ionizing radiation who subsequently developed hundreds of 2- to 4-mm-diameter nodular BCCs in radiation ports on the scalp, neck, and spine. Approximately 12% of his BSA was involved. He had the hypertelorism, macrocephaly, intracranial calcifications, mandibular cysts, and bifid ribs associated with NBCCS. There was no family history of NBCCS or BFHs, and he had no signs of hypotrichosis or hypohydrosis. The lack of family history; sparing of the face, scalp, and ears; and absence of hypotrichosis or hypohydrosis differentiated him from those with the generalized BFH syndrome or other previously described syndromes with diffuse BFHs.

**PHOTODYNAMIC THERAPY**

Treatments were approved by the Roswell Park Cancer Institute Investigational Review Board, and the patients' legal guardians provided informed consent. The ALA was freshly mixed in a cream base (Moisturel; Westwood Squibb Pharmaceuticals Inc, Buffalo, NY). Initial studies in patient 1 examined ALA concentrations of 2.5% to 20% (wt/wt), but most treatments were with 20% ALA. The drug was applied to areas up to approximately 22% of the BSA under plastic wrap occlusion covered by light-proof non-adhesive dressings. For patient 3, the hair was shaved before ALA application to the scalp. After 18 to 24 hours, excess drug was removed and multiple fields were illuminated with red light from 2 different sources. An argon laser–pumped dye laser (models 171 and 375; Spectra-Physics, Mountain View, Calif) at 633 ± 2 nm, coupled to 1 to 4 optical fibers fitted with microlenses, was used for 2- to 7-cm-diameter fields, and a filtered tungsten-halogen lamp (590-700 nm) that allows adjustment of the diameter of the illumination field (DUSA Pharmaceuticals, Inc, Wilmington, Mass) was used for larger fields with up to a 16-cm diameter. To minimize treatment time, multiple fields were illuminated simultaneously and sequentially using both sources. Each irradiation took 20 to 50 minutes. Total treatment times during a session ranged from 3 to 6 hours. Because of limitations in the time available for PDT during a single session, generally we did not treat the entire involved areas. Thus, multiple PDT sessions were used for both initial irradiation and re-treatments. The discomfort caused by ALA-PDT increases with treatment area, and local anesthesia is impractical for large illumination fields. Therefore, treatments were performed with general anesthesia, since this is safer in children than conscious sedation.

**EVALUATIONS**

Responses were evaluated 3 to 12 months after PDT. Using both photographs and acetate templates that demarcated the treatment fields and the countable lesions within the fields, we defined treatment response as the change in the number of BCCs. If
patients had lesions that were too numerous to count, responses to each treatment were based on overall percentage of tumor clearance compared with pretreatment photographs. The senior investigator (A.R.O.) routinely performed these evaluations to limit intraobserver variability. We tracked both the incremental response to each treatment and the overall response compared with initial presentation. Initial treatment responses were evaluated for sites that had not previously received ALA-PDT.

The confidence interval (CI) for the expected initial response rate of a treated field on each patient was based on the exact binomial distribution. The distributions of these initial responses were compared among patients using the Kruskal-Wallis and Wilcoxon 2-sample (Mann-Whitney U) test. These calculations were performed using procedures from SAS/STAT statistical software, version 8.1 (SAS Institute Inc, Cary, NC). A 3-parameter Hill equation was fit to the light dose-field response data for patient 1 using the 3-parameter sigmoid procedure in the Regression Wizard of SigmaPlot, version 8.02 (SPSS Inc, Chicago, Ill).

Figure 2. Response of patient 2 to 5-aminolevulinic acid photodynamic therapy (ALA-PDT). A, Back 24 hours after PDT with both lamp and laser irradiation, showing initial reaction; this was the maximal inflammatory response. Arrows indicate surgical scars. B, After an average of 2 treatments, the field of basal cell carcinomas (BCCs) is essentially clear. Hyperpigmented areas are sites of laser treatment 6 months previously; they resolved during the next 3 months. C, Left shoulder, demonstrating more than 60 small translucent and flesh-colored papules, which are histologically basaloid follicular hamartomas (bar=5 mm). D, Same area as in C after 1 laser treatment showing essentially complete clearance (bar=5 mm). E, Basaloid follicular hamartoma in superficial dermis showing complex anastomosing strands and cords of basaloid cells within a central keratinizing core. No mitotic activity, apoptosis, or cytologic atypia was identified. No connection to the overlying epidermis was present in this tissue plane (hematoxylin-eosin, original magnification ×100).

RESULTS

TREATMENT CONDITIONS AND INITIAL RESPONSE RATES

Drug and light dose-ranging studies were conducted in patient 1. In the first session, different treatment conditions were randomly assigned to 2-cm-diameter fields (Figure 1B). The ALA concentrations of 2.5% to 20% were
used, with light doses and light dose rates (irradiances) of 33 to 100 J/cm² at 40 to 100 mW/cm² (laser) and 60 to 200 J/cm² at 50 to 100 mW/cm² (lamp).

In the ranges that were examined, we found no relationships between responses and ALA concentration or irradiance. In the subsequent sessions for patient 1, larger areas up to 7 cm in diameter (laser) or 16 cm in diameter (lamp) were treated with 20% ALA.

When initial responses for patient 1 were examined as a function of laser light doses (circles in Figure 3), the data were fit by a 3-parameter Hill curve. From the shape of the curve in Figure 3, laser light doses higher than 90 to 100 J/cm² improved outcomes, with a prediction that doses of 150 J/cm² or greater would give a median treatment response of 85% or more. Median initial response to lamp irradiation was 75% (range, 25%-95%). However, in contrast to the laser, initial responses to the lamp appeared independent of light dose (data not shown).

On the basis of the results for the first patient, patient 2 was treated with laser light doses of 150 J/cm² and a lamp light dose of 100 J/cm² (Table 2). Only the BCCs with diameters larger than 1 mm were quantitatively evaluated (Figure 2A and B), but the myriad papules with diameters less than 1 mm that primarily were BFHs (Figure 2C) had similar responses (Figure 2D). Patient 3 subsequently was treated with higher laser light doses of 200 J/cm² and mean lamp light doses of 136 J/cm². For patients 2 and 3, all treatments used 20% ALA. Areas up to approximately 2000 cm² were photoirradiated in a session (Table 1). Initial laser treatment responses for patients 2 and 3 are presented in Figure 3. Although there is some variation in response rates, the median responses are consistent with the dose-response curve generated for patient 1.

For laser light doses greater than 95 J/cm², the median initial responses for patients 1, 2, and 3 were 85% (95% CI, 80%-90%), 82% (95% CI, 50%-91%), and 93% (95% CI, 85%-97%), respectively, as summarized in Table 3. There was no significant difference between patients 1 and 2 (P=.23), but the responses of patient 3 were significantly better than those of either patient 2 (P=.006) or patient 1 (P=.03). This finding is consistent with the larger light dose received by patient 1.

### Table 1. Treatment Areas

<table>
<thead>
<tr>
<th>Patient No./ Sex/ Age, y</th>
<th>No. of Treatments</th>
<th>Total BSA, cm²</th>
<th>BSA Involved With BCCs, cm²</th>
<th>Median Treated BSA per Session (Range), cm²</th>
<th>Median % Total BSA Treated per Session (Range), cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/6</td>
<td>7</td>
<td>10 100</td>
<td>2530</td>
<td>1300 (113-1984)</td>
<td>13 (1.1-20)</td>
</tr>
<tr>
<td>2/M/10</td>
<td>6</td>
<td>12 200</td>
<td>2030</td>
<td>779 (202-2030)</td>
<td>6 (2-17)</td>
</tr>
<tr>
<td>3/M/17</td>
<td>4</td>
<td>16 400</td>
<td>1970</td>
<td>427 (390-876)</td>
<td>4 (3-5)</td>
</tr>
</tbody>
</table>

*Abbreviations: BCCs, basal cell carcinomas; BSA, body surface area.

*At time of first treatment.

### Table 2. Treatment Parameters

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Laser</th>
<th>Lamp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Light Dose (Range), J/cm²</td>
<td>Mean Irradiance (Range), mW/cm²</td>
<td>Mean Light Dose (Range), J/cm²</td>
</tr>
<tr>
<td>1*</td>
<td>147 (60-240)</td>
<td>129 (60-150)</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>60 (50-70)</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>95 (85-150)</td>
</tr>
</tbody>
</table>

*Treatments 2 to 7 in patient 1.
3 and the rising slope of the light dose–response curve in Figure 3. The wide range of responses for patient 2 may in part be due to the varying pigmentation of his BCCs, which can reduce the effective light dose. For the lamp treatments, median initial responses for patients 1, 2, and 3 were 75% (95% CI, 70%-80%), 50% (95% CI, 44%-60%), and 75% (95% CI, 60%-78%), respectively (Table 3). Again, the BCC pigmentation in patient 2 may have contributed to his lower response rate. The lamp appeared less effective than the laser for each patient (P<.001 to P=.04), but the locations of the treatment sites and the sizes of the treatment areas differed.

**CUMULATIVE RESPONSE RATES AND DURABILITY**

Because initial treatments did not always give complete responses, individual areas were re-treated 1 to 2 times. In some cases, small clusters of BCCs that remained in large lamp fields were re-treated with the laser (Figure 2B), whereas in other cases the lamp was used to illuminate residual BCCs in multiple laser fields.

For the 3 patients, 291 fields (183 laser, 108 lamp), ranging from 2 to 16 cm in diameter (3-200 cm²) with a median diameter of 6 cm (28 cm²), were treated. Up to 36 fields were covered in a single session, using both laser and lamp illumination. The fraction of total BSA receiving ALA-PDT in a single session ranged from 1% to 20%, with respective medians in the 3 patients of 12%, 6%, and 3% (Table 1). To cover the affected areas and re-treat those with incomplete responses, patients 1, 2, and 3 thus far have had 7, 6, and 4 treatment sessions, respectively (Table 1).

The cumulative treatments have produced more than 98%, 90%, and 85% clearance in patients 1 (Figure 1C), 2 (Figure 2B and D), and 3, with respective follow-up times of 6, 1.8, and 1.8 years after their last treatment and 8.9, 4.9, and 3.2 years after their initial treatments. There is no evidence of new BCCs in the treated areas. After essentially complete clearing of her BCCs, patient 1 was treated by her local physicians for approximately 4.5 years. During this interval, she received oral retinoids (10 mg twice daily) for 20 months, discontinuing therapy because of skeletal symptoms. Although the areas on her torso that had received ALA-PDT remained essentially clear, she developed extensive BCCs on her scalp, as well as occasional lesions on the face and eyelids and scattered BCCs on the torso separate from the treated zones. She returned in September 2002 for evaluation of the scalp and received PDT to that site in June 2003, with a 75% mean initial response rate and minimal effects on hair growth (data not shown).

**TREATMENT EFFECTS**

Before treatment, the Woods lamp illumination showed bright PpIX fluorescence from BCCs exposed to ALA, with much less fluorescence from adjacent skin. Circulating blood porphyrin levels at the time of treatment were very low at a mean ± SD of 0.05±0.02 µg/mL compared with 4.0±0.7 µg/mL at the time of treatment with 1 mg/kg of porfimer sodium (Photofrin; Axcan Pharma, Birmingham, Ala) used in other patients.20 Treated fields developed moderate erythema, preferentially affecting the BCCs, and mild edema, maximal 24 to 36 hours after PDT (Figure 2A for patient 2). Mild discomfort was alleviated with ice and analgesics. During the next week, superficial desquamation that resembled a mild sunburn reaction was relatively localized to the BCCs. Epidermal damage was minimal, with no vesiculation or erosion. There were no ulcerations or other signs of dermal damage. Erythema resolved throughout 3 to 6 weeks without atrophy or scarring. Postinflammatory pigmented changes, most apparent in patient 2 (Figure 2B), resolved in 6 to 9 months. Before treatment, patient 3 had sparse hair as a result of his prior radiation therapy for medulloblastoma; ALA-PDT to the scalp caused an initial 30% to 50% decrease in hair density, but some regrowth is apparent. To evaluate possible tumor-promoting effects of ALA-PDT, we treated a clinically uninvolved area of skin on the back of patient 1. The area has remained free of BCCs for 8 years.

**COMMENT**

To our knowledge, this study is the first report of topical ALA-PDT for very large BSAs as well as the first application of this therapy in children. Our results demonstrate that topical ALA-PDT is both effective and safe for treating large areas of BCCs and BFHs in children with NBCCS. Substantial benefit is evident, with clearing of fields of papular-nodular BCCs that range from less than 1 mm to 3 to 4 mm in diameter without significant injury to healthy skin. The myriad BFHs in patient 2 also cleared with ALA-PDT. As noted, the combination of BCCs and BFHs in patient 2 is consistent with increased hedgehog pathway activation,8 but the association of NBCCS and BFHs has been described only once previously.21

We found that topical ALA can be applied using overnight occlusion to as much as 20% of the BSA without significantly elevated circulating PpIX levels or systemic toxicity and that with our treatment conditions, wide-area PDT causes lesion-selective damage and negligible scarring. Median responses to a single treatment were 82% to 90% with laser illumination and 50% to 75% with lamp illumination. The BCC clearance improved with re-treatment, without a decrease in efficacy or cumulative toxic effects.

Table 3. Treatment Outcomes

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Initial Response With Laser (95% CI), %</th>
<th>Initial Response With Lamp (95% CI), %</th>
<th>No. of Treatment Sessions</th>
<th>Cumulative Response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>85 (80-90)</td>
<td>75 (70-80)</td>
<td>7</td>
<td>&gt;98</td>
</tr>
<tr>
<td>2</td>
<td>82 (50-91)</td>
<td>50 (44-60)</td>
<td>6</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>93 (85-97)</td>
<td>75 (60-78)</td>
<td>4</td>
<td>85</td>
</tr>
</tbody>
</table>

*Light doses greater than 95 J/cm² (patient 1).
Because they have only 1 functional copy of the patched gene, patients with NBCCS are highly susceptible to DNA damage from therapies such as ionizing radiation. However, we found no evidence of ALA-PDT inducing or promoting BCCs in these patients. Instead, the treatment may prevent the appearance of new carcinomas. Topical PDT also resolved the radiation dermatitis seen in patient 1, although its efficacy for this condition needs to be examined in a larger study.

TREATMENT PARAMETERS

Direct PDT effects are primarily due to singlet oxygen, so we can define the PDT dose as a measure of the amount of singlet oxygen produced by the treatment and the PDT dose rate as the rate of production of the singlet oxygen. With adequate oxygen, the PDT dose rate and dose are proportional to the respective products of the photosensitizer concentration and the absorbed light dose rate and total absorbed light dose. Depletion of oxygen by the photodynamic process or by reduced perfusion will decrease the PDT dose rate but may not significantly affect the clinical PDT dose to a carcinoma. For ALA-PDT, the PDT dose and dose rate are determined by choices of light dose and irradiance (ie, light dose rate), ALA concentration, and application time. There have been substantial variations in these treatment parameters among different investigators. We found that relatively high light doses improved the clinical outcome (Figure 3). Tissue oxygen depletion that resulted from consumption by the photodynamic process was previously demonstrated for clinical porfimer-PDT.23 We expected this to be more of an issue with ALA-PDT because topical ALA produces higher skin photosensitizer levels than porfimer (A.R.O. and D.A.B., unpublished data, 2004). To reduce photodynamic oxygen depletion and thus maximize PDT dose and PDT dose rate, the irradiance were chosen to be as low as possible while still allowing delivery of the light dose to each treated area within 25 to 50 minutes.

We used ALA concentrations that ranged from 2.5% to 20%, with most treatments at 20%. Our responses were unrelated to drug concentration, since the ALA is likely in excess of the amount needed to maximally drive the biosynthetic pathway for PpIX.12,16 In our patients, we used overnight (18-24 hours) ALA application with occlusion, with light treatment the following morning. The overnight application was chosen both to enhance penetration of the ALA into papular BCCs and BFHs, which had intact stratum corneum and deep extension into the dermis, and to allow us to start long treatment sessions early in the morning. In addition, in adult patients, we had found that with our high light dose and irradiance treatments, 18- to 24-hour ALA applications caused less PDT-induced healthy skin damage than 4- to 6-hour ALA, without loss of treatment efficacy, even though the longer ALA application times led to greater PpIX levels in both carcinomas and perilobal skin (A.R.O., unpublished data, 2003; see also Peng et al38). Similar protective effects of high PDT dose rates in healthy skin have been reported for PDT with porfimer.25,30,38

The lower efficacy of the lamp compared with the laser may be in part because the mean delivered light doses from the lamp were lower than from the laser (Table 2). However, even for equal delivered doses, the lamp appears less efficient than the laser, possibly because not all of the broad-band spectral output of the lamp is absorbed by PpIX and its photoproducts. Nonetheless, the lamp is very useful because of the large areas that can be covered and its lower cost.

Although our treatment conditions were effective, the high PDT doses and dose rates and the large treatment areas led to significant treatment-associated pain. Local anesthetics are impractical in these circumstances. In adults, we have successfully used conscious sedation. In children, however, general anesthesia poses less risk and is the preferable choice. Although systemic anesthesia adds complexity, it would also be necessary in children for conventional treatments, such as surgery or wide-scale laser ablation. It is possible that other PDT treatment conditions would be less painful while maintaining efficacy, and we are investigating this possibility. Short-contact ALA and/or pulsed light sources have been used for extended areas on the face without significant discomfort, but these conditions deliver a small PDT dose, and these approaches have not been substantially effective for BCC. Photodynamic therapy with ALA methylester has been used for individual BCCs and may cause less discomfort, although pain has been reported; the surface preparation used in these studies would be impractical for our patients.

RESPONSE RATES

In each patient, we treated ensembles of BCCs with varying size, pigmentation, intrinsic biologic characteristics, and permeability to ALA. Thus, we expected a range of responses. For laser light doses greater than 95 J/cm², median response rates to initial treatments varied from 82% to 97%, with a 50% to 100% range (Figure 3). A similar variation was found with the lamp (data not shown). The initial response rates for laser irradiation are consistent with a sigmoidal Hill curve relationship between light dose and response, with a dose of 150 J/cm² giving an approximately 85% median response, with a suggestion of increasing response with light dose.

For multiple treatments, if the responses to additional treatments are similar to those obtained with the initial PDT, then if the initial response rate = R1, with a failure rate of F = 1 – R1, the response rate after a second treatment would be R2 = (1−F 2) and after 3 treatments would be R3 = (1 − F 3). Thus, for example, different initial response rates of 50%, 70%, or 85% (with failure rates of 0.5, 0.3, or 0.15) would give respective cumulative responses of 75%, 91%, or 98% after 2 treatments and 87.5%, 97.0%, or 99.7% after 3. These estimates are consistent with the observed cumulative response rates after 1 to 3 treatments, given the initial response rates. Our results are comparable with or better than those of others who used single or repetitive ALA-PDT for individual BCCs, particularly for nodular lesions. The Hill curve light dose–response relationship raises the possibility that variable outcomes in some of these prior studies may have been due to insufficient light or PDT doses.
The treatment areas of patient 1 have been essentially free of carcinomas for 6 years, although multiple BCCs occurred in untreated areas on the scalp and untreated areas of the torso and might have been expected to develop within the treatment zones. In patient 2, the responses of both BCCs and BFHs to individual sessions have persisted for as long as 4.9 years. Thus, the treatment appears durable, although we cannot exclude a 5% to 10% recurrence rate. The lack of appearance of BCCs in the treated areas compared with the rest of the body in both patient 1 and patient 2 suggests that ALA-PDT may inhibit new BCC development, as well as new BFHs in patient 2. Whether this inhibition is due to destruction of subclinical lesions or possibly to a local PDT-induced immune response is currently being investigated.

In conclusion, although there are many available treatment options for individual BCCs and BFHs, in our cases the excellent outcomes could not have been readily achieved by surgery or other conventional techniques or by PDT with systemic agents. Topical ALA-PDT is of extraordinary benefit to young patients with widespread BCCs because it is tissue sparing, is well tolerated, and yields outstanding cosmetic and functional results. In addition, wide-area topical ALA-PDT may play a significant therapeutic role in adults who develop extensive cutaneous carcinomas from long-term sun exposure, organ transplantation, or radiotherapy.

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