Acta Derm Venereol (Stockh) 1999; 79: 204–206

Photodynamic Therapy by Topical Aminolevulinic Acid, Dimethylsulphoxide and Curettage in Nodular Basal Cell Carcinoma: a One-year Follow-up Study

ANA MARIA SOLER[1], TROND WARLOE[1], JOHAN TAUSJØ[2] and AASMUND BERNER[3]

[1]Photodynamic Out-patient Clinic, Department of Surgical Oncology, [2]Department of Oncology and [3]Cytology Unit, Department of Pathology, The Norwegian Radium Hospital, Oslo, Norway

Fifty-eight patients with 119 nodular (2 mm or more in thickness) basal cell carcinomas successfully treated with photodynamic therapy were included in this 1-year follow-up study. The initial cure rate at 3–6 months was 92% after photodynamic therapy, which included an initial debulking procedure and topical application of dimethylsulphoxide in order to enhance penetration of 5-aminolevulinic acid (20% in cream) to which the lesions were exposed for 3 h prior to exposure to light. At examination 12–26 months (mean 17 months) after treatment 113 lesions (95%) were still in complete response. Six lesions (5%) had recurred, located on the face, scalp and ear. The cosmetic outcome was evaluated as excellent to good in 91%. Microscopic examination of biopsies taken from healed areas in 7 patients did not reveal any sign of damage in 5 and only minor alterations in 2. ***Key words: photodynamic therapy; nodular basal cell carcinoma; 5-aminolevulinic acid; curettage; dimethylsulphoxide.***

(Accepted October 26, 1998.)

Acta Derm Venereol (Stockh) 1999; 79: 204–206.

A. M. Soler, Photodynamic Out-patient Clinic, Department of Surgical Oncology, The Norwegian Radium Hospital, Montebello, NO-0310 Oslo, Norway.

Photodynamic therapy (PDT) is a treatment method based on the use of a photosensitizer and light to induce cell and tissue damage. PDT has been used experimentally for the treatment of multiple cancers for decades. During the past few years a haematoporphyrin derivative has been approved for certain indications. The drug is administered systemically causing a prolonged period of skin photosensitization (1, 2).

The compound 5-aminolevulinic acid (ALA) is a precursor in haem synthesis, and when given in excess, induces production and accumulation of protoporphyrin IX (PpIX), a highly photosensitive substance. In 1990 Kennedy et al. (3) showed that ALA administered topically induces a strong fluorescence in superficial basal cell carcinomas (BCCs) and, when subsequent red light is applied, the lesions show a complete remission rate of about 90% after a single treatment session. For nodular BCCs a much lower response rate has been reported (4–6), even if repeated treatment sessions have been shown to improve the results (4). In deep tumour lobules of nodular BCCs, little or no fluorescence is induced by ALA applied topically (7).

Peng et al. (8) have demonstrated that both the depth of penetration and the fluorescence intensity were increased by the use of dimethylsulphoxide (DMSO), either as a pre-treatment or as an adjunct to the ALA-containing cream. In clinical application, the addition of DMSO improved the remission rate of thin nodular BCCs (9). By adding curettage as a debulking procedure prior to DMSO pre-treatment the cure rate was 90% even for thick nodular BCCs, as reported by Warloe et al. (10).

The current report is a follow-up study of patients with nodular BCC treated with curettage and photodynamic therapy, carried out in order to assess the clinical results with respect to cure rate and cosmetic result 1–2 years after treatment.

MATERIAL AND METHODS

Patients

From January 1994 to May 1995, 158 BCCs from 84 patients (age range 36–86 years) were treated with topical ALA-based PDT. Clinical evaluation at 3–6 months after treatment resulted in 146 complete responding lesions from 73 patients. A total of 12 partial responding lesions in 11 patients were referred either for surgery or for radiotherapy.

Patients with complete responding lesions were invited to participate in the follow-up study. A total of 15 patients with 27 lesions were lost to follow-up and their lesions were consequently excluded from this report. Five patients reported that they were free of visible tumour, but could not participate in the follow-up study.

A total of 58 patients with 119 lesions appeared for follow-up consultation and were included. The period of observation from the last treatment ranged from 12 to 26 months (mean 17 months). An average of 2 lesions were treated in each patient. Initially 110 lesions (92%) had received a single session of curettage-PDT and achieved complete response. In 9 lesions (8%) the treatment had been repeated once or twice before complete response was achieved. In 34 of 119 lesions a previous PDT treatment without curettage had resulted in incomplete cure. Of the 25 lesions located on the nose, 21 had achieved complete response after curettage-PDT applied once. Of these, 11 had previously been treatment failures after PDT without curettage.

Twenty patients were asked to provide biopsy specimens from healed lesions on the trunk or extremities and from normal skin. These were used as controls. Seven patients accepted and 13 refused to undergo the procedure.

No patients with nevoid basal cell carcinoma syndrome were included in the current study.

Lesions

All lesions were initially verified by histology or cytology and were evaluated as ulcero-nodular BCCs with clear margins and of 2 mm or more deep or thick. A total of 12 lesions were recurrences after surgery (8), cryosurgery (3) and radiotherapy (1). Among the total of 119 nodular BCCs included, 62 lesions (52%) were located on the face and 57 lesions (48%) were located elsewhere on the body.

Treatment procedure

Eventual crusts at the surface were removed and skin covering the tumour was shaved off using the point of a needle. Curettage as a simple debulking procedure was performed by removing only visible parts of the tumour using a small surgical curette (House, 3-9 French, Elcon, Tutlingen, Germany). Complete removal of the tumour tissue was not

 ISSN 0001-5555

attempted, sparing adjacent normal skin and underlying dermis. This was performed with a minimum of bleeding and no local anaesthesia was necessary. Subsequently, a small piece of gauze soaked in DMSO 99% (Janssen Chimica, Geel, Belgium) was applied to the lesion for 10–15 min. ALA 20% (Norsk Hydro, Oslo, Norway) mixed with Unguentum Merck (Merck, Darmstadt, Germany) and DMSO 2% w/w was applied for 3 h covered by a semi-permeable dressing. After removal of the dressing, the lesion area was exposed to light emitted from a filtered broad-band halogen light source (produced by the instrumentation department of the hospital), with an emission spectrum of 550–700 nm at light doses of 100 J/cm^2 and fluence rate varying from 150 to 200 mW/cm^2.

Clinical and cosmetic evaluation

Responses were evaluated as complete (CR, complete disappearance of tumour), partial (PR, more than 50% reduction of tumour volume) or no response (NR, less than 50% reduction of tumour volume). The cosmetic outcome of the complete responding lesions was classified as excellent (absence of any sign of lesion or stigmata of treatment), good (slightly visible fibrosis, atrophy or change of pigmentation), fair (moderate visible fibrosis, atrophy or change of pigmentation) or poor (marked fibrosis, atrophy or change of pigmentation). The clinical and cosmetic results were scored by the same physician for all lesions.

Histological examination

A 4-mm cone biopsy was taken from healed lesions located on the trunk or extremities. A contralateral biopsy from normal skin served as a control. Due to the possibility of scar formation after biopsy, no such biopsies were taken from the face or neck. The biopsies were fixed in buffered 4% formalin, processed and embedded in paraffin. Sections 5 μm thick were stained with haematoxylin and eosin before light microscopic examination.

Cytological examination

Skin scrapings from suspicious lesions were taken in order to verify BCC and tumour recurrence The scrapings were smeared on object glasses, air-dried and Diff-Quick-stained before cytological evaluation.

RESULTS

At clinical evaluation, supplemented in cases of doubt by cytological evaluation, 113 lesions (95%) were scored as healed.

Out of 25 lesions located on the nose 23 were still in complete response and 19 and 4 lesions were scored as excellent and good.

Relapses

Six lesions recurred, representing 5% of the lesions re-examined. Three relapsing tumours were located on the scalp and temple partly covered by hair. Three were located on the nose and ear.

Cosmetic results

The cosmetic result was considered excellent in 71 lesions and good in 32 lesions. Nine lesions were scored as fair and 1 as poor. Since the follow-up at 3–6 months, the cosmetic result had improved in 19 lesions and none had a lower score.

Histological results

Five of 7 biopsies from healed lesions revealed normal skin without histological changes or remaining tumour. In 1 a slight superficial inflammation was found and in another some dermal fibrosis was present.

DISCUSSION

Several methods have been used in the treatment of nodular BCC. Mohs' micrographic surgery is the most successful, with a 5-year recurrence rate of 1–5.6% (11). Radiotherapy in the treatment of nodular BCC has a reported cure rate of 89–95% (12). Curettage with electrodesiccation and cryosurgery reports 5-year cure rates of 92% (13).

For superficial BCC, topical ALA-based PDT has proven to be an efficacious treatment modality, with a recurrence rate as low as 2% at 10 months (9). Follow-up observations for 3–5 years by our group (unpublished) have shown that most recurrences of superficial BCCs appear during the first 12 months and are rare thereafter. In our previous series of nodular BCCs treated prior to the introduction of debulking curettage, the observed cure rate was around 50% for lesions thicker than 2 mm, with a recurrence rate of approximately 5% during a mean observation time of 10 months after treatment (9). The previously reported clinical response of nodular BCC after 1 treatment with curettage and ALA-PDT is about 85% (10). In the current study the initial cure rate was 92% due to repeated treatment sessions.

A major advantage of ALA-based PDT is that the cosmetic outcome scored excellent or good in 91% of cases. Such a favourable result is advantageous for lesions on the face. The main stigma seen was scarring after an eventual diagnostic biopsy, which also made the clinical evaluation of treatment response more difficult. Skin scrapings from suspicious tumour recurrences did not affect the cosmetic results. By scraping the lesions, the consistency of the lesion was revealed. Cystic nodular tumours were easy to shave, whereas infiltrative or sclerotic lesions were more difficult to debulk completely. However, morphea type elements in a mixed ulcero-nodular BCC may be verified only by histology.

No residual deep tumour was detected in the 7 biopsies investigated. An increased number of biopsies would have strengthened the study. However, most patients eligible for punch biopsies refused. In our experience over more than 5 years of using PDT with large nodular tumours, an incomplete cure often arrives in small separate spots within cured areas, and a punch biopsy would not be representative for the entire lesion area treated. Due to the limited malignant potential of the tumours an waiting attitude concerning deep residual tumour may be adopted. Clinical evaluation and cytology might be adequate for safe follow-up.

Certain areas of tumour localization, i.e. on the nose, ear and hairy scalp, are found to be difficult to treat with our therapeutic method, as with alternative treatments. Here, repeated treatment sessions may be necessary.

Using curettage and DMSO as pre-treatment improves the penetration of ALA and thereby the possibility of PpIX production in the deeper layer of the nodular lesion. ALA is a molecule of low lipid solubility and certain ALA-derivatives (esters, ethers) have shown improved properties of penetration and induction of PpIX due to their more lipophilic molecular structure (14, 15). Ongoing studies may reveal whether the improved properties of these ALA derivatives will prevail or whether mechanical and chemical pre-treatment may nevertheless be necessary.

The current report shows that topical ALA-based PDT offers a therapeutic option even for nodular BCCs when the lesions are pre-treated by curettage and DMSO. Therapy may be repeated successfully in cases of non-cure or recurrence without cosmetic impairment or deterioration of skin structure. The challenge is to determine which BCC lesions are suited to various treatment methods as a primary treatment.

ACKNOWLEDGEMENT

We thank Ruth Riste for helping prepare the manuscript.

REFERENCES

1. Dougerthy TJ. Photosensitisation of malignant tumours. Semin Surg Oncol 1986; 2: 24 – 37.
2. Wilson BD, Mang TS, Stoll H, Jones C, Cooper M, Dougherty TJ. Photodynamic therapy for the treatment of basal cell carcinoma. Arch Dermatol 1992; 128: 1597 – 1601.
3. Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. J Photochem Photobiol B: Biol 1990; 6: 143 – 148.
4. Svanberg K, Andersson T, Killander D, et al. Photodynamic therapy of non-melanoma malignant tumours of the skin using topical delta-amino levulinic acid sensitisation and laser irradiation. Br J Dermatol 1994; 130: 743 – 751.
5. Wolf P, Rieger E, Kerl H. Topical photodynamic therapy with endogenous porphyrins after application of 5-aminolevulinic acid. J Am Acad Dermatol 1993; 128: 17 – 21.
6. Fijan S, Hönigsmann H, Ortel B. Photodynamic therapy of epithelial skin tumours using delta-aminolevulinic acid and desferrioxamine. Br J Dermatol 1995; 133: 282 – 288.
7. Martin A, Tope WD, Grevelink JM, et al. Lack of selectivity of protoporphyrin IX fluorescence for basal cell carcinoma after topical application of 5-aminolevulinic acid: implications for photodynamic treatment. Arch Dermatol Res 1995; 287: 665 – 674.
8. Peng Q, Warloe T, Heyerdahl H, Moan J, Steen HB, Giercksky K.-E. Distribution of 5-aminolevulinic acid-induced porphyrins in nodulo-ulcerative basal cell carcinoma. J Photochem Photobiol 1995; 62: 906 – 913.
9. Warloe T, Peng Q, Moan J, Steen HB, Nesland JM, Giercksky K.-E. Photodynamic therapy with 5-aminolevulinic acid induced and DMSO/EDTA for basal cell carcinoma. SPIE 2371. 1994: 226 – 235.
10. Warloe T, Heyerdahl H, Giercksky K.-E. Curettage and topical ALA-based photodynamic therapy for nodular ulcerative basal cell carcinomas. Thesis. ISBN 82-7722-038-3, 1995; paper VI. University of Oslo.
11. Rowe DE. Comparison of treatment modalities for basal cell carcinoma. Clinics Dermatol 1995; 13: 617 – 620.
12. Olbricht SM. Treatment of malignant cutaneous tumors. Dermatol Plastic Surg 1993; 20: 167 – 180.
13. Rowe DE, Carroll RJ, Day CL Jr. Long term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patients follow-up. J Dermatol Surg Oncol 1989; 15: 315 – 328.
14. Peng Q, Moan J, Warloe T, Iani V, Steen HB, Bjørseth, Nesland JM. Build-up of esterified aminolevulinic-acid-derivative-induced porphyrin fluorescence in normal mouse skin. J Photochem Photobiol B: Biol 1995; 34: 95 – 96.
15. Kloek J, Beijersbergen van Henegouwen GMJ. Prodrugs of 5-aminolevulinic acid for photodynamic therapy. J Photochem Photobiol B: Biol 1996; 6: 994 – 1000.