Photodynamic Therapy of Residual or Recurrent Basal Cell Carcinoma after Radiotherapy using Topical 5-Aminolevulinic Acid or Methylester Aminolevulinic Acid

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This study was conducted to assess the efficacy of aminolevulinic acid-based photodynamic treatment for residual or recurrent basal cell carcinomas after radiotherapy. Photodynamic therapy with either topical 5-aminolevulinic acid 20% and dimethylsulfoxide 99% pretreatment or topical methylester aminolevulinic acid 20% w/w in cream and subsequent light illumination of 50–200 J/cm^2 was performed after an initial skin shaving procedure in 20 patients with 22 residual or recurrent basal cell carcinomas. Three lesions were treated once, while twelve, three, one and two lesions received two, three, four and five treatment sessions respectively. At examination, 6–40 months (mean 22 months) after the last treatment, 18 lesions were in complete remission. All lesions were considered excellent or good with regard to cosmetic outcome. Three lesions responded only partially to photodynamic therapy and a fourth lesion recurred 21 months after photodynamic treatment. Two of these four lesions were confirmed as the morpheaform type of basal cell carcinoma.

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Basal cell carcinomas (BCC) recurring after radiotherapy can be aggressive and invasive tumours in which cure may be difficult to achieve (1). Mohs micrographic surgery (MMS) is reported to give the highest cure rates for such tumours compared with surgical excision or further radiotherapy (2).

Photodynamic therapy (PDT) has been investigated during the past decade as a new treatment method for BCC. The principle of PDT is based on a photosensitizer that accumulates in malignant tissue and induces cytotoxic singlet oxygen production when activated by light (3). 5-Aminolevulinic acid (ALA) is a natural precursor of protoporphyrin IX (PpIX) in the biosynthetic pathway of heme. PpIX accumulates in the mitochondria, lysosomes and membranes of the cell (3). ALA itself is photo-inactive, but given in excess, it is converted to the highly phototoxic PpIX, possibly owing to a relatively deficient ferrochelatase activity in malignant cells (3).

In several studies, PDT for superficial BCCs has given complete remission rates of up to 95–100% using 20% topical ALA and red light from either a broad wavelength lamp or laser (4–8). For nodular BCCs the results have been disappointing, with cure rates of up to one-third (5–8), probably because of insufficient penetration of the hydrophilic ALA through the epithelial layer covering nodular BCCs. The penetration of ALA in nodular BCCs may be enhanced by removing the epithelial layer either physically by shaving or chemically by increased permeability with dimethylsulfoxide (DMSO). The PpIX production in the tumour has been shown to be increased by this procedure (9–11). ALA-based PDT, combining DMSO and shaving, shows cure rates from 0 to 32% up to 85% to 90% in nodular BCCs at 3–6 months after treatment (11, 12). BCC recurrences following radiotherapy have been treated with the same procedure with promising results at a 3-month evaluation (11). Methylester ALA (M-ALA) is more lipophilic than free ALA and penetrates more effectively through cutaneous tissue, resulting in higher porphyrin fluorescence in mouse skin (13). A recent study shows higher lesional selectivity towards normal skin in solar keratosis using M-ALA compared with using ALA (14).

The aim of this study was to investigate the efficacy of topical PDT as a treatment for residual or recurrent BCC after radiotherapy.

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MATERIAL AND METHODS

This study is retrospective and non-randomized.

Patients and lesions

From January 1996 to November 1997, 20 patients (12 women and 8 men, mean age 71 years, range 43–100 years) with 22 BCC were included in the current study (Table 1). All lesions, verified as BCCs by histology or cytology, had been previously treated with radiotherapy and were considered as treatment failures. All patients were selected to PDT at the oncological outpatient clinic at the hospital and evaluated by an oncologist (JT) before treatment with PDT. All tumours that were either residual or recurrent tumours after radiotherapy and subsequently treated with PDT in this specific period of time were included in the retrospective study. These tumours were selected to PDT because surgery was supposed to give a poor cosmetic result.

Fourteen lesions had been previously treated with radiotherapy only, while six and two lesions had recurred after surgery and cryosurgery, respectively, before the radiotherapy. After radiotherapy, six lesions in four patients were already observable at the 6-weeks follow-up and were thus classified as residual tumours, while 16 lesions recurred at 9–336 months (mean 107 months) and were classified as recurrences. Twenty lesions had been treated with superficial radiotherapy (50 kV) and two lesions located on the nose and ear had received radiotherapy with electrons (6 MeV, 5 bolus and 8 MeV, 0.5 bolus, respectively). Radiation doses varied from 30 to 60 Gy (mean 47 Gy) in 4–20 fractions (mean 11 fractions).

Nineteen patients had one lesion each and the last patient presented with three lesions. Twenty lesions were located in the face and two lesions were located on the trunk. Six and 10 of these lesions were central or border recurrences, respectively. Tumour diameter in 21 tumours ranged from 2 to 70 mm (mean size 15 mm). Tumour size data were missing in lesion 14 located on the shoulder.

Drugs

Two different formulations were used:
Drug A—5-aminolevulinic acid (ALA) 20% (PhotoCure ASA, Oslo, Norway) in Unguentum Merck (Merck, Darmstadt, Germany) and dimethylsulfoxide (DMSO) 2% w/w (Janssen Chimica, Geel, Belgium).
Drug B—Methylester aminolevulinic acid (M-ALA) 20% (PhotoCure ASA, Oslo, Norway) in Unguentum Merck.

Treatment procedure

All lesions were shaved using the point of a needle and a small surgical curette. Removal of the epithelium was followed by intra-tumoural curettage sparing the basal part of tumour and adjacent normal skin. No local anaesthesia was necessary.

Table 1

Patient characteristics, tumour localization, previous treatment and radiation therapy in 20 patients with recurrent or residual tumours after radiotherapy

Patient no.	Lesion no.	Age	Sex	Localization	Previous treatment	Radiation (Gy) dose[1]	Fractions	Time to observed recurrence (months)
1	1	53	M	Nose		37.5	5	156
2	2	43	F	Nose		48	12	17
3	3	71	F	Nose	Cryo	50	20	108
4	4	59	F	Nose	Surgery	57	11	180
5	5	70	F	Temple	Surgery	40	4	216
6	6	60	M	Nose	Surgery	51[1]	17	23
7	7	60	F	Nose		48	12	non-Cr[2]
8	8	54	F	Chin	Surgery	48	12	9
9	9	83	F	Forehead		60	6	196
10	10	80	M	Chin		48	12	non-Cr[2]
	11			Nose		48	12	non-Cr[2]
	12			Nose		48	12	non-Cr[2]
11	13	81	F	Temple	Surgery	40	10	non-Cr[2]
12	14	73	M	Ear		40	10	10
13	15	89	M	Nose		30	5	16
14	16	70	M	Shoulder		42.5	5	48
15	17	69	M	Forehead		52	13	102
16	18	80	F	Ear	Cryo	48[1]	12	12
17	19	56	M	Forehead	Surgery	45	15	105
18	20	72	F	Chin		60	12	336
19	21	83	F	Back		45	9	171
20	22	100	F	Medical canthus		40	8	non-Cr[2]

[1] Radiotherapy with electrons.
[2] Not complete response to radiotherapy.

Table 2

Tumours in complete response after PDT

Patient no.	Localization	Tumour size (mm)	Tumour type	No. of PDT fractions	Cosmetic results
1	Nasal dorsum	15	Morpheaform	1	Excellent
2	Ala nasi	3	Nodular	2	Excellent
3	Nasal dorsum	15	Nodular	1	Excellent
4	Ala nasi	4	Nodular	3	Excellent
5	Temple	25	Nodular	1	Excellent
6	Ala nasi	4	Nodular	2	Excellent
7	Nasal dorsum	15	Nodular	2	Good
8	Chin	3	Nodular	2	Excellent
9	Forehead	20	Nodular	2	Excellent
10	Chin	20	Nodular	2	Excellent
10	Nasal dorsum	7	Nodular	5	Excellent
10	Ala nasi	5	Nodular	2	Excellent
13	Ala nasi	2	Nodular	2	Good
14	Shoulder	M*	Nodular	3	Excellent
15	Forehead	10	Nodular	2	Excellent
17	Forehead	30	Morpheaform	2	Good
18	Chin	15	Nodular	2	Excellent
19	Back	20	Nodular	2	Excellent

M* = missing value.

Owing to the development of M-ALA during the study period, both ALA and M-ALA treatment procedures were used.

– ALA treatment procedure. A small piece of gauze soaked in DMSO 99% was applied to the lesion for 5–10 min. ALA 20% with DMSO 2% was applied to the lesion area underneath a seem-permeable dressing (3M, St Paul, MN, USA) for 3 or 24 h.
– M-ALA treatment procedure. M-ALA was applied to the lesion area for 3 h underneath a seem-permeable dressing (3M). No pretreatment with DMSO 99% was done.

Table 3

Distribution of drugs and intervals in PDT treatment

Patient no.	Lesion no.	Treatment drug[1]	No. of PDT fractions	Treatment intervals[2]	Rank of treatment drug
1	1	M	1		
2	2	A	2	2	
3	3	A	1		
4	4	M	2	29	
5	5	A	1		
6	6	A	2	3	
7	7	A,M	2	3	M,A
8	8	A,M	2	1	M,A
9	9	A	2	1	
10	10	M	2	1	
10	11	A,M	5	1, 12, 1, 6	M,M,A,A,M
10	12	M	2	1	
11	13	A,M	5	1, 12, 1, 12	A,M,M,M,A
12	14	A,M	3	3	A,A,M
13	15	M	2	2	
14	16	A	3	18, 31	
15	17	A,M	2	18	A,M
16	18	M	3	4, 5	
17	19	A	2	9	
18	20	A,M	2	2	M,A
19	21	A	2	32	
20	22	M	2	18	

[1] M = methylester ALA; A = 5-aminolevulinic acid; M,A = both drugs used alone in one (or more) treatment sessions(s).
[2] Week(s) between each treatment.

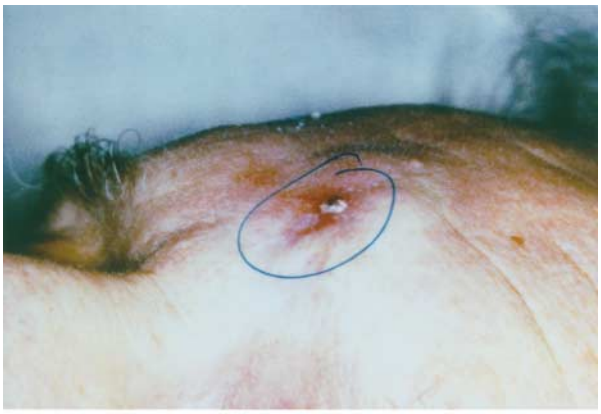

Fig. 1

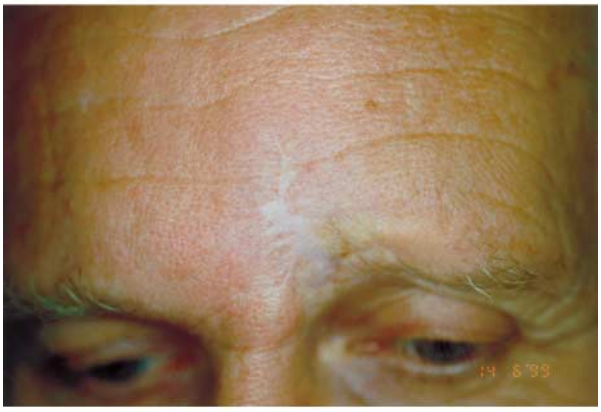

Fig. 2

Fig. 1. Patient no. 17 with a recurrent morpheaform tumour after surgery and radiation before PDT.

Fig. 2. Patient no. 17 with complete healed lesion 33 months after PDT.

After removal of the cream, the lesion area was exposed to light from a filtered broadband halogen light source (PhotoCure ASA) with an emission spectrum of 570–670 nm at light doses of 50–200 J/cm^2 (mean light dose 99 J/cm^2). Three lesions were treated with PDT once. The remaining 19 lesions received two (13 lesions), three (three lesions), four (one lesion) and five (two lesions) treatment sessions respectively (see Tables 2 and 3). Eight of 22 lesions were treated with ALA alone. During the study M-ALA became available for a period of time and seven of a total of 22 lesions were treated with M-ALA only in a non-randomized fashion, while another seven lesions were treated with both M-ALA and ALA, but in different treatment sessions. Four lesions had ALA as the drug in the last treatment and M-ALA was the drug in the last treatment session in the remaining three lesions (see Table 3).

Clinical and cosmetic evaluation

Response after PDT was evaluated as complete (CR: complete remission of tumour) or incomplete (non-CR: not complete remission of tumour). Cosmetic outcome of the CR lesions was classified as excellent (no visible signs of treatment), good (slightly visible discolouration, fibrosis or atrophy), fair (moderate visible change of pigmentation, fibrosis or atrophy) or poor (marked discolouration, fibrosis or atrophy). All 16 recurrent lesions had some degree of hypopigmentation and atrophy before PDT owing to previous radiation therapy, surgery or cryotherapy, and the change of cosmetic outcome was duly recorded.

RESULTS

The follow-up period from the last PDT session ranged from 6 to 40 months, with a mean observation time of 22 months.

A total of 18 of 22 lesions were evaluated as CR after PDT in the follow-up period (Figs. 1 and 2 and Table 2).

For the lesions evaluated as CR, the cosmetic outcome was considered excellent in 15 lesions and good in three lesions (Table 2). No lesion was scored as fair or poor compared to baseline.

Three lesions were treatment failures to PDT and one lesion recurred after PDT treatment. Two of these lesions had been treated with M-ALA (Table 3). Two of the four non-successfully treated lesions were classified as morpheaform lesions by histology, a well-known high-risk

Table 4

Photodynamic treatment failures

Patient no.	Location	Response to radiotherapy	Tumour size	Histology	No. of PDT fractions	Time to recurrence (months)[1]
11	Temple	Residual	70 mm	Morpheaform	5	0[2]
12	Dorsum of the ear	Recurrence	12 mm	Morpheaform	3	0[2]
16	Conchae of the ear	Recurrence	5 mm	Nodular	3	24
20	Medial canthus of the eye	Residual	10 mm	Nodular	2	0[2]

[1] Time of recurrence after PDT.
[2] No response to PDT.

tumour difficult to cure by any treatment modality. These four lesions were all located in 'high-risk areas': ear, temple (hairy area) or near the eyes. Acute phototoxic reactions after illumination as local oedema and redness were less pronounced with M-ALA than following ALA with DMSO.

DISCUSSION

The 5-year recurrence rate after radiotherapy of primary BCCs is reported to be about 7% (15). Recurrent BCCs after radiotherapy are more difficult to cure than primary tumours, as evidenced by a recurrence rate of about 12–25% after retreatment by surgical resection (2, 16). After MMS of recurrent tumours following radiotherapy, the recurrence rate is reported to be 7% at 25 months (2). MMS is time-consuming, costly and should be performed only by trained persons, but gives high cure rates compared with simple surgical resection (1, 15).

PDT is a simple procedure that can be performed on an outpatient basis. The most important advantages of PDT are low cost and simple treatment, with only minor discomfort to the patient as well as favourable cosmetic results. PDT can be repeated several times without damage to the adjacent normal skin (17).

However, in our experience, PDT is not recommended for tumours on the nose or ear with invading underlying cartilage. Morpheaform BCCs may be difficult to cure with PDT. Two of the four PDT failures in this study were morpheaform lesions. However, another two morpheaform tumours located on the forehead and medial canthus of the eye were successfully cured with PDT. The results of our study show that up to three to four treatments of weekly intervals with PDT may be necessary to achieve success in difficult cases (Table 2). Two treatment sessions once a week are preferable for most of the tumours in this study (Table 4). Treatment pain and acute local reaction as redness and oedema were more pronounced with ALA/DMSO than that with M-ALA. The clinical response was not different in this study between ALA/DMSO and M-ALA, but a randomized study of sufficient strength must be conducted to compare the efficacy between the two drugs.

This study shows that some difficult tumours as residual and recurrent BCCs after radiotherapy may be cured by PDT. Further studies with longer follow-up periods are necessary before PDT can be established as an alternative treatment method for residual or recurrent tumours following radiotherapy.

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