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ORIGINAL PAPER

Adjunctive treatment of keloids: comparison of photodynamic therapy with brachytherapy

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Abstract
Background The aesthetic result after brachytherapy, especially hypopigmentation, remains a significant problem. Given that brachytherapy may be carcinogenic, it is difficult to recommend this treatment in young patients. For these reasons, there is a need for alternatives to radiation.
Methods The purpose of this study was to evaluate the effectiveness of adjuvant photodynamic therapy (PDT) using aminolevulinic acid after keloid excision and to compare it to keloid excision followed by brachytherapy. To assess outcome, the Patient and Observer Scar Assessment Scale (POSAS) was used.
Results Thirty-four patients treated for 45 keloids were evaluated. Twenty-two patients (27 lesions) received brachytherapy and 12 (18 lesions) received PDT. The observers scored a mean POSAS of 19.1 (range 13.0–34.0) for brachytherapy and 24.6 (range 11.0–37.0) for PDT (p=0.005). The independent observers scored a mean POSAS of 14.6 (range 10.0–20.0) for brachytherapy and 18.6 (range 9.0–42.0) for PDT (p=0.018). The patients reported a significantly better mean POSAS score after brachytherapy (22.8, range 7.0–53.0) than following PDT (34.2, range 11.0–63.0). The patients' POSAS score showed no significant difference for the item "general impression" for both treatment groups; the observers scored significantly higher for PDT treatment. The independent observers revealed a higher score for general impression after PDT although not reaching significance.
Conclusions Patients and observers appear to be more satisfied with the results after brachytherapy than PDT. However, patients still have a positive general impression after PDT. Adjunctive aminolevulinic acid–PDT for the treatment of keloids could be used as an alternative for brachytherapy. Level of Evidence: Level IV, therapeutic study.

Keywords Brachytherapy · Keloid · Aminolevulinic acid · Photodynamic therapy · POSAS

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Introduction

Keloid is defined as scar tissue that extends beyond the borders of the original lesion. Keloids do not regress spontaneously and tend to recur frequently following excision [1]. Keloids may arise following injury to the deep dermis, including lacerations, abrasions, surgery, piercings, vaccinations, burns, etc. The disease appears to run in families, but the mode of inheritance is not clear. Site susceptibility to keloids is also recognized, with the presternal area, back, earlobe, and the posterior neck being the predilection sites. Keloids tend to occur more frequently in individuals with dark skin phenotypes (i.e., phototypes) [2]. These lesions appear to affect male and female subjects at equal rates;

however, individuals with ear piercings are at greater risk. Keloid occurs from around 0.1 % in Middle Europe to 12 % in Central Africa [3–5]. Lesions commonly cause symptoms of pain, burning, and itching and can restrict motion of the affected limb. Furthermore, keloid scars can be extremely disfiguring and therefore adversely affect the patient's quality of life by causing both physical and psychological impairments [6]. Keloids have proven to be difficult clinical entities to treat, since they demonstrate a notoriously recurrent behavior after classical treatment approaches. Modern research, however, has led to an increased understanding of the pathophysiologic processes of wound healing and scar formation. Furthermore, the advancement of technology has allowed for the development of more specific and localized therapies. Current treatment options include a large variety of primary treatment modalities, e.g., surgical excision, laser ablation, intralesional injections, pressure therapy, silicone dressings, topical preparations, oral agents, external beam radiotherapy, brachytherapy, and cryotherapy. Although there are many different types of effective therapy, no consensus has been reached as to how to treat these lesions best. Surgery alone leads to recurrence rates of 45 to 100 % [7]. In the only randomized trial of any treatment for keloids, surgery and radiotherapy combined appeared to be more effective than surgery and corticosteroid injections (respectively, 12.5 versus 33 % percent relapse at 12 months after treatment) [7–9]. Adjunctive interstitial radiotherapy or brachytherapy using ^{192}Ir after surgical removal of the scar has shown to be very effective in clearance of the disease and is therefore routinely used in our department. In the treatment of keloid scars, the aesthetic result, e.g., hypopigmentation, obviously remains of significant concern. Given that brachytherapy may also be carcinogenic, it is often difficult to recommend this treatment when one is dealing with young adolescent patients. For these reasons, there is a need for alternatives to radiation therapy as the main treatment mode.

Photodynamic therapy (PDT) has been in clinical development since the late 1970s and has been used for oncological diseases in many different specialties. A photosensitizer (or a precursor) is administered to the patient and after a particular time interval; the tissue is exposed to light with an appropriate wavelength. Typically, red light is used to maximize tissue penetration. In our department, topical aminolevulinic acid (ALA) is used routinely to treat skin (pre-)malignancies. Given the ease of administering topical PDT using porphyrin precursors, it is surprising that there has only been a single case study reporting its use for the treatment of intact keloids [10]. Since the topical application of porphyrin precursors may limit the depth of lesions that can be effectively treated, we investigated the use of adjunctive ALA-PDT after surgical excision in the same way as we apply interstitial brachytherapy.

While the mechanism(s) underlying the response of keloids and normal tissue susceptible to keloid formation to PDT is(are) unknown, some authors have suggested the potential importance of modulation of growth factors and cytokine expression. PDT generates reactive oxygen species, notably singlet oxygen that can cause cell apoptosis and/or necrosis and leads to damage to cellular membranes such as those of the mitochondria. These events activate many signaling pathways involving for example TNF-α. In vitro, PDT has been shown to have a significant influence on the balance of collagen synthesis [11] and fibroblast proliferation [12]. In addition ALA-PDT has been shown to have significant effects on the local vasculature [13] and leads to the induction of local immunological responses that are dependent on the illumination scheme [14, 15].

Pain during light exposure is a significant side effect of ALA-PDT since nerves cut during surgery may take up ALA and synthesize protoporphyrin IX. The purpose of the present study was to evaluate the effectiveness of PDT and compare it to keloid excision followed by brachytherapy (BT). To assess outcome, the Patient and Observer Scar Assessment Scale (POSAS) was used.

Patients and methods

Seventy-five patients with 117 lesions were enrolled in this retrospective cohort study between January 2000 and December 2009. Lesions were surgically excised with a narrow margin and closed preferably in a straight line and received either adjunctive interstitial BT or ALA-PDT. Surgery was done by the plastic surgeons (specialist) in our institution. One and the same radiotherapist (specialist) was responsible for the BT and PDT.

Treatment protocols

The BT protocol was as follows: two standard after-loading catheters were implanted subcutaneously, 1.5 cm apart, both equidistant to the closure site (=scar) of the excised lesion. After simulation, films were obtained and treatment planning was performed with the most distant localization according to protocol being 1.5 cm outside the target. After optimization of the implant, two fractions of 9 Gy, prescribed to the temporarily positioned Pb markers on the skin and/or to a distance of 0.5 cm from the source train, were applied. The interfraction time interval was minimally 6 h.

At the start of the inclusion period, PDT had not been reported in the literature for the treatment of keloids. Since ALA-PDT is known to cause significant necrosis and inflammation associated with a local immunological response, we performed a pilot study in a small number of lesions using three interstitial treatment sessions as described below.

Subsequent patients received additional treatment sessions using topically applied ALA at weekly intervals for 6 weeks. The PDT protocol was as follows: immediately before surgical closure, ALA solution (20 % *w*/*w*, ALA hydrochloride (Sigma) in Instillagel® (Medeco)) [16] was applied in excess to the wound bed and surrounding skin with a 1-cm margin. A transparent catheter was then inserted in the wound bed and sutured at a depth of approximately 1 cm. The wound was closed and the patient returned to the ward. Four and 6 h after the application of ALA, scars received ALA-PDT in a dose of 20 Jcm^{-1} by inserting a cylindrical diffuser of appropriate length into the interstitial catheter couple to a 2-W, 630-nm diode laser (Zeiss, DE). Figure 1 shows an example of the interstitial illumination procedure. The treated area was then covered with a light-occluding dressing. Three days later, the area was exposed and ALA solution was reapplied with a 1-cm margin surrounding the visible scar. Four hours later, the scar received a third interstitial illumination of 20 Jcm^{-1}. For each illumination, the fluence rate was measured at the center, within the illumination catheter, and confirmed to be between 50 and 100 $mWcm^{-2}$. The catheter was then removed and the patient was discharged from the hospital. In the study group, patients returned to the outpatients' clinic at approximately weekly intervals. Topical ALA was applied under occlusion for 4 h and scars received 20 Jcm^{-1} of light which was delivered from a diffuser/catheter placed directly on the surface of the lesion. The fluence rate was again measured at the center, within the illumination catheter, and confirmed to be between 50 and 100 $mWcm^{-2}$. Six topical ALA-PDT treatment sessions were performed at weekly intervals.

Pain management

Patients reported very intense burning sensation during each interstitial illumination. This was the most intense for the two illuminations on the day of surgery. Intravenous analgesics (opioids) were essential during these treatment sessions. Topical PDT in the outpatients' clinic required oral (NSAID's, morphine) or transdermal (fentanyl) administration of analgesics and was well tolerated.

Cosmetic outcome

All patients were seen in routine clinical follow-up to score the aesthetic outcome. For scoring outcome, we used the Patient and Observer Scar Assessment Scale that was translated into Dutch. The POSAS is the most frequently used scar assessment scale at present and consists of two scales: the patient scale and the observer scale [17, 18]. The patient scale contains the items scar color, pliability, thickness, relief, itching, pain, and general impression. The observer scale contains the items vascularization, pigmentation, thickness, relief, pliability, surface area, and general impression. Each item has a ten-point score with the score 10 reflecting the worst imaginable scar or sensation. During the outpatient visit, the patients were asked to complete the POSAS patient scale. Photographs of the scar(s) were taken by a professional medical photographer of the Department of Radiation Oncology. In order to reduce bias in the assessment of outcome, an assessment panel of eight persons, not connected to the therapy, was assembled. This consisted of four radiotherapists, one plastic surgeon, and three independent observers: a general practitioner, a school teacher, and an administrative assistant. The POSAS observer scale was digitalized (Fig. 2) to be used as a user-friendly scoring system. The parameters pliability and surface area were eliminated from the observer scale since, in order to score pliability, one must palpate the scar and, in order to score surface area, preoperative photographs were needed, and these were unfortunately not available for all the patients.

Data analysis

Statistical analyses were performed using Stata® 11.0 (StataCorp, TX, USA). The Kruskall–Wallis rank test was used

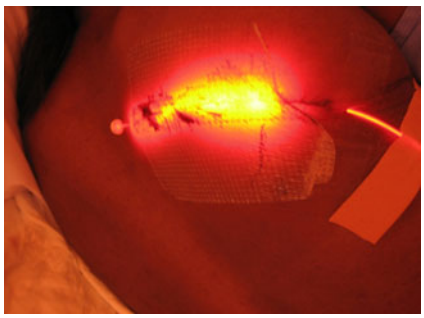

Fig. 1 An example of the light field during an interstitial illumination the scar

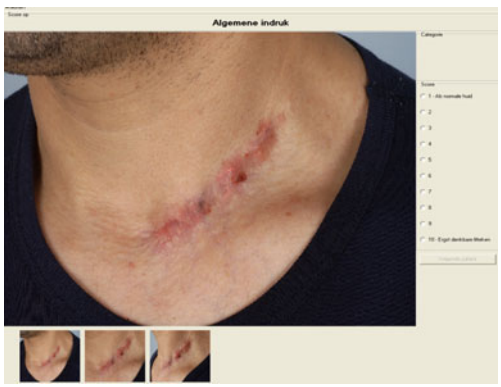

Fig. 2 Example of the digitalized observer scale item general impression and response to BT 60 months after therapy

for nonparametric significance tests. All significant tests were two-sided and p values <0.05 were considered statistically significant.

Results

A total of 53 patients (75 lesions) received BT and 21 patients (36 lesions) received PDT. Three patients (four lesions) did not return for all of the outpatient treatment sessions. One lesion in one patient was only excised and not treated by BT. Thirty-four patients responded to our invitation to complete a POSAS assessment of outcome. The remaining patients were not traceable; a large proportion have emigrated. Of the 75 patients enrolled in the study, 22 (27 lesions) who received BT and 12 (18 lesions) who were treated with PDT were available for outcome analysis (Table 1).

Lesions treated using ALA-PDT in the pilot group that received three fractions on days 1 and 4 following surgery did not show any adverse inflammatory responses and therapy was well tolerated apart from the pain associated with the illumination, as described below. Figures 2 and 3 show examples of scars at the time of POSAS analysis treated with BT and PDT, respectively. Following PDT, the most encouraging responses were characterized by relatively flat scars with minimal erythema at the margins particularly at the ends of their long axes. All the POSAS scores for the 34 patients were available for analysis. In the group treated with BT, the mean POSAS score of all observers

Table 1 Characteristics of the study group patients

Treatment	BT	PDT
No. of patients	54	21
Lesions treated	75	36
Treatment modality	BT	PDT
No. of patients	22	12
No. of lesions	27	18
Caucasian	10	6
Non-Caucasian[a]	12	6
Gender[b]		
Women	10 (45 %)	8 (67 %)
Men	12 (55 %)	4 (33 %)
Total patients	22 (100 %)	12 (100 %)

The mean follow-up period for BT was 64 months (range 9.5–108 months) and 34.4 months for PDT (range 12.5–52.2 months)

BT brachytherapy, *PDT* photodynamic therapy

[a] Non-Caucasians (African, Chinese, Indian, and mix types)

[b] There was no significant imbalance in gender among the two groups (p=0.429, logistic regression)

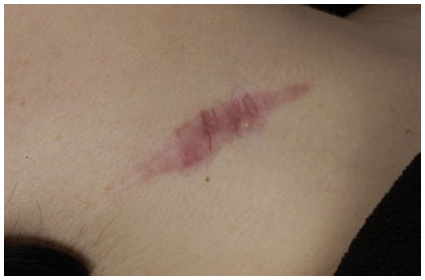

Fig. 3 Example of the response to ALA-PDT of the neck 9 months after therapy

was 20.3±9.2 (range 6.0–53.0) for brachytherapy and 25.2±10.1 (range 9.0–63.0) for PDT (p<0.001). The observers assessed a mean POSAS of 19.1±5.2 (range 13.0–34.0) for BT and 24.6±6.6 (range 11.0–37.0) for PDT. The independent observers assessed a mean POSAS of 14.6±3.3 (range 10.0–20.0) for BT and 18.6±6.8 (range 9.0–42.0) for PDT.

The patients reported a significantly (Kruskall–Wallis rank test) better mean POSAS score after BT (22.8±13.5, range 7.0–53.0) than following PDT (34.2±18.4, range 11.0–63.0) (Table 2). The analyses for the item "general impression" are summarized in Table 3.

Discussion

In this study, we evaluated the effectiveness of adjuvant ALA-PDT following surgical excision of keloids by comparing outcome with conventional adjuvant brachytherapy. Apart from a single case study using topical methyl aminolevulinate–PDT [10], this is the first large-scale study investigating the clinical use of PDT for keloids and the first study comparing the effect of PDT with conventional adjuvant brachytherapy.

The rationale for treating keloids using PDT is clear: the pathogenesis of keloid formation after surgical excision appears to be rather complex, but there is evidence that normal tissue developing into keloids seems to have an inability to prevent the formation of excessive amounts of collagen. Keloid tissue can have more than four times the collagen content of normal unscarred skin [19]. Fibroblasts in keloids overexpress growth factors such as vascular endothelial growth factor, transforming growth factor, and platelet-derived growth factor alpha. In other similar skin pathologies, PDT using porphyrin, precursors have been shown to modulate these signaling pathways, leading to a reduction in fibroblast proliferation and collagen synthesis [20, 21]. Given this clear rationale for the use of PDT to modulate collagen production and fibroblast proliferation in normal tissues that are susceptible to the formation of keloids, it

Table 2 POSAS scores for treatment method: BT versus PDT

	BT		PDT		*p* value, Kruskall–Wallis rank test
	Mean (range)	SD	Mean (range)	SD	
Patients score	22.8 (7.0–53.0)	13.5	34.2 (11.0–63.0)	18.4	$p=0.039$
Observers	19.1 (13.0–34.0)	5.2	24.6 (11.0–37.0)	6.6	$p=0.005$
Independent observers	14.6 (10.0–20.0)	3.3	18.6 (9.0–42.0)	6.8	$p=0.018$

No. of patients: BT 22 patients, PDT 12 patients. All the POSAS scores for both groups were available for analysis. A higher POSAS score reflects the worst imaginable scar

BT brachytherapy, *PDT* photodynamic therapy, *POSAS* Patient and Observer Scar Assessment Scale

remains difficult to apply optimally. It is difficult to determine the optimal dose of PDT to be delivered since this is determined by both by the level and biodistribution of photosensitizer in, and by the dose of light delivered to, the target tissue. It is also unknown for what time period and at what frequency PDT should be administered.

Given these uncertainties, our results using adjunctive ALA-PDT following surgical excision are encouraging when compared to brachytherapy. The PDT group had a shorter mean follow-up (34.4 months) compared to the brachytherapy group (64 months), because PDT treatment was only started in 2007 at our department as an alternative to brachytherapy. We started PDT because of hypopigmentation and risk of carcinogenesis after radiation, especially in young patients [22]. Most of the brachytherapy patients were treated before 2007. In the present study, it was not our intention to investigate recurrence rates in both groups. To investigate this correctly, a larger patient population and longer follow-up are needed.

Overall, patients reported significantly better POSAS scores after brachytherapy than after PDT treatment With the POSAS observer scale, both observers and independent observers scored significantly better for brachytherapy than PDT treatment. We should interpret these results cautiously since we excluded two POSAS items: pliability and surface area. Our impression was that scars were somewhat more pliable after PDT than following brachytherapy. Unfortunately, it was not possible for us to arrange a setting in which every patient was seen by all observers and pretreatment pictures were not available for surface comparisons.

In this study, we did not evaluate whether age, gender, race, size of the lesion, and location of the lesion had any influence on the outcomes. The literature does suggest that women feel stigmatized more often than men [23]. Younger patients may have higher expectations of the treatment with respect to aesthetic outcome than older patients, especially for scars in visible regions like ears, chest, and neck. So location of the scar and treatment results could influence the general impression and result in higher scores. Our study population was too small to prove if this association was statistically significant.

The item general impression was analyzed separately. The patients' score showed no difference for general impression for both treatment groups. Conversely, for the item general impression, the observers scored higher for PDT treatment in comparison with brachytherapy. We presume that the observers evaluated the lesions more critically with certain expectations. The independent observers revealed a higher score for general impression after PDT.

Table 3 POSAS item general impression for treatment method

	BT		PDT		*p* value, Kruskall–Wallis rank test
	Mean (range)	SD	Mean (range)	SD	
Patients score	3.2 (1–7)	2.2	4.8 (1–9)	3.0	$p=0.111$
Observers	3.5 (1–8)	1.7	4.8 (1–9)	2.0	$p<0.001$
Independent observers	5.7 (1–10)	2.2	6.3 (2–10)	2.3	$p=0.067$

No. of patients: BT 22 patients, PDT 12 patients. All the POSAS scores for both groups were available for analysis. A higher POSAS score reflects a bad general impression

BT brachytherapy, *PDT* photodynamic therapy, *POSAS* Patient and Observer Scar Assessment Scale

Conclusion

To conclude, our study is the first to evaluate the effectiveness of PDT treatment in comparison to conventional treatment (brachytherapy) for keloids. Patients and observers seem to be more satisfied with the results after brachytherapy than PDT. However, patients have a good general impression after PDT treatment. We believe that adjuvant ALA-PDT could be an alternative for some patients with keloids.

Conflict of interest None

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