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Original Article

Safety of photodynamic therapy combined with surgical excision in patients with actinic keratosis and risk factors for secondary cutaneous squamous cell carcinoma

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Abstract: Objective: To investigate the efficacy of photodynamic therapy combined with surgical excision on the prognosis of patients with actinic keratosis (AK) and to analyze the risk factors for secondary cutaneous squamous cell carcinoma (cSCC). Methods: Clinical data of 114 patients with AK treated at the West China Hospital from March 2014 to November 2018 were enrolled to this retrospective analysis. Among them 55 patients who underwent surgical resection alone were the control group (CG) and the other 59 who received photodynamic therapy combined with surgical resection were in the research group (RG). The treatment efficacy, lesion area, quality of life, incidence of adverse effects, and incidence of secondary sSCC in 3 years were compared, and the risk factors for sSCC were analyzed by multivariate logistics analysis. Results: The treatment efficacy of the RG was dramatically higher than that of the CG ($P<0.05$), and there was no obvious difference in the incidence of adverse reactions between the two groups ($P>0.05$). The lesion area and dermatology life quality index of the RG were dramatically lower than those of the CG after treatment ($P<0.05$), and the 3-year incidence of secondary cSCC in the RG was not statistically different from that of the OG ($P>0.05$). A greater number of lesion sites, a family history of tumor, and a history of skin disease were independent risk factors for secondary cSCC. Conclusion: Photodynamic therapy combined with surgical excision has better therapeutic efficacy in AK with a high safety.

Keywords: Photodynamic therapy, surgical excision, actinic keratosis, cutaneous squamous cell carcinoma

Introduction

Actinic keratosis (AK), also known as solar keratosis, is a precancerous lesion caused by prolonged exposure of the skin to sun damage or ionizing radiation. It is predominantly an epidermal hyperkeratosis, and its prevalence is increasing in middle-aged and elderly people as environmental damage increases and UV light is enhanced [1, 2]. Data have suggested that the prevalence of AK is as high as 49% in men over 45 years old and 28% in women [3, 4]. AK mostly occurs on exposed areas such as the face, ears and back of the hands, and the main symptoms are red, brown and grayish-white keratotic patches with adherent scales on the surface [5]. About 20% of AK patients can develop cutaneous squamous cell carcinoma (cSCC) if the condition is untreated, which seriously affects the appearance and safety of the patients [6]. cSCC is a malignancy of the epidermis associated with UV radiation, chemical carcinogens and viral infections. Besides, certain precancerous skin diseases such as AK can also develop secondary cSCC [7]. Although the overall malignant aggressiveness and metastasis rate of cSCCs is low, there are still aggressive cSCCs with poor prognosis, especially in the elderly population. Early detection and treatment for AK has a positive effect to prevent further invasion or metastasizing [8].

Currently, AK is still treated by traditional surgery. Because facial AK is mostly diffuse, traditional surgical treatment is effective but invasive and damaging, with slow recovery, which is difficult for some elderly patients [9]. As laser medicine develops, photodynamic therapy

(PDT) has gradually matured in clinical application and has been widely recognized [10]. PDT is a laser technology that treats diseases with light, photosensitizers and oxygen, which destroys tissue cells and closes the aberrant capillary network [11]. PDT is a fast-acting, less invasive and painful, well-tolerated and repeatable treatment, and it has played a key role in the treatment of solid tumors, skin cancer, vascular diseases and ophthalmology [12]. Kiss et al. [13] treated 10 AK patients with PDT, and a complete response was observed in 3 patients, and a partial response was observed in 7 patients. AK patients tend to have a hypertrophic lesion surface covered with thicker scabs, and the depth of photodynamic treatment is about 0.3 cm. If the lesion is not thinned with pretreatment, the penetration of the photosensitizer and the light source will not reach the deep lesion, which may lead to treatment failure. Therefore, a combination of other treatment options is needed to enhance the efficacy [14].

Therefore, this study used PDT combined with surgical resection to treat AK patients, and we conducted a 3-year follow-up to compare the incidence of secondary cSCC and analyzed the risk factors for secondary cSCC.

Methods and materials

General data

Clinical data of 114 patients with AK treated at the West China Hospital from March 2014 to November 2018 were enrolled to this retrospective analysis. Among them, 55 patients who received surgical resection were in the control group (CG), with 34 males and 21 females, and a mean age of (62.04±6.12) years, and the remaining 59 patients received PDT combined with surgical resection were in the research group (RG), with 32 males and 27 females, and a mean age of (60.8±7.13) years. This study was conducted with the approval of the West China Hospital Ethics Committee (Ethical lot number: 2019-556).

Inclusion and exclusion criteria

Inclusion criteria: Patients who were diagnosed with AK after histopathological examination; Patients who did not receive other relevant treatment within 3 months; Patients with lesions located on exposed areas such as the head, face or the back of the hands; Patients with lesions up to 2 cm in diameter; Patients who gave informed consent and signed an informed consent form; Patients with complete medical records.

Exclusion criteria: Patients who were intolerant to treatment regimens; Patients with other similar symptomatic skin diseases; Patients with a history of keloid or hypertrophic scarring; Patients with poor compliance to the treatment; Pregnant or lactating women.

Treatment regimens

In the CG, surgical treatment was performed. The area of the lesions was disinfected, and local anesthesia was administered. Then, the skin was incised approximately 0.2-0.5 cm lateral to the edge of the lesion. The skin lesions were completely removed. The incisions were sutured directly in patients with small skin lesions and low skin tension. For those with large skin lesions and high skin tension, skin grafting or adjacent skin flap transfer was followed by suture dressing. In the RG, 5-aminoketovaleric acid (produced by Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co. Ltd.) was prepared in saline to a concentration of 20% before treatment, applied externally to the lesion and its surrounding area of 1-3 cm, and sealed with sterile plastic film for 3-4 h. Patients were protected from light for 4-6 h in a dark environment, and then irradiated with a red light PDT instrument with a wavelength of 635 nm (produced by Wuhan YAG Photoelectric Medical Equipment Co., Ltd.) at a dose of 80-100 J/cm^2 each time, once/week, for a total of 4 weeks.

Evaluation criteria for treatment efficacy

Lesion regression rate = (pre-treatment lesion area-post-treatment lesion area)/pre-treatment lesion area ×100%. Cure: 100% regression rate of lesion, disappearance of lesions leaving only hyperpigmentation or hypopigmentation. Effective: 50% to 90% regression of lesion area. Improved: 30% to 59% regression of lesion area. Ineffective: <30% regression of lesion area or no response. Total response rate = (cured + effective + improved) cases/total cases ×100%.

Outcome measures

(1) The treatment efficacy was compared between the two groups. (2) The adverse reactions that occurred during treatment were counted in both groups. (3) The lesion area in both groups was counted before and after three months of treatment, and was used to evaluate the quality of life of patients. The scale contains four aspects: Clothing selection, symptoms and somatic feelings, daily activities, and psychological feelings. Each sub-item was accessed by a 0-3 point four-level scale according to the severity, with a total score of 30 points. Higher score indicated worse quality of life [15]. (4) Patients were followed up for 3 years after treatment by telephone, outpatient review and online follow-up. Follow-up was conducted every 3 months in the first year and every 6 months in the next 2 years. The incidence of secondary cSCC in the two groups was counted, and the independent risk factors for cSCC were investigated by multivariate analysis.

Statistical analysis

All statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) software. The counting data were assessed using Chi-square test, expressed as χ^2. K-M curves were plotted to analyze the patients for secondary cSCC at 3 years using log rank test. All measurement data conformed to a normal distribution and were evaluated using the independent samples t-test. Independent risk factors for secondary SCC were explored by logistic regression analysis. P<0.05 was considered statistically significant.

Results

Patient baseline data

It was found that there was no statistical difference (P>0.05) between the two groups in terms of sex, age, course of disease, lesion site, number of lesion sites, Röewert-Huber classification, outdoor work, history of long-term medication, history of smoking, history of skin disease and family history of tumor (**Table 1**).

Comparison of treatment efficacy between the two groups

It was found that the cure rate and total response rate of the RG were dramatically higher than those of the CG, and the differences were statistically marked (P<0.05) (**Table 2**).

Comparison of incidences of adverse reaction between the two groups

By comparing the incidences of adverse reactions, we found that there was no statistical difference in the incidences between the two groups (P>0.05) (**Table 3**).

Changes in lesion area and quality of life before and after treatment

The changes in lesion area and DLQI before and after treatment were observed in the two groups. No obvious difference was found in the two indictors before treatment (P>0.05). The lesion area and DLQI were dramatically lower in both groups after treatment (P<0.05), and the those in the RG were lower than those in the CG after treatment (P<0.05) (**Figure 1**).

Comparison of 3-year incidence of secondary cSCCs between the two groups

Patients in both groups were followed up for 3 years, and a total of 6 cases of secondary cSCCs were found in the RG within 3 years, with an incidence of 8.47%, while 9 were found in the CG, with an incidence of 16.36%. Although the incidence of cSCCs was lower in the RG than in the CG, the difference was not statistically different (P>0.05) (**Figure 2**).

Univariate analysis of risk factors for secondary cSCCs

We divided all patients into a poor prognosis group and a good prognosis group according to whether they had secondary cSCCs within 3 years. There were 15 patients in the poor prognosis group and 99 in the good prognosis group. A univariate analysis of the clinical data revealed statistical differences in the course of disease, number of lesion sites, Röewert-Huber classification, outdoor work, history of long-term medication, history of skin disease and family history of tumor (P<0.05) (**Table 4**).

Multivariate analysis of risk factors for secondary cSCCs

Logistic regression of indicators with differences in univariate analysis found that course of disease, Röewert-Huber classification, outdoor work and long-term medication history were not

Table 1. Baseline data

	Research group (n=59)	Control group (n=55)	χ^2/t	P
Sex			0.671	0.413
Male	32 (54.24)	34 (61.82)		
Female	27 (45.76)	21 (38.18)		
Age (year)	60.8±7.13	62.04±6.12	0.993	0.323
Course of disease (month)	8.1±2.95	7.62±3.17	0.837	0.404
Lesion site			1.134	0.567
Face	25 (42.37)	20 (36.36)		
Trunk	18 (30.51)	15 (27.27)		
Limb	16 (27.12)	20 (36.36)		
Number of lesion sites			0.344	0.557
>3	11 (18.64)	8 (14.55)		
≤3	48 (81.36)	47 (85.45)		
Röewert-Huber classification			1.676	0.433
Grade I	13 (22.03)	18 (32.73)		
Grade II	38 (64.41)	30 (54.54)		
Grade III	8 (13.56)	7 (12.73)		
Outdoor work			0.265	0.607
Yes	24 (40.68)	25 (45.45)		
No	35 (59.32)	30 (54.55)		
History of long-term medication			0.344	0.557
Yes	11 (18.64)	8 (14.55)		
No	48 (81.36)	47 (85.45)		
History of smoking			0.181	0.671
Yes	12 (20.34)	13 (23.64)		
No	47 (79.66)	42 (76.36)		
History of skin disease			0.527	0.468
Yes	14 (23.73)	10 (18.18)		
No	45 (76.27)	45 (81.82)		
Family history of tumor			1.004	0.316
Yes	9 (15.25)	5 (9.09)		
No	50 (84.75)	50 (90.91)		

Table 2. Treatment efficacy

	Research group (n=59)	Control group (n=55)	χ^2	P
Cure	22 (37.29)	11 (20.00)	4.136	0.042
Effective	19 (32.20)	22 (40.00)	0.751	0.386
Improved	15 (25.42)	12 (21.82)	0.205	0.651
Ineffective	3 (5.08)	10 (18.18)	4.833	0.028
Total response	56 (94.92)	45 (81.82)	4.833	0.028

independent risk factors for secondary cSCCs in patients, while a greater number of lesion sites, a family history of tumor and a history of skin disease were independent risk factors (**Table 5**).

Discussion

The development of skin tumors is a complex process affected by multiple components and factors, and exposure to UV radiation is the

Table 3. Adverse effects

	Research group (n=59)	Control group (n=55)	X^2	P
Hypopigmentation	2 (3.39)	1 (1.82)		
Pigmentation	5 (8.47)	4 (7.27)		
Superficial scar	2 (3.39)	2 (3.64)		
Red and swollen	3 (5.08)	2 (3.64)		
Total adverse reactions	12 (20.34)	9 (16.36)	0.299	0.584

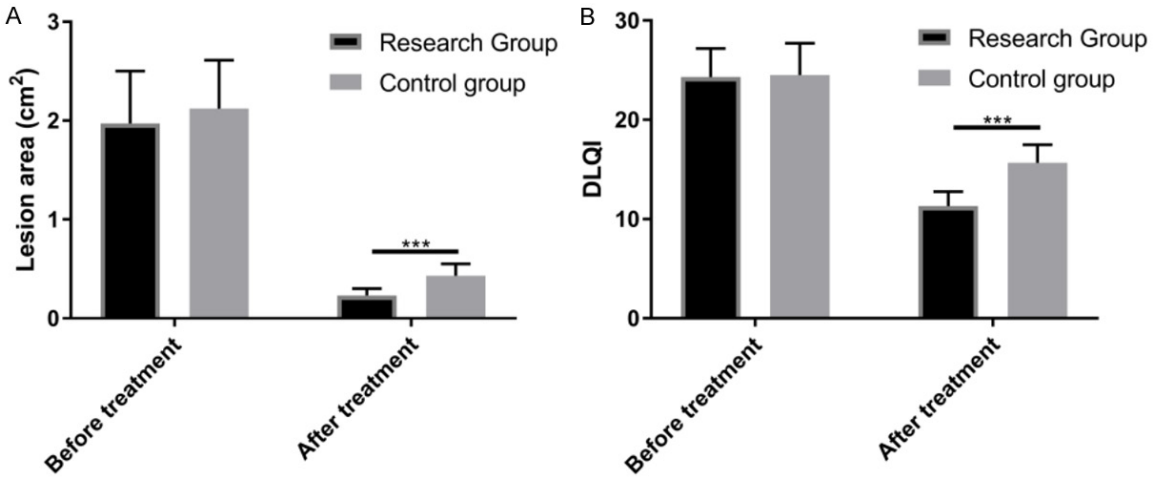

Figure 1. Changes in skin lesion area and quality of life before and after treatment. A. The area of skin lesions was significantly less in the research group than in the control group after treatment (P<0.001). B. Dermatology life quality index (DLQI) was significantly lower in the research group than in the control group after treatment (P<0.001).

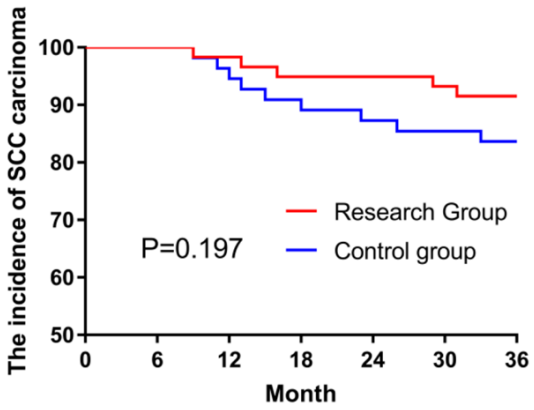

Figure 2. The incidence of squamous cell carcinoma (SCC) carcinoma (SCC) at 3 years was not statistically different between both groups of patients (P=0.197).

greatest risk factor for SCC, a common malignant non-melanoma skin cancer [16]. Because AK develops in exposed areas and tends to be diffuse, some cases may transform into SCC, which endangers the patients and leads to stress, anxiety and fear of the disease [17, 18]. Therefore, early detection and active treatment are necessary.

PDT is a combined drug-mechanical therapy applying a photosensitizer and a light source with photosensitizer, light and tissue oxygen [19]. These active substances damage cell membranes and vascular endothelial cells and selectively kill diseased cells without damaging adjacent normal tissue cells, thus achieving therapeutic purposes [20, 21]. In this study, the cure rate and total response rate of the RG were found to be dramatically higher than those of the CG, and the lesion area and DLQI of the RG were lower. This suggests that the combination therapy can provide patients with better treatment outcomes, as well as a better quality of life after treatment. The possible reason is that surgical excision cleans up the scab, epidermal hyperplastic tissue and superficial dermis by mechanical force, as well as removes abnormal tissue and rough and uneven epidermal layers. The fresh trauma after pretreatment is conducive to the penetration and absorption of photosensitizer ALA. The reduced thickness promotes light penetration and provides favorable conditions for subsequent PDT, thus improving the efficacy. PDT is also effective in treating some subclinical lesions with

Table 4. Univariate analysis of risk factors for secondary cSCCs

	Poor prognosis group (n=15)	Good prognosis group (n=99)	χ^2/t	P
Sex			0.545	0.460
Male	10 (66.67)	56 (56.57)		
Female	5 (33.33)	43 (43.43)		
Age (year)	62.67±5.55	61.2±6.82	0.795	0.428
Course of disease (month)	9.47±3.42	7.63±2.94	2.211	0.029
Lesion site			0.389	0.823
Face	7 (46.67)	38 (38.38)		
Trunk	4 (26.67)	29 (29.29)		
Limb	4 (26.67)	32 (32.32)		
Number of lesion sites			6.771	0.009
>3	6 (40.00)	13 (13.13)		
≤3	9 (60.00)	86 (86.87)		
Röewert-Huber classification			6.463	0.040
Grade I	4 (26.67)	27 (27.27)		
Grade II	6 (40.00)	62 (62.63)		
Grade III	5 (33.33)	10 (10.10)		
Outdoor work			3.953	0.047
Yes	10 (66.67)	39 (39.39)		
No	5 (33.33)	60 (60.61)		
History of long-term medication			6.771	0.009
Yes	6 (40.00)	13 (13.13)		
No	9 (60.00)	86 (86.87)		
History of smoking			3.294	0.070
Yes	6 (40.00)	19 (19.19)		
No	9 (60.00)	80 (80.81)		
History of skin disease			10.830	<0.001
Yes	8 (53.33)	16 (16.16)		
No	7 (46.67)	83 (83.84)		
Family history of tumors			7.106	0.008
Yes	5 (33.33)	9 (9.09)		
No	10 (66.67)	90 (90.91)		
Treatment			0.956	0.328
Surgical treatment alone	9 (60.00)	46 (46.46)		
Combination therapy	6 (40.00)	53 (53.54)		

cSCC, cutaneous squamous cell carcinoma.

atypical skin lesions because of its low trauma, and its photothermal effect can promote tissue collagen regeneration with better cosmetic effects [22]. Liu et al. [23] mentioned that PDT was effective in removing lesions with excellent final cosmetic results. Furthermore, there was no statistical difference in adverse reactions between the two groups, indicating that PDT did not increase the incidence of adverse reactions. Heerfordt et al. [24] discovered that AK had the potential to progress malignantly regardless of the thickness. When we looked at the incidence of secondary cSCCs over 3 years, no statistical difference was found between the two groups. Also, we performed a multifactorial analysis and found that a greater number of lesion sites, a family history of tumor and a history of skin disease were independent risk factors for the secondary cSCCs. This also suggests the need for clinical attention to AK patients who present with the above factors. Fontanillas et al. [25] confirmed that a family history of tumors and an associated history of skin disease were risk factors for the develop-

Table 5. Multivariate analysis of risk factors for secondary cSCCs

	B	S.E	Wals	Sig.	Exp (B)	95% C.I. of EXP (B)	
						Upper limit	Lower limit
Course of disease	0.180	0.123	2.136	0.144	1.198	0.940	1.526
Number of lesion sites	2.326	0.855	7.401	0.007	10.234	1.916	54.665
Röewert-Huber classification	0.778	0.572	1.851	0.174	2.177	0.710	6.675
outdoor work	0.518	0.813	0.406	0.524	1.679	0.341	8.255
Long-term medication history	1.577	0.803	3.853	0.050	4.841	1.002	23.380
Family history of tumors	2.718	0.962	7.980	0.005	15.146	2.298	99.823
History of skin disease	2.680	0.847	10.016	0.002	14.592	2.774	76.741

cSCC, cutaneous squamous cell carcinoma.

ment of SCC. Also, many studies have shown that prolonged light exposure is one of the risk factors for SCC, and often patients who are exposed to light for long periods will have a greater number of lesion sites and a history of skin disease [26, 27].

This study still has some shortcomings. First, whether this treatment is effective for other types of keratosis needs to be explored in subsequent studies. Second, animal experiments are needed to investigate the specific mechanisms of PDT. Also, an expanded sample size is needed to further corroborate our findings.

In conclusion, PDT combined with surgical excision has better therapeutic efficacy in AK and has a high safety profile, which is worth promoting.

Disclosure of conflict of interest

None.

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