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ABSTRACT

Introduction: Actinic keratoses (AK) are a common precancerous skin condition in dermatology practice. Photodynamic therapy (PDT) is an effective but painful treatment of fields of cancerization. Two studies showed that textile PDT was not inferior to conventional PDT. FLUXMEDICARE® (FLX-PDT) is the first medical device marketed. We realized a real-life study to evaluate efficacy and tolerance of this device.

Methods: We carried out a single-center retrospective study. We collected data from patients treated with FLX-PDT for AKs localized on scalp and temples between November 2018 and November 2019. The primary endpoint was complete clearance rate (CR) at 3 months-follow up.

Results: Data of 39 patients were reviewed in the study, with a total of 417 AKs. The CR rate was 72.6% (95%CI 67.9-77.0) at 3 months-follow up and 67.5% (95%CI 61.2-73.3) at 6 months-follow up. The median pain felt during the session was 0 and there wasn't erythema after the session for 64.1%.

Conclusion: Our real-life study confirms efficacy and safety of textile PDT by FLUXMEDICARE device in the treatment of scalp and temples AKs, with excellent tolerance.

CAPSULE SUMMARY

What's already known about this topic?

- Photodynamic therapy is an effective but painful treatment for actinic keratosis.
- FLUXMEDICARE® is the only and the first marketed device, and presents some differences in tissue conformation compared to PHOS-ISTOS® device.

What does this study add?

- Our real-life study confirms efficacy, safety and tolerance of textile PDT by the first marketed device (FLUXMEDICARE®) in the treatment of scalp and temples AKs.
- The efficacy of textile PDT appears to be good in immunocompromised subjects.

INTRODUCTION

Actinic keratoses (AKs) are a very common precancerous skin condition in daily dermatology practice[1]. AKs are a marker of UV-induced skin damage and precancerous lesions that carry a risk of evolving into a squamous cell carcinoma (SCC)[2–4].

Multiple treatment options are available but have heterogeneous efficacy with sometimes high recurrence rates[5]. To date, no AKs treatment demonstrated a long-term efficacy on lesion clearance[6]. The role of "fields of cancerization"[7–9] is increasingly highlighted in publications, and many authors consider that treatments should target the entire affected area where subclinical lesions could be found[10, 11].

Photodynamic therapy (PDT) is an effective treatment for "fields of cancerization", with response rates between 80 and 90% at 3 months[11–14]. In Europe, conventional PDT (C-PDT) uses Methyl aminolevulinate (MAL) cream as a photosensitizer (Protoporphyrin IX or PpIX) precursor, and the AKTILITE CL 128® device (Galderma SA, Lausanne, Switzerland) for an illumination of 7 to 10 minutes after a 3 hours incubation of MAL in the dark, under a light protective dressing. The main limitation of C-PDT is pain during the sessions[12, 13, 15] due to the photodynamic reaction, that could be explained by the high delivered irradiance (75mW/cm^2) and by PPIX accumulation during a long Drug Light Interval (DLI) (3 hours)[16]. Two randomized studies (FLEXITHERALIGHT®[17] and PHOS-ISTOS®[18] protocols) evaluated the efficacy of PDT using light emitting fabrics with lower fluence and irradiance (respectively 37J/cm^2 and 12.3 mW/cm^2 in FLEXITHERALIGHT® ; 12J/cm^2 and 1.3 mW/cm^2 in PHOS-ISTOS®). The results of FLEXITHERALIGHT® and PHOS-ISTOS® studies showed that PDT using light emitting fabrics was not inferior to conventional PDT (C-PDT), and reported AK complete clearance rate of 66% at 3 months with FLEXITHERALIGHT® device, and 79.3% at 3 months and 94.2% at 6 months with PHOS-ISTOS® device versus 80.7% at 3 months and 94.9% at 6 months with C-PDT. The medical device received a European EC labeling (to meet EU safety, health and environmental protection requirements) on 2018 and is marketed for clinical use under the name FLUXMEDICARE® (MDB Texinov, Saint Didier de la Tour, France). FLUXMEDICARE® delivers same fluence and irradiance as the device used in PHOS-ISTOS® study, but with some slight differences in tissue conformation. The aim of this study was to evaluate the efficacy and tolerance of FLUXMEDICARE® in a real-life practice.

PATIENTS AND METHODS

Study design

We carried out a single-center retrospective study in the dermatology department of the Lille University hospital. We collected data from patients treated with textile PDT using the FLUXMEDICARE® device (FLX-PDT) for actinic keratoses between November 2018 and November 2019.

This study has been declared to and accepted by the CNIL (Commission Nationale Informatique et Libertés), organization in charge of the ethical use of data collected for scientific purposes in France (DEC19-364). All patients agreed and signed a written consent to take and use photographs of their lesions for scientific purposes. In line with the French Data Use Act, patients were informed in writing of the anonymous use of their medical data and the possibility of removing their consent at any time.

Study population

The medical records of patients treated by FLX-PDT for AK lesions on scalp and temples in Lille University hospital from November 2018 to November 2019 were reviewed. We collected the following informations from patients' medical files: demographic characteristics, history of skin cancer, immune status, Fitzpatrick's phototype, profession, past sun exposure, smoking habits, and history of previous AKs treatments, number of AKs, grade of AKs (according to the classification of Olsen *et al.*[19]), AKASI (Actinic Keratosis Area and Severity Index) score[20, 21]. AKASI score is designed to quantitatively evaluate the severity of AK on the head, ranging from 0 to 18 and correlated with fields of cancerization severity[20]. AKASI score is associated with the incidence of SCC and seemed of interest as an assessment tool for standard patients follow-up[21].

Features of the FLUXMEDICARE device

The FLUXMEDICARE device is the only textile-PDT device currently available on the market. It consists of a light source connected to strips of knitted light emitting fabrics that can be adapted to various skin areas. The device is calibrated to deliver red light with a wavelength of 638nm, an irradiance of 1.3 mW/cm^2 for 150 minutes and a fluence of 12 J/cm^2 (Figure 1). Moreover, the DLI is only 30 minutes in our treatment protocol. We used the TEXTLIGHT1 (Figure 2A) band

(illuminated surface 18x20cm) for the treatment of the scalp and forehead and the TEXTLIGHT 3 (Figure 2B) bands (2 devices of 6x20cm allowing a simultaneous bilateral treatment of the 2 temples). Since the luminous textile is positioned in contact with the skin surface, there is no light emitted in the room. No eye protection is therefore necessary during the sessions.

Treatment

Pre-treatment: The usual protocol in our center consists of prescribing to the patient a 20% urea dosed keratolytic preparation to be applied during 10 days before session on the to-be-treated area. A gentle curettage of lesions is performed before PDT session.

Treatment: A thin layer of MAL is applied on AKs with a margin of about 1 cm around each lesion and on the whole affected area (field of cancerization). The treatment area is covered by a transparent occlusive dressing or a transparent cap. The textile device TEXTLIGHT 1 (for scalp and forehead) or TEXTLIGHT 3 (for temples) is applicated and fixed by a net and covered by an opaque cap. The MAL cream is incubated in the dark for 30 minutes before illumination. The MAL cream is not removed, so incubation is not stopped during the illumination. Then, we deliver a 635nm red light through the light-emitting fabric previously knitted on the inside of a cap for 150 min. Afterwards, we advise the patient to apply simple healing ointment for a few days after sessions to improve healing process and we recommend avoiding sun exposure.

Patients were followed-up at 3 months after the first PDT session to assess the efficacy. When patients had more than four unresolved AKs after the first session, they received a second FLX-PDT.

When patients had less than five unresolved AKs after one session, a targeted treatment such as cryotherapy was performed to clear the remaining lesions. A satisfaction questionnaire completed by the patient after the PDT session was provided by the company during the first year of use of the device. This questionnaire evaluated: adaptability of the device, comfort, pain, light-induced discomfort, if the patient recommend the device, what the patient did during the treatment, if he had to interrupt the treatment and why, and if he had any comment or improvement about the device. The data from this questionnaire was collected.

End points

The primary end point was PDT clinical efficacy defined by a AKs complete clearance rate (CR) at 3 months. The secondary endpoints were AKs CR at 6 months, AKASI score at 3 to 6 months, pain during illumination, erythema at the end of illumination, and the patient satisfaction. Pain was assessed by a simple numerical scale between 0 (no pain) and 10 (worst pain)[22]. Erythema was ranked as 0 (no erythema), 1 (mild erythema), 2 (moderate erythema) and 3 (severe erythema)[23].

Statistical analysis

Continuous variables were expressed as means and standard deviations in case of normal distribution or as medians and interquartile ranges otherwise. Normality of the distribution was checked graphically and using the Shapiro-Wilk test. The categorical variables were expressed as frequencies and percentages.

The complete response rate at 3 months was compared according to the grade, the localization, the immunocompromised status and the number of previous AK treatment, using the generalized linear mixed model to take into account for the correlation between repeated lesions within subjects by including a random coefficient. All of the statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Patients

Data of 39 patients were reviewed in the study, with a total of 417 AKs. 35 patients were treated for scalp AKs, 3 for scalp and temples AKs, and 1 for temples AKs only. Patients had an average of 11.5 AKs (ranging from 5 to 25). PDT was the first line treatment for 10 patients. Eighteen patients had previously been treated with conventional PDT. Lesions were asymptomatic in 51.3% of our patients. 28% complained of pruritus and 12.8% of aesthetic discomfort. The average AKASI score at the first visit was 4.3. Five patients were immunocompromised and 3 were receiving PD1 inhibitors for an unrelated disease.

36 patients were evaluated at 3 months after FLX-PDT (3 patients died of an unrelated cause before reevaluation). Due to at least five remaining AK lesions, 14 patients received a second PDT session. Twenty-two patients were evaluated at 6 months of the follow-up. The remaining

patients had not yet been reassessed at the time of writing. Patients' baseline characteristics are presented in Table 1.

Efficacy

The CR rate was 72.6% (95%CI 67.9-77.0) at 3 months-follow up. It was significantly higher for grade I AK (77.9%) compared to grade II AK (61.9%) (p = 0.011). The CR rate for scalp AK lesions and temples AK lesions were similar (respectively 72.3% and 75.6%), and no significant difference were highlighted (p = 0.75).

Twenty-two patients were evaluated at 6 months. The global CR rate was 67.5% (95%CI 61.2-73.3). The median AKASI score was 1.2 (IQR, 0.6 to 2.4) at 3 months and 1.8 (IQR, 0.8 to 2.8) at 6 months.

Five patients in our cohorts were immunocompromised (three patients were renal transplant patients with immunosuppressive therapy, one patient had high-dose corticosteroid therapy for diffuse interstitial lung disease, and one patient had rheumatoid arthritis treated with Rituximab). The CR rate at 3 months follow-up in this subgroup of patients was 78.0% versus 71.7% in the general population. No significant difference was highlighted between the 2 groups (p = 0.48).

We compared patients who received 0 or 1 AK treatment prior to our study with patients treated more than once. The CR rate in the group "0 or 1 previous AK treatment" was significantly higher than multi treated patients (respectively 82.5% and 66.8%, p = 0.015), but this difference was no longer significant after adjustment for lesion grade and AKASI (p = 0.15).

Tolerability

Pain

The median pain felt during the first session was 0 (range, 0 to 5) on the simple numerical scale. Five patients needed to take a break during treatment (less than 5 min), but none because of pain.

Erythema

The erythema observed at the end of the session was 0 (no erythema) for 25 patients (64.1%), 1 (mild erythema) for 11 patients (28.2%), 2 (moderate erythema) for 3 patients (7.7%). No patient had severe erythema following treatment. One patient consulted 4 days after PDT because of a mild skin inflammatory reaction that healed rapidly without further complication.

Satisfaction

35 of the 39 patients completed the satisfaction standardized questionnaire. 22 (62.9%) of them found the device very convenient, 12 (34.3%) of them found it fairly convenient. 9 (25.7%) patients felt the device was very comfortable and 22 (62.9%) found it fairly comfortable. More than half patients stated the treatment was painless, 14 reported very little pain, 1 patient mild pain and 1 patient severe pain. Among the 35 patients who answered the questionnaire, 31 patients recommended FLX-PDT, and 4 of them refused to complete it because they were waiting for the final result to deliver a judgement.

DISCUSSION

This study confirms the positive results of the previous textile PDT clinical trials[17, 18]. We observed 72.6% of CR rate at 3 months, which is comparable to the results published by Vicentini *et al.*[17] (66%) and Mordon *et al.*[18] (79.3%).

Few studies assess the long-term response of AKs. The data in the literature suggest a prolonged efficacy, with response rates around 70-80% at 12 months of treatment with conventional PDT or daylight PDT[24,25]. We do not yet have the results at 12 months, but the CR rate was 67.5% at 6 months which suggest a prolonged efficacy. However, our response rates at 6 months are lower than reported by Vincentini et al.[17] (84%) and Mordon *et al.*[18] (94%). The difference could be explained by various sample size between the three studies and slightly more severe patients in a real life setting. We could also argue that different physicians were involved in our study which leads to differences in skin preparation and lesion evaluation. Interestingly, patients who received multiple treatments have worse response rates than those who were did not. This result can be explained by the fact that these patients are multi-treated because they have more or more severe lesions, as shown in adjusted analysis, but we hypothesize also that AKs could become resistant after multiple therapies.

Despite limited number of patients, the response rate in immunocompromised patients appears to be comparable to immunocompetent subjects. Several studies in the literature confirm the effectiveness of PDT in treating AKs in transplanted subjects[26,27].

The FLX-PDT procedure is based on a short DLI of 30 minutes and a low irradiance of 1.3 mW/cm2 for 150 minutes, which allows a continuous metabolization and photodegradation of PpIX, thus ensuring low PpIX accumulation[28]. Furthermore, the continuous photobleaching prevents an unnecessarily high PPIX accumulation that could reach the dermis nerves and accentuate pain. Therefore, we obtained an excellent tolerance with a median pain of 0/10 during FLX-PDT, thus a high level of patients' satisfaction unlike to C-PDT with 55-60% of patients experiencing moderate pain[29, 30]. The patients' satisfaction rates are similar to FLEXITHERALIGHT® and PHOS-ISTOS® studies (median pain of 0,4/10 and 0,3/10). We found a similar tolerance to Daylight PDT[29,30],with almost no pain. The FLX-PDT device allows treatment all year round, with precise control of irradiance which is not possible in Daylight PDT[33]. Other low-irradiance indoor PDT devices are developed, with a comparable tolerance to ours, and very good efficiency[32,33]. In order to improve tolerance, many other low irradiance schemes are being developed. Moreover, increasing the distance from the lamp with longer illumination time could also give good results[36].

Most patients were followed-up and reassessed by a single physician, which is a bias in our study's results. In addition, the response was clinically evaluated (with the help of diagrams and photographs). No biopsy was performed to look for a potential subclinical residual dysplastic cell.

Vicentini *et al.* showed a flat light source cannot deliver a sufficient and homogeneous dose of light on a convex surface such as a scalp[37]. One of the advantages of a conformable textile device is that it adapts to the convexity of the scalp. One limitation is the shape of the TEXTLIGHT 1 band that is a rectangle measuring 18x20cm. Despite good conformability, it does not treat the entire surface of the skull and AK can often persist in the posterior area of the scalp. A device with a helmet (as PHOS-ISTOS® device) that covers the entire scalp should be considered. To treat limbs, circular devices or sleeves could be interesting in the future. The

light emitting fabrics is also interesting for treating areas that are difficult to illuminate, like vulvar areas (PAGETEX® protocol in Paget's vulvar disease Clinicaltrials.gov Identifier: NCT03713203).

The FLUXMEDICARE® device does not require eye protection. Unlike C-PDT, the patient can remain alone and does not need medical surveillance. The limit of this treatment is the duration of session. However, compared with the overall duration of C-PDT including a 2.5 hours of DLI, there was essentially no increase the time spent in hospital with the FLX-PDT procedure. Moreover, several studies show that the fluence required to treat AKs is probably lower, and that DLI could be reduced without loss of efficiency. So, treatment duration could be reduced[16] in the long term.

Conclusion

Our real-life study confirms the efficacy, safety, and practical aspects of FLX-PDT with FLUXMEDICARE® device in the treatment of scalp AKs, with excellent tolerance. Good efficacy is obtained in immunocompromised patients, but larger studies are needed to confirm these results.

Table I : Demographics and clinical characteristics of patients before treatment
Values are presented as frequency (percentage) unless otherwise indicated.

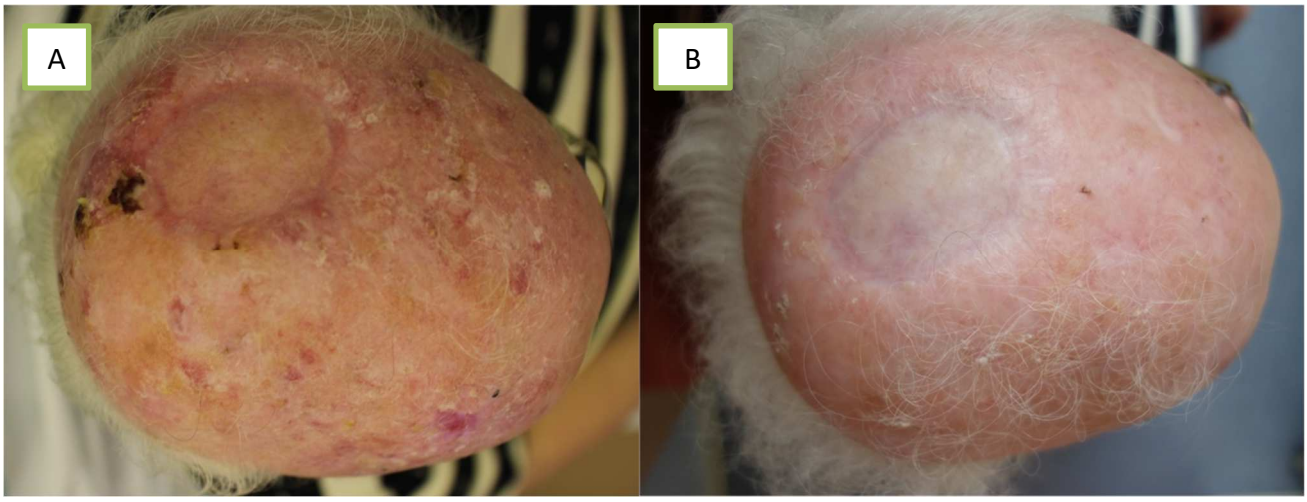
Patients	n = 39
Age (years)	
Mean +/- SD	75.0 ± 9.3
Range	57-92
Sex	
Male	38 (97.4)
Female	1 (2.6)
Fitzpatrick skin phototype	
I	4 (10.3)
II	28 (73.7)
III	7 (17.9)
Immune status	
Immunocompetent	34 (87.2)
Immunocompromised	5 (12.8)
Smoking status	
Active	0 (0)
Detoxed	39 (100)
History of skin cancer	
Basal cell carcinoma	15 (38.5)
Squamous cell carcinoma	11 (28.2)
Melanoma	8 (20.5)
Other skin cancer	3 (7.7)
Previous treatments	
Median (Interquartile Range)	1 (0 to 2)
Range	0 to 6
Number of AK lesions	417
Grade I	290 (69.5)
Grade II	127 (30.5)
AKASI score	
Median (Interquartile Range)	3.8 (2.4 to 5.6)
Range	1.6 to 11.2

Figure 1. FLUXMEDICARE® device f

Figure 2A. FLUXMEDICARE® device (TEXTLIGHT 1)

Figure 2B. FLUXMEDICARE® device (TEXTLIGHT 3)

Figure 3 A. Patient before treatment B. Efficacy at 3 months



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