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Light emitting fabrics for Photodynamic Therapy: technology, experimental and clinical applications.

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Abstract

A homogeneous and reproducible fluence rate delivery during clinical PDT (PhotoDynamic Therapy) plays a determinant role in preventing under- or overtreatment. The development of a flexible light source able to generate uniform light on all its surface would considerably improve the homogeneity of light delivery. The integration of plastic optical fibers into textile structures offers an interesting alternative. This article aims to describe briefly the technology used to develop Light Emitting Fabrics (LEF) and their use in vitro (CELL-LEF), in vivo (VIVO-LEF) for experimental evaluation of PDT. At last, the use of LEF for clinical applications is given by 3 examples. For in-vitro applications, the CELL-LEF device allows the illumination of several 96-well cell culture plates. For the VIVO-LEF, the system developed for PDT can treat 3 mice simultaneously with a homogeneous and high irradiance. The medical LEF systems developed for PDT in Dermatology for the treatment of actinic keratosis demonstrate their superiority thanks to a uniform light distribution due to the flexibility of LEF. Interestingly, the technology used for manufacturing LEF is very well known by the textile industry, leading to very competitive production costs. The fact that optical fibers can transmit light from 400 nm to 1200 nm allows the connection of LEF to different laser sources covering the light spectrum of all photosensitizers used for medical applications. New developments should allow to use the LEF inside cavities such as the pleural or the peritoneal cavities.

Principle of LEF

The different technologies based on optical fibers for large area were described by Mordon et al [1]. The technology developed in Lille used optical fibers. Briefly, optical fibers are optical structures, which allow incident light, usually from an optical source, to be guided by a series of internal total reflections that occurs under angular conditions, with minimum losses [1]. Standard step-index optical fiber is composed of a core and a surrounding cladding of cylindrical shapes, and with respective refractive indices n_1 and n_2 . Geometrical optics defines a particular angle called θ_{crit} as the smallest angle of incidence of a ray at which no refraction occurs at the boundary of two media when $n_1 > n_2$. General angular condition of total reflection of an incident light ray of angle θ is given in (1).

$$\theta \geq \theta_{crit} = \text{Arcsin}\left(\frac{n_2}{n_1}\right) \quad (1)$$

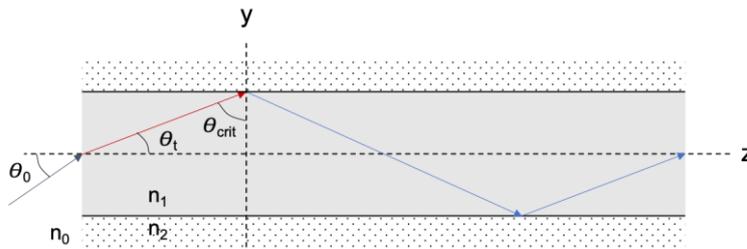


Figure 1: principle of light propagation in an optical fiber

In the optical fiber, total internal reflection occurs for light rays of smaller angles than the angle of acceptance θ_0 , defined as the minimum angle of incidence to obtain a refracted light ray of angle θ_t that satisfies the general angular condition of total reflection (1). Otherwise, the portion of the incident light rays reflected and/or refracted is described by the Fresnel equations.

$$n_0 \sin \theta_0 \leq \sqrt{n_1^2 - n_2^2} \quad (2)$$

Local microscopic variations of core medium density from manufacturing process (variation in density, orientation or molecular composition of the material) lead to local variations in the refractive index, and generate losses by scattering of the light rays. Linear attenuation corresponds to the sum of all absorption and scattering losses that occur in the optical fiber, and is defined by the attenuation coefficient α [2].

$$P_{out} = P_{in} \times e^{-\alpha L} \quad (3)$$

Additional bendings can increase the optical fiber attenuation coefficient, by inducing light leakage through the core. Macrobending is defined as a mechanical stress, which can be punctual or repeated [3], and is characterized by the critical radius of curvature R_c which represent the bending radius from which macrobending losses become significant [4]. When an optical fiber is bent with a bending radius R smaller than the critical bending radius R_c , the angle of incidence θ of the ray may become smaller than θ_{crit} and the ray refracts within the cladding and part of the ray may be refracted outside the optical fiber [2] (figure 2). The bending radius is associated with the angle of curvature γ which gives information on the length of the bent section[5] [6] .

$$R_c = \frac{3 n_2 \lambda}{4\pi (n_1^2 - n_2^2)^{\frac{3}{2}}} \quad (4)$$

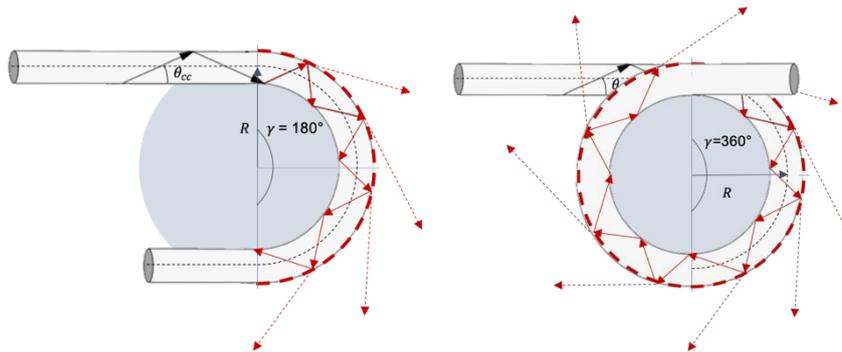


Figure 2: principle of light emission by optical fiber due to bending

Bending light losses within optical fibers are typically characterized with the objective of minimizing them as much as possible, especially for telecommunication or power transmission applications. In some cases, they are quantified to measure deformations within materials using fiber optic sensors, and maximized when homogeneous light emitting surfaces are desired [7]

By integration of plastic optical fibers within knitted or woven structure, light emission can be obtained over flexible textile surfaces. Homogeneity of spatial light distribution can be obtained under the condition of controlling the density of the fibers and the angles and radii of curvature [8].

Optical fibers are generally woven as conventional yarn according to various satin weave structures along the fabrics length to control light emission [9-11]. As knitting involves bending radii that are too severe to be supported without risk of breakage if the optical fiber

is knitted, optical fibers are mainly laid in a partial weft in a warp or weft knitted structures [12] in a straight line or in special patterns [13].

Plastic optical fibers can be gathered and glued within a metallic bundle in order to be coupled to any LASER source by the mean of 2 beam expanders (figures 3 & 4). The injection of light at each end of the textile, allows to balance the bending losses providing a more uniform and intense lateral emission [14].

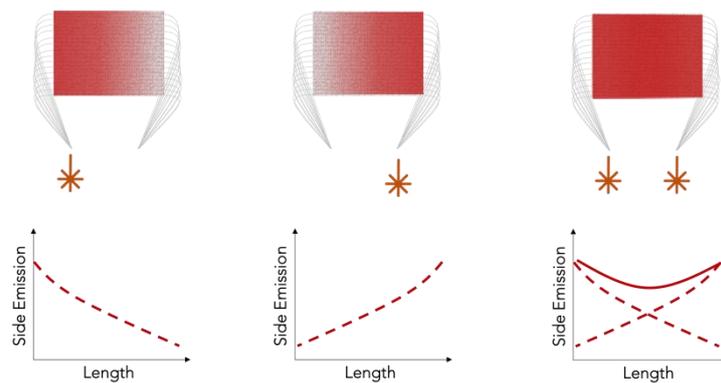


Figure 3: LEF is illuminated by injecting light at each end of the fibers gathered in a bundle

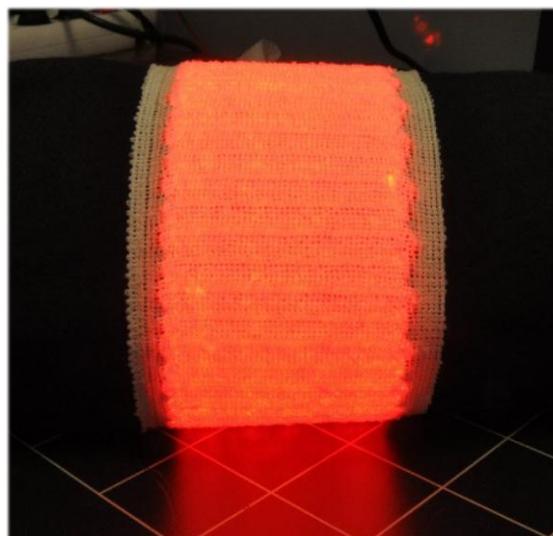


Figure 4: Light Emitting Fabrics obtained by a knitting process connected to a red laser source (635nm)

LEF is composed of plastic optical fibers. Consequently, it can be connected to lasers of any wavelength from 400 nm to 1200 nm (figure 5).



Figure 5: LEF can emit several wavelengths from violet to infrared

In vitro use of LEF : CELL-LEF

Published PDT preclinical studies described various kinds of light sources. In many cases, the light source is handmade with optical fibers connected to laser or with LED panels [15] [16]. However, OF can deliver light only on small areas, while LED panels provide incoherent light with broad spectral width. Although easy to use and quite inexpensive, optical fibers and LED panels do not allow an effective homogenous illumination.

In vitro PDT studies often require illumination of several cells plates either all at once or all within a short period of time. In this context, a cells illuminator, CELL-LEF, able to illuminate several 96-well cell culture plate simultaneously with a homogeneous light has been designed (Figure 6).

CELL-LEF embeds two large LEF (total illumination surface: 750 cm^2) sandwiched and kept in place between two rigid, transparent plastic sheets. These sheets also allow protection of the LEF and easy disinfection of CELL-LEF before and after use. Before being sandwiched, the two LEF are jointly sewn on a white textile in order to reflect the light emitted by the bottom face and therefore increase the quantity of light on the top face. A template is placed on the top plastic sheet in order to indicate the emplacement of the 6 multi-well plates (resulting illumination surface: 657 cm^2). Finally, a lightproof cover can be used to protect cells from stray light, which could lead to undesired activation of the PS.

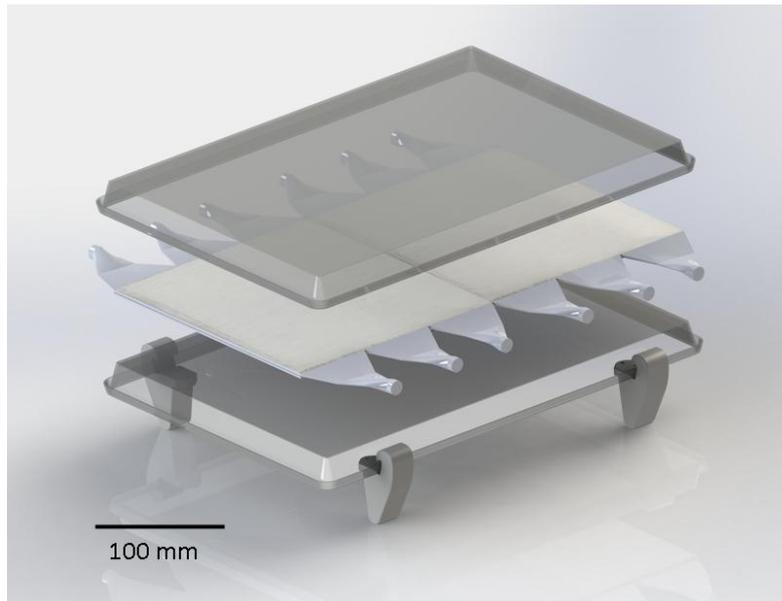


Figure 6: Schematic view of CELL-LEF, which is made of several layers, from top to down: first rigid transparent plastic sheet, light emitting fabrics (LEF), reflecting white textile, second rigid transparent plastic sheet, and support feet.



Figure 7: Photograph of one CELL-LEF device. <http://www.oncothai.fr/about-the-research-unit/technologies/361-preclinical-illumination-device-in-vitro>

For all measurements, CELL-LEF was connected to a 635 nm laser (ONCO THAI, Lille, France) set to achieve a target mean irradiance of 1 mW/cm^2 . Different tests were performed in order to evaluate the homogeneity of irradiance, temperature evaluation of cell during illumination of 96-well cell culture plates. The measurement methodology has been already described [17]

With the CELL-LEF illuminator, irradiance values range from 0.81 to 1.18 mW/cm² (mean: 0.98 mW/cm²; standard deviation: 0.11 mW/cm²). To obtain these values, a laser output power of 2.6 W was required. Homogeneity was determined using an automatic measurement system specifically developed for this purpose. A homogeneity of 90.9% was recorded. CELL-LEF was classified exempt risk group for all hazard groups according to the IEC 62471 standard, and does not exceed Accessible Emission Limits of class 1 defined by IEC 60825 standard

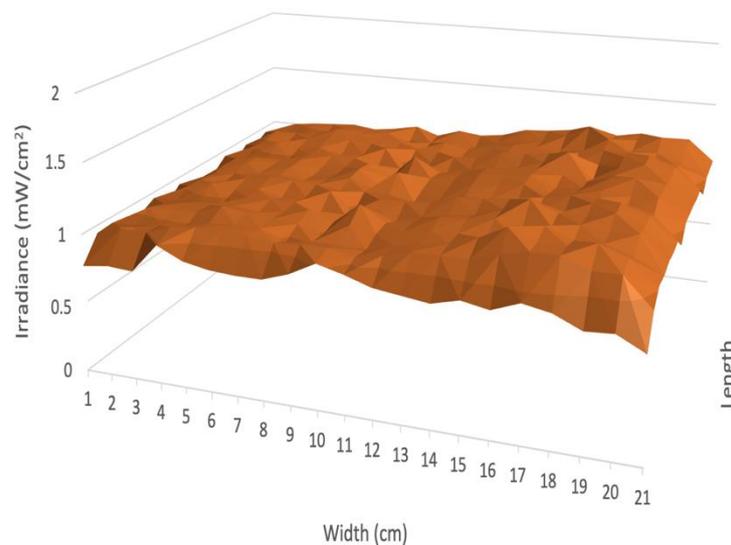


Figure 8: 3D representation of irradiance distribution over the light emitting fabric surface

At last, temperature elevation measurements inside 96 well plate gave the following results 45 minutes of CW illumination: for a well with cells with 5-ALA, an increase of +1.14 °C was measured but it was only +0.88 °C inside a well with cells without 5-ALA [18].

CELL-LEF was already used in experimental studies to evaluate a new folate receptor-targeted photosensitizer on peritoneal ovarian cancer cells [19] and in four pancreatic adenocarcinoma (ADKP) cell lines: Capan-1, Capan-2, MiapaCa-2, and Panc-1. [20]

LEF for in vivo experimental evaluation of PDT (VIVO-LEF)

In the framework of the development of an original humanized SCID mouse model of ovarian peritoneal carcinomatosis, a specific device dedicated to mice illumination. A mice box, called VIVO-LEF was developed to illuminate three mice simultaneously with a homogeneous light (Figure 9). VIVO-LEF consists of two separated white 3D-printed plastic bases, on which two light emitting fabrics (LEF) are fixed. The bases are designed to form three cavities, in which mice can be placed in prone position (Figure 10). The materials used make VIVO-LEF strong and lightweight. The total surface of illumination of 250 cm² allows to

cover the whole body of the three mice. For the in vivo experiments performed on the SCID mouse model of ovarian peritoneal carcinomatosis, an irradiance of $11.08 \pm 0.58 \text{ mW/cm}^2$ is delivered. Since, LEF are secondary light source, VIVO-LEF does not emit heat. Thanks to these performances, VIVO-LEF is far superior to OLED which are limited by their low irradiance and important temperature increase [21].

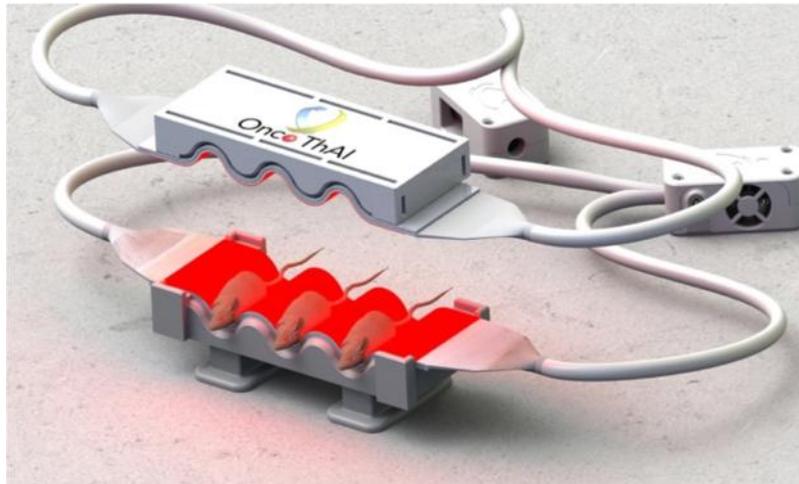


Figure 9: 3D illustration of the VIVO_LEF device.



Figure 10: VIVO-LEF can illuminate 3 mice simultaneously with homogeneous light

Clinical study #1: Evaluating illumination of actinic keratosis with a flexible LEF compared to the conventional photodynamic therapy with a LED panel: NCT03076918

In dermatology, PDT is used to treat actinic keratosis. Actinic keratosis are common pre-invasive cancerous lesions in sun-exposed skin which negatively affect the quality of life in patients and may progress to invasive squamous cell carcinoma. Actinic keratosis usually

develop on areas that are frequently exposed to the sun (e.g., face, ears, scalp, neck, forearms, and back of the hands). Studies have shown that if actinic keratosis are untreated, actinic keratosis may regress, or alternatively, may progress to squamous cell carcinoma, with significant morbidity and possible lethal outcome. Predicting which actinic keratosis may progress to squamous cell carcinoma is not possible, nor is the conversion rate for an actinic keratosis to squamous cell carcinoma clear: the transformation rate from an actinic keratosis lesion to squamous cell carcinoma within one year has been reported to be <1:1000. The malignant potential and the fact that it is impossible to predict which actinic keratosis will evolve into squamous cell carcinoma, have led to the common consensus that actinic keratosis have to be treated. Because of the high prevalence of actinic keratosis, their treatment represents a substantial workload, and must therefore be efficacious and easy to perform. Moreover, for patients an ideal treatment should be well tolerated and result in good cosmesis. The most commonly used treatments for actinic keratosis are cryotherapy, topical chemotherapy and, more recently, photodynamic therapy (PDT) [22]. However, for this application, PDT is carried out with a wide variety of light sources delivering a broad range of more or less adapted light doses. Due to the complexities of the human anatomy, these light sources do not in fact deliver a uniform light distribution to the skin. For example, in the case of the LED system used usually in Dermatology, Moseley et al demonstrated that the irradiance may be as low as 38% of the central area at a distance of only 2 cm [23].

The device consists of 3 flexible light-emitting fabrics (size 21.5 cm × 5 cm each) for a total area of $3 \times 21.5 \text{ cm} \times 5 \text{ cm} = 322.5 \text{ cm}^2$. Each one is illuminated sequentially with a 635 nm laser at low fluence rate (12.3 mW/cm^2) for one minute, such as a fractionated irradiation (1 minute light, 2 minutes dark) is achieved (figure 11). An irradiation time of two and a half hours enables to deliver a total light dose of about 37 J/cm^2 anywhere in the treated area ($12.3 \text{ mW/cm}^2 \times 9000 \text{ s} \times 1 \text{ minute light} / (1 \text{ minute light} + 2 \text{ minutes dark})$) [24].

The protocol involved a 30-minute incubation with MAL followed by a 2.5 h irradiation with a light-emitting fabric-based device (FLEXI-PDT). Due to the short incubation time, this device aimed to provide a nearly pain-free, all year round alternative to conventional PDT (C-PDT) performed with a LED panel, 3 hours after MAL application with 75 mW/cm^2 for 10 minutes [25]. Moreover, the high flexibility of the light-emitting fabric-based device ensured an optimal conformation of the device to the area to be treated, offering clear advantages over other protocols.



Figure 11: Each LEF sequentially emits 635 nm red light for one minute resulting in a fractionated irradiation (1 minute light, 2 minutes dark).

| | FLEXI-PDT | C-PDT | Superiority p value for comparison between randomized group |
|---|-----------|-----------|---|
| Number of lesions | 156 | 154 | |
| Complete lesion response rate (%) at 3 months | 66.0 | 59.1 | p=0.070 |
| Complete lesion response rate (%) at 6 months | 84.0 | 76.8 | p=0.086 |
| Pain experienced during the 1 st treatment | 0.4 ± 0.6 | 5.0 ± 2.6 | p < 0.0001 |
| Pain experienced during the 2 nd treatment | 0.2 ± 0.5 | 5.0 ± 2.2 | p < 0.0001 |

Table 1: Complete response rate (lesion-level) achieved with FLEXI-PDT and C-PDT at 3 and 6 months [7].

For this clinical protocol, 27 patients were included in the study. Two patients dropped out for personal reasons before treatment. 25 patients with a total of 310 actinic keratosis were treated and examined at three months after the treatment. Due to remaining actinic keratosis, a second treatment session was required for 20 patients with a total of 252 actinic keratosis. Between three and six months following the first treatment session, one patient dropped out due to a serious adverse event not related to the treatment and one patient did not return for the 6-month visit for personal reason. 23 patients with 286 actinic keratosis therefore completed the study at 6 months.). Most of them had phototype II (76.0%). A total of 156 actinic keratosis, the majority of which were in grade I (42.3%) and II (56.4%),

received FLEXI-PDT. 154 actinic keratosis (grade I: 42.2%; grade II: 56.5%; grade III: 1.3%) received C-PDT[26].

At 3 month follow up, with 91 actinic keratosis in complete response and 63 actinic keratosis in incomplete response. C-PDT achieved a lesion complete response rate at three months of 59.1% vs 66.0% with FLEXI-PDT. At six months following treatment, the lesion complete response rate achieve 84.0% with FLEXI-PDT vs 76.8% with C-PDT. The response rate at six months for FLEXI-PDT (respectively, C-PDT) was around 1.3 (respectively, 1.3) times higher than that at three months. Similar local side effects, such as erythema and oedema, were observed with both FLEXI-PDT and C-PDT. Usual in dermatological PDT, these effects did not require any special care.

Evaluating illumination of actinic keratosis with an helmet incorporating a LEF compared to the Conventional Photodynamic Therapy: NCT03076918

The second clinical evaluation of the LEF technology was carried out with an improved version of the previous device. The clinical protocol was similar to the one used except that the irradiance has been reduced from 12.3 mW/cm^2 to 1.3 mW/cm^2 and the light dose from 37 J/cm^2 to 12 J/cm^2 . Furthermore, the device has been redesigned so as to be more ergonomic and compact (figure 12). A $21 \text{ cm} \times 18 \text{ cm}$ surface (378 cm^2) LEF was integrated inside an ergonomic helmet. This device was classified as exempt risk group according to IEC 60601-2-57/2012. [24]



Figure 12: image of the helmet delivering an irradiance of 1.3 mW/cm^2 for 150 minutes for the treatment of Actinic Keratosis

For this clinical protocol, 47 patients were included in the study. (C-PDT) was performed as usual with a LED panel, 3 hours after MAL application with 75 mW/cm² for 10 minutes. The final analysis of this study gave the following results: One patient withdrew consent and did not receive treatment. Forty-six patients for a total of 560 actinic keratosis were treated in a split-face manner with C-PDT (285 actinic keratosis) and P-PDT (285 actinic keratosis), and evaluated at 3 months of follow-up. Due to at least one remaining actinic keratosis, 19 patients were required to undergo a second PDT session. Of these, one dropped out after the 3-month visit for fear of a pain as intense as that experienced with C-PDT during the first PDT session. As a result, only 18 patients (for a total of 105 remaining actinic keratosis of the 204 initial actinic keratosis at the first treatment session) were retreated. Forty-five patients completed the study at 6 months. All patients were men, aged 49-89 years (mean age 72.4 years). Most patients had Fitzpatrick skin types II (63.8%). Of the 285 actinic keratosis randomized to receive C-PDT (respectively, P-PDT), 45.6% (respectively, 44.9%) were in grade I and 54.4% (respectively, 55.1%) were in grade II [27].

At 3 month follow up, P-PDT was non-inferior to that obtained with C-PDT (79.3% vs. 80.7%, respectively. Six months following the first treatment session (after one PDT session for 27 patients and two PDT sessions for 18 patients). Whatever the protocol, almost all patients reported adverse effects throughout the study (100% with C-PDT vs. 97.8% with P-PDT). However, the incidence of adverse effects was lower with P-PDT than with C-PDT (161 vs. 264).

The more important observation was the quasi-absence of pain with P-PDT. With all the pain scores ranging from 0 to 2.7, P-PDT was reported to be almost pain-free. Regarding the first PDT session (46 patients), the treatment-related pain at the end of irradiation is significantly lower with P-PDT compared to C-PDT (0.3 ± 0.6 vs. 7.4 ± 2.3 , $p < 0.0001$). The same finding was also observed for the second PDT session (18 patients) (Figure 4) (0.2 ± 0.4 for P-PDT vs. 7.7 ± 1.8 , $p < 0.0001$ for C-PDT).

| | P-PDT | C-PDT | Superiority p value for comparison between randomised group |
|---|---------------|---------------|---|
| Number of lesions | 280 | 280 | |
| Complete lesion response rate (%) at 3 months | 80.7 | 79.3 | p=0.34 |
| Complete lesion response rate (%) at 6 months | 94.9 | 94.2 | p=0.66 |
| Pain experienced during the 1 st treatment | 0.3 ± 0.6 | 7.4 ± 2.3 | p < 0.0001 |
| Pain experienced during the 2 nd treatment | 0.2 ± 0.4 | 7.7 ± 1.8 | p < 0.0001 |

Table 2: Complete response rate (lesion-level) achieved with P-PDT and C-PDT at 3 and 6 months [8].

PAGETEX

Primary Extramammary Paget's disease (EMPD) of the vulva is a rare skin cancer that mainly affects the genital region of elderly female population. Patients develop red eczematous and pruriginous plaques with a chronic evolution. Common dermatological symptoms and the lack of knowledge of the Paget's disease often lead to late diagnosis. To control disease progression and symptoms usually experienced by patients, surgical excision is the mainstay of treatment. The excision can be a total vulvectomy, or be delimited to the lesions with common margins of 2 cm in width and 0.5 cm in depth. However, recurrences are common (up to 58% within 15 months to 14 years) [28] [28], and recurrent patients suffer from severe functional and sexual alterations. Alternative treatments are studied like topical chemotherapy, laser ablation or radiotherapy but the adverse effects are numerous and the results are not enough superior to surgical excision. To date, none of these treatments can be considered as a solid alternative [29]. PDT is also studied [30-33] but unfortunately, the benefits of using photodynamic therapy for vulvar EMPD remains a challenge to demonstrate, because of the inhomogeneous illumination of vulvar and perianal areas, and the extreme pain that patients usually experienced during the illumination procedure that may lead to premature end of treatment [34, 35]. Inspired from the PHOS-ISTOS® study light parameters [36], the PAGETEX protocol (NCT03713203) involves the application of MAL cream for 30 minutes followed by 2.5 hours of illumination, without removing MAL-cream, such that a total light dose of approximately 12 J/cm² is delivered

The PAGETEX® device was developed to fit the body shapes and provides a homogeneous light at the entry of the vagina, under the lips and on perianal region safely, [7, 14]. During the PDT treatment, the PAGETEX® device is placed over the vulva and maintained by pants (figures 13, 14). Patients can even slightly move during the illumination session, and also be accompanied while keeping intimacy.



Figure 13: PAGETEX® device connected with 635 nm LASER source – flat device (Left), folded device (Right)

Transparent occlusive panties keep the PAGETEX device completely isolated from the patient's skin and thus to be reusable after specific cleaning.



Figure 14: PAGETEX® device connected with 635 nm LASER source during treatment of a patient

This clinical study is in progress and reporting of results is expected in 2022.

Conclusion

The different applications of Light Emitting Fabrics for photodynamic treatment show that this technology is well suited for homogeneous illumination of large areas. The technology used for manufacturing this LEF is very well known by the textile industry, leading to very competitive production costs. The fact that optical fibers can transmit light from 400 nm to 1200 nm allows the connection of LEF to different laser sources covering the light spectrum of all photosensitizers used for medical applications. New developments should allow to use the LEF inside cavities such as the pleural or the peritoneal cavities. At last, other applications such as baby jaundice treatment are already forecast.

Conflicts of interest

The LEF technology is now commercialized by the company, MDB Texinov in France. However, no author of this article has financial interest in the development of the LEF device with this company and consequently the authors have no conflicts to declare.

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Light emitting fabrics for Photodynamic Therapy: technology, experimental and clinical Applications" (Manuscript ID : tbio. 202000005. R2)

Graphical abstract :



By integration of plastic optical fibers within knitted or woven structure, light emission can be obtained over large and flexible textile fabrics. Homogeneity of spatial light distribution is obtained by controlling the density of the fibers and the angles and radii of curvature. These Light Emitting fabrics (LEF) can be connected to any light source from 400nm to 1200 nm. LEF are now used for preclinical and clinical applications of photodynamic therapy. Several examples are given into this article.