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INSIDE

A Review of the European Society for Photodynamic Therapy (Euro-PDT) Annual Congress 2018

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This congress took place on 16th–17th March 2018 in Nice, France.

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Meeting Summary

This article reviews new data presented at the recent European Society for Photodynamic Therapy (Euro-PDT) Annual Congress 2018. The role of topical photodynamic therapy (PDT) in the treatment of actinic keratoses (AK), among other therapies, was reviewed, along with updates on rising incidence of nonmelanoma skin cancer (NMSC), awareness of skin cancer risk in outdoor workers, and the potential of PDT as a treatment for prevention of AK and NMSC. A novel scoring method for AK and potential biomarkers for skin cancer, as well as those predictive of PDT response, were presented. Several studies highlighted real-world use of daylight (DL)-PDT across Europe and of its use in novel indications, including acral AK, application following organ transplant, and the option for home-based DL-PDT. New data on PDT combined with other therapies, as well as using novel light sources, will broaden the appeal of PDT to patients and practitioners. Optimisation of PDT using pretreatments and improving the tolerability of the treatment will boost efficacy and patient preference for this therapy. Evidence for off-label use of PDT presented at the congress included antimicrobial and aesthetic indications.

INTRODUCTION

On the first day of the congress, during the opening plenary session, Prof Basset-Seguin, Paris, France (C01), reviewed current evidence confirming a rise in incidence of NMSC worldwide, due to several factors including ultraviolet and sunlight exposure, increased outdoor activities, change in clothing style, and increased longevity. NMSC was recognised in 2015 as an occupational disease for outdoor workers in Germany; Dr Zink et al.,[1] Munich, Germany (C02), reported a cross-sectional study among 353 farmers, gardeners, and roofers using an online survey to

assess perceptions, beliefs, and risk behaviour of outdoor workers. A low perceived skin cancer risk was significantly associated with poor use of sunscreen, long-sleeved shirts, sunglasses, and headgear, and 43.4% of the participants never used sunscreen during work.[1] Dr Zink concluded that sustainable target group-oriented awareness prevention programmes are needed.

The following three presentations focussed specifically on the measurement, treatment, and prevention of AK. AK area and severity index (AKASI) is a new quantitative tool for clinical evaluation of AK of the head, aiding the assessment of response to treatments.[2] Prof Dirschka et al.,[2] Wuppertal, Germany (C03), observed that existing classification systems focus on individual lesions rather than the entire area affected. The results of a pilot validation study showed that AKASI and Physician's Global Assessment are very similar.

Dr Morton, Stirling, UK (C04), reviewed the published guideline evidence to inform practitioners of therapy choices for AK. PDT is particularly suitable for sites of confluent lesions and wider field therapy, receiving an 'A' strength recommendation. Studies indicate conventional PDT to be at least as effective as two freeze-thaw cryotherapy cycles, topical 5-fluorouracil, imiquimod, and ingenol mebutate. Five randomised control trials in Europe and Australia confirmed the equivalent efficacy of DL and conventional PDT, but with superior tolerance and ease of use for large fields with DL therapy.[3] Dr Bernad, Pamplona, Spain (C05), then presented the results of a randomised, evaluator-blinded, intraindividual comparison trial of six cycles of methyl aminolevulinate (MAL) DL-PDT (two sessions, 15 days apart at baseline, 3, and 9 months), or cryotherapy (at baseline, 3, and 9 months), for the prevention of AK and NMSC in organ transplant recipients (OTR). MAL DL-PDT showed fewer new lesions compared with cryotherapy at 3 and 9 months, and the patients were better able to tolerate PDT compared with cryotherapy.

NEW DIAGNOSTIC TOOLS AND BIOMARKERS

In the following plenary session, focussing on new diagnostic tools and biomarkers, Dr Moscarella, Naples, Italy (C06), described morphological clues from reflectance confocal microscopy that help in the classification of nonpigmented skin tumours.[4] Management of patients would be improved if biomarkers could accurately predict risk of AK progression. Dr Schmitz, Bochum, Germany (C07), observed that current biomarkers do not predict a possible progression risk of AK lesions. Recent approaches indicate an important role of dermal factors such as cancer associated fibroblasts. Moreover, promising results have been reported regarding gene expression and mutations in AK, including fibronectin, cadherin-3, kallikrein-related peptidase 6, peptidase inhibitor 3, and kinetochore genes, which may allow for risk stratification due to the specific mutations of a patient. Along with biomarkers that may help predict metastasis of malignant lesions, there is the need for further study to help establish benefits and reliability in clinical practice.

Dr Rocio Lucena, Madrid, Spain (C08), reported on the assessment of biomarkers and how they can help predict responsiveness of Bowen's disease and basal cell carcinoma (BCC) following MAL-PDT. Higher expression of p53, cyclin D1, and epidermal growth factor receptor in Bowen's disease, and β-catenin in BCC, were biomarkers associated with responsiveness to MAL-PDT.[5]

To overcome limitations around prevailing weather conditions required for DL-PDT, a novel tuneable light source is currently under development by O'Mahoney et al.[6] The source replicates the spectral distribution of a protoporphyrin-IX-weighted solar spectrum and delivers uniform illumination to both flat and curved surfaces with a uniform illumination over a 35x20 cm treatment area. Dr Eadie et al. Dundee, UK (C09), reported that artificial light sources that could better simulate DL would be of great benefit in many parts of the world with seasonal restrictions for the provision of DL-PDT.[6]

REAL-WORLD USE OF PHOTODYNAMIC THERAPY

At the beginning of the third plenary session, Prof Fargnoli, L'Aquila, Italy (C10), presented the results of an observational study on real-world clinical use of MAL DL-PDT for face or scalp AK in 52 departments across six European countries.[7] Along with assessment of efficacy and adverse events, patient-reported outcomes

were assessed by questionnaires. Overall, 325 patients, predominantly diagnosed with Grade I (39.4%) or Grade II (33.2%) lesions, received a single treatment; the proportions of patients and physicians that were satisfied or very satisfied with MAL DL-PDT were 80.4% and 90.3%, respectively.

The description of an ambitious German interventional study of the prophylactic effects of DL-PDT in preventing AK was presented by Prof Karrer, Regensburg, Germany (C11). In this multicentre, prospective, randomised, controlled, two-armed, observer-blinded trial, patients with a minimum of five mild-to-moderate AK on photodamaged facial skin were randomly allocated to either MAL DL-PDT (five treatments over 18 months) or cryosurgery.[8] The primary outcome parameter used was the cumulative number of AK lesions observed between visits two and six.[8] Secondary outcome parameters were complete clearance of AK, new AK lesions since the previous visit, cosmetic results, patient-reported pain, satisfaction with cosmetic results, and patient-reported quality of life.[8]

Dr Savary, Paris, France (C12), described a prospective study of the use of DL-PDT for mild-to-moderate AK, which involved 154 dermatologists in France. In addition to reduced pain over conventional PDT, DL-PDT offers the advantage of not requiring specific equipment and permits treatment of large fields of cancerisation in a single treatment session. Prof Szeimies, Recklinghausen, Germany (C13), led a highly informative auditorium-based survey on DL-PDT that sought to highlight variation in treating AK, reflecting differences in disease distribution and awareness, different healthcare systems, and access of patients to specialists and economic aspects in Europe. There was consensus in many areas, but selection of PDT for AK, clearly varies across Europe and shared learning will help enable more patients to access this therapy.

Few studies have systematically investigated the effects of PDT on acral AK that appear to be more resistant and difficult-to-treat than those located on the face or scalp. Dr Fai, Lecce, Italy (C14), reported in the next plenary session focussing on DL-PDT preliminary data on the use of MAL DL-PDT for AK on the forearms. Treatment sites received 10% urea cream for 10 days followed by two DL-PDT sessions 1 week apart. Three months after the last treatment, the mean complete response rate was 74% for total lesions.[9]

Prof Bedane, Limoges, France (C15), presented a pilot study of 16 patients to determine the feasibility and efficacy of home-based DL-PDT. Following use of a keratolytic ointment for 2 weeks, patients undertook lesion preparation, prescribed sunscreen and MAL, and were advised to perform PDT within 4 days. Response rates of 87% after 1 month and 88% after 3 months were similar to the literature for supervised DL-PDT.[10] The median visual analogue scale score was 2 and there was no observed increase in adverse events, e.g., sunburn.

Reflecting the inconvenience of the standard protocol for PDT for BCC that requires two visits 1 week apart, Dr Rianne Gerritsen, Nijmegen, Netherlands (C16), presented results from a multicentre pilot trial of a single session of fractionated MAL-PDT for superficial BCC. Twenty-one patients were randomised to receive two illuminations either after 3 and 4 hours following MAL application, or 3 and 5 hours (with split light dosing: 20+55 J/cm^2). No significant differences were observed with 3-month complete response rates of 80% versus 91%, respectively.

Dr Ulrich, Berlin, Germany (C17), detailed the specific needs of OTR. This population is at severe risk of developing high numbers of NMSC and precursors due to the iatrogenic chronic immunosuppression.[11] PDT and especially DL-PDT are of high value in the control of NMSC in these patients with low levels of side effects like pain and discomfort. Continuing with this topic, Dr Lear, Salford, UK (C18), presented a pilot study utilising DL-PDT for the management of AK in renal transplant recipients. In this pilot study of five patients, three of the five patients achieved complete clearance of treated areas with this treatment modality, which was judged as highly satisfactory and tolerable by the patients.

Long-term data and real-life experiences are crucial for the overall assessment of a therapy. Dr Basso, Genoa, Italy (C19), presented data on DL-PDT for various grades of photodamage, different sites of body involvement, and results and side effects both in the short and long term.

ENHANCING PHOTODYNAMIC THERAPY

In the final session on Friday evening, Prof Haedersdal, Copenhagen, Denmark (C20), gave an update on the potential of skin pretreatment to enhance penetration of photosensitising agents. The major pretreatment procedures, with evidence-proven results, are fractional lasers, dermabrasion, and microneedling.[12] Another possibility to enhance treatment efficacy is the use of combination strategies. Prof Piaserico, Padova, Italy (C21), presented new data on combination of DL-PDT with 5% 5-fluorouracil cream, ablative fractional laser systems, or pretreatment with calcipotriol. Prof Torezan, São Paulo, Brazil (C22), focussed on pretreatment with vitamin D. In a comparative study with 20 patients in a split-design manner, one side of the scalp was pretreated for 15 days with topical calcipotriol.[13] On the final day, both sides of the scalp received conventional MAL-PDT. Overall, AK clearance was higher on the pretreated side, totalling 92.1% versus 82.0%, respectively.[12] Fluorescence intensity was also higher on the pretreated side, indicating that vitamin D enhances the synthesis of photoactivatable porphyrins.

The doyen of PDT, Prof Wulf, Copenhagen, Denmark (C23, C24), shared the latest insights of PDT mechanism of action with innovative treatment options. He showed that to reach the same amount of protoporphyrin IX without curettage versus with curettage, incubation time had to be increased.

In a study of 25 patients, the incubation time was prolonged by 30 minutes (1 hour in total), with 2 hours DL exposure versus curettage, 30 minutes incubation, and DL exposure; the results in lesion response rate were the same. It is to be noted that most of the lesions were Grade I according to the Olsen classification (>86%). Efficacy rates were similar to DL-PDT with and without curettage (C23, 24).[13]

The first plenary session on Saturday morning focussed on light devices for illumination. Prof Mordon, Lille, France (C25), presented, for the first time, clinical data from a binational study on light-emitting fabrics for PDT (PHOS-ISTOS). Simulating DL-PDT, patients with AK on the scalp received MAL application followed by a 150-minute illumination of red laser light delivered via a knitted fabric that perfectly fitted the curved surface of the head of the (primarily male) patients with field cancerised areas. Classical red-light PDT with conventional LED light sources served as a control. There was no statistical difference in AK clearance; however, pain was significantly lower at the site with the light-emitting fabric. Furthermore, a treatment approach with a helmet was presented by Dr Fonda-Pascual, Madrid, Spain (C27). In their approach, a low-level laser cap was developed and was equipped with a high number of miniature light sources, ensuring a uniform distribution of light. A similar approach was presented by Prof Ibbotson, Dundee, UK (C28), during recent work with organic LED that are integrated in a portable device. The patient activates the device after application of the photosensitiser; following an incubation period of 3 hours, the device starts illumination by itself. Studies with ambulatory PDT in BCC and Bowen's disease were undertaken with excellent results.[15]

Prof Calzavara-Pinton, Brescia, Italy (C29), reported the cost-effectiveness of DL-PDT, not only in Italy but also for numerous other European countries, considering the different costs for drugs and procedural treatments. Since costs are strongly related to the surface area to be treated, DL-PDT is a very cost-effective treatment throughout Europe.[16]

In the next plenary session, Dr Osman-Ponchet, Nice, France (C30), presented a study on alternative skin preparation techniques.[17] Skin preparations with an abrasive pad or microneedling increased transepidermal water loss, which is a good surrogate marker of MAL penetration.

Due to the simplicity of the DL-PDT procedure, it is anticipated that educated patients could perform this therapy at home. Dr Garcia-Malinis, Huesca, Spain (C32), presented their clinical experience, together with the improvements in patient satisfaction and efficiency following introduction of home-based DL-PDT in Spain.

Besides pain as a main side effect of PDT, which has not been noted following DL-PDT, patients also complain of illumination-associated erythema and crust formation after treatment. It is obvious that these side effects are a sign of effectiveness; however, if there are strategies to overcome these skin reaction patterns,

patients may benefit significantly. Prof Wiegell, Copenhagen, Denmark (C33), presented the concept of pulse-PDT whereby MAL application under occlusion is limited to 30 minutes, followed by illumination with red light at adequate doses after 3 hours.[18] This procedure limited erythema after PDT for facial and scalp AK. Further reduction of erythema was achieved through the use of topical clobetasol. The use of brimonidine tartrate, a topical potent vasoconstrictor intended for use in rosacea, reduced PDT-induced erythema when applied after treatment.

Dr von Dobbeler, Wuppertal, Germany (C34), reported on a study with a new light source, Medisun DL 9000 PC booth, delivering a DL-adjusted spectrum. It was used for 1 hour after 1 hour of MAL incubation on AK patients. The patients demonstrated a good improvement and the illumination was almost painless, making the procedure feasible as a method of office-based simulated DL-PDT.

A report from the Netherlands by Dr Kessels, Maastricht, Netherlands (C35), compared fractionated aminolevulinic acid (ALA)-PDT, 20 and 80 J/cm^2 4 and 6 hours after ALA application, with conventional MAL-PDT for superficial BCC.[19] The two-fold ALA-PDT resulted in fewer recurrences, but it was not statistically significant (p=0.091). ALA-PDT resulted in higher pain scores and more side effects compared with MAL-PDT.

Dr Zaar, Göteborg, Sweden (C36), demonstrated, in a retrospective study[20] of 423 Bowen's disease lesions in Sweden, an initial complete response rate of 77.5% with a following recurrence rate of 18.3%, giving a final complete response rate of 63.4%. Large lesion size (≥2 cm) and a single PDT session were risk factors for recurrence.[20]

In patients with more prominent AK lesions, representing the real-life situation, lesion intensified field treatment may be a suitable approach. Dr Braun, Düsseldorf, Germany (C37), discussed adjunctive procedures to enhance the efficacy of classical and DL-PDT.[21] Dr Petering, Hildesheim, Germany (C38), focussed on the increased risk of development of NMSC in patients who received anti-tumour necrosis factor therapies for the treatment of their psoriatic disease; a perfect treatment option in these cases is the use of classical and DL-PDT.

OTR are at high risk of developing AK and NMSC. In a study[22] presented by Dr Togsverd-Bo, Copenhagen, Denmark (C39), 20 renal transplant recipients were randomised to receive PDT in one skin area every 6 months for 5 years and were assessed 1 year post-treatment. The contralateral side served as a control. The median time to first onset of AK was 30 months in untreated skin, and 42 months in PDT-treated skin, and a much higher number of AK occurred in untreated skin, demonstrating that PDT is a useful prophylactic treatment of OTR.[22]

Prof Sotiriou, Thessaloniki, Greece (C40), presented a comparison of DL-PDT with conventional PDT. The focus in this trial was a long-term follow-up period. Twelve months after treatment showed 71.8% and 73.7% complete responses for DL-PDT and conventional PDT, respectively.[23] This is another confirmation that DL-PDT is as effective as conventional PDT.

Patients with oculocutaneous albinism are at high risk of developing skin cancer early in their lives, especially when they live in extremely sunny areas. In a study from Brazil of patients with oculocutaneous albinism and AK, Dr Galvao, Fortaleza, Brazil (C41), showed a clearance rate of 68% after two sessions of DL-PDT, making it a useful therapy for these patients.

The Immunology Frontier Research Center at Osaka University, Osaka, Japan (C42), presented results with synthesised hybrid polyamine porphyrins. Using cancer cells, the research team showed that the porphyrin with the longer amine chain localised mainly in the mitochondria and exhibited a strong PDT efficacy.[24] Dr Taba indicated that *in vivo* mice studies are now underway.

PDT has been shown to be effective in the treatment of cutaneous leishmaniasis; Dr Bay, Fez, Morocco (C43), presented a case report of successful treatment of leishmaniasis of the ear. PDT has also been explored for use in alopecia areata of the scalp and vitiligo of the body. Dr Moscarella, Rome, Italy (C44), presented 16 patients with severe alopecia areata and 10 patients with vitiligo, who were treated several times with ALA-PDT. Partial regrowth and total regrowth of the hair was observed in 10% and 20% of alopecia areata patients, respectively, while in vitiligo patients, almost 40% obtained a total repigmentation of the lesions treated.

For high PDT efficacy, a variety of factors are crucial. Uniformity of light during the illumination process is one of these influential factors. Dr Thecua, Lille, France (C46), reported on the difference in irradiance when AK lesions on the face and scalp are treated with a flat illumination device. In the final talk of this session, Prof Bjerring, Vejle, Denmark (C47), presented his views on the off-label use of drugs and treatment procedures, a common phenomenon in medicine and PDT is no exemption. PDT has been tested in a large number of dermatological diseases with various results. It is a safe and simple off-label treatment option for many dermatological diseases because it is practically pain free, offers limited down time, and is a relatively easy technique for performance in the office or even at home.

ALTERNATIVE USES

Since PDT is increasingly used for aesthetic treatment, in particular for the face as rejuvenation treatment, Dr le Pillouer Prost, Marseille, France (C45), focussed on the new protocols for this purpose. So far, there are many variations and combination protocols used. Among these, DL-PDT is used, and includes intensified PDT, using PDT in combination with ablative and non-ablative fractional CO_2 or Er:YAG laser, microneedling, or sandpaper abrasion. Since these procedures enhance drug penetration and probably deliver a rejuvenational effect by themselves, further possible treatment enhancers include the use of light sources such as intense pulsed light combined with PDT.

Prof Gilaberte, Zaragoza, Spain (C31), provided an update on basic and clinical studies in the field of antimicrobial PDT. Antibiotic resistance is a serious concern in human medicine and beyond, so the possible use of PDT for this purpose is of growing importance. Prof Gilaberte also presented recent data from studies in which antimicrobial PDT was combined with classical antibiotics, thus exerting a synergistic effect in killing of micro-organisms.[25]

PRESENTATION AWARDS

Prior to his closing remarks, Prof Braathen, President of the Euro-PDT, announced the winners of the three poster prizes; a total of 12 posters were displayed during the congress and were discussed during the congress breaks. The third prize was won by Janne Räsänen, Tampere, Finland (P12), who presented a prospective, randomised, non-sponsored, multicentre, split-face study of 69 patients with 767 AK who received DL-PDT with either ALA-nanoemulsion or MAL. The second prize went to Raquel Cavalcante, São Paulo, Brazil (P7), for a study on DL-PDT with MAL in patients with field cancerisation who were evaluated for >3 months with clinical inspection, histological evaluation, and confocal microscopy evaluation. Pablo Fonda-Pascual and his group, Madrid, Spain (P2), were awarded the first prize for their work on an indoor DL-like PDT device that utilises low-level laser light mounted in a cap. All poster prize winners received a certificate and a financial reward.

The winners of the best oral presentations were Pablo Fonda-Pascual (C27) (third place), Lutz Schmitz (C07) (second place), and Serge Mordon (C25) (first place). Prof Braathen thanked the presenters for their excellent contributions and then closed the conference. In his final speech, Prof Braathen thanked Mr Yves Hochedez for the excellent logistic services, and praised the excellent and high scientific value of all contributions. Lots of new data were presented outlining the bright future for PDT in dermatology. Finally, he invited the audience to attend the next EURO-PDT conference in 2019.

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