Photodynamic Therapy/Assisted Photorejuvenation

Riccardo Rossi*, Torello Lotti, Nicola Bruscino

Division of Dermatology II, Department of Critical Care Medicine and Surgery, University of Florence, Florence, Italy.
Email: rossidermatologo@tiscali.it, r.rossi@med.unifi.it
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ABSTRACT

Photodynamic therapy (PDT) shows great efficacy and high tolerability for the treatment of non-melanoma skin cancer (actinic keratosis, basal cell carcinoma, Bowen's disease) especially in patients with large and multiple lesions, in poor-healing sites and patients immunosuppressed or with co-morbidities. Besides, more recently, PDT has been used, widely and with great success, for many off-label diseases and in cosmetic dermatology, especially on photorejuvenation, therefore further and larger prospective studies with long-term follow-up are required to verify its efficacy and safety in treating these condition. The treatment of ageing skin remains a very hot topic, and many systems have been reported as having varying degrees of success. Nowadays our experience and literature data show how topical PDT can be considered a new non-invasive device for the treatment o photoaging skin with no/minimal side effects and able to bridge the world of medical and cosmetic dermatologic surgery.

1. Introduction

Aging is a complex and multifactorial process that occurs in all individuals at a variable rate, influenced by environmental, hormonal and genetic factors which result in several functional and aesthetic changes in the skin. Skin rejuvenation, particularly of the face, remains an extremely popular elective procedure. Photoaging is manifested clinically by fine and coarse wrinkling, roughness, dryness, laxity, sallowness, pigmentary mottling, teleangectasias, and, in many

cases, with preneoplastic and neoplastic changes. Many systems have been reported as having varying degrees of success. Relatively recent technological breakthroughs in minimally invasive procedural dermatology have offered a multitude of options to improve overall aesthetic appearance. Chemical peelings (superficial, medium, or deep) are the oldest and the most widespread aesthetic procedures for skin rejuvenation (eg. pigmentary spots, fine wrinkles, acne scars). They can be used alone, the most used are alpha-hydroxy acids (glycolic acid) and beta-hydroxyacids (salycilic acid), or in conjunction with other nonsurgical methods for skin rejuvenation such as botulinum toxin A, dermal fillers or microdermoabrasion treatments. The choice of the compound depends on the indications and on the depth of the desired peeling [1]. Fillers are another important tool in the physician's armamentarium to combat ageing phenomena, especially wrinkles, and to restore volumes. A wide variety of filler substances are now available. Currently, the most commonly used fillers are hyaluronic acid and porcine collagen preparations. Poly L lactic acid (PLLA) has gained its place in the filling of adipose tissue; other common products include silicone and calcium hydroxylapatite (CAHA) fillers. Permanent fillers may be of advantage but carry the risk of permanent adverse reactions [2]. The combination of different fillers with botulin toxin injections may give optimal aesthetic results, especially in the lower face treatments [3]. After years of clinical success and consistent safety Botulinum toxin type A is included in the forefront of minimally invasive techniques of facial rejuvenation. Botulinum toxin is the most effective tool in reducing dynamic facial lines and rhitydes, especially in the upper face, for which it is considered the treatments' cornerstone [4]. Botulinum toxin can be used as adjunctive therapy with fillers to increase the efficacy and duration of results and in conjunction with laser resurfacing. Lasers and intense pulsed light (IPL) offer numerous therapeutic options in the field of cutaneous conditions; the combination of effective wavelengths, fluences, pulse durations and pulse intervals facilitates the treatment of a wide spectrum of lesions: hirsutism, pigmentary changes associated with photoaging, vascular lesions such as teleangiectasias or vascular malformations, acne scars and wrinkles [5]. Nevertheless, as actinic keratosis (AK) can be considered the end stage of the skin ageing process, and has been successfully treated for several years using photodynamic therapy (PDT) with important therapeutical and cosmetic outcome, PDT has been suggested to be used in skin photorejuvenation and we would like to focus, on this paper, our attention on this therapy and its role alone or in conjunction with a variety of lasers

and light for cosmetic purposes in the treatment of many facets of photoaging, like tactile skin roughness, crow's feet appearance, dyschromias and teleangectasias. Actinic keratosis (AK) is an important feature of chronic sun damage and helps to identify a population at risk of developing an invasive squamous cell carcinoma (SCC) either from a pre-existing AK or from the surrounding skin. PDT Treatment not only of the AK lesion but also of the field cancerization is part of an optimal strategy aimed at resolving both the clinically obvious alterations as well as those of the surrounding skin that probably is already the site of genetic alterations and of an initial gradual replacement of normal cells.

2. Discussion

Topical PDT use in dermatological practice is thoroughly discussed and debated in the scientific literature because although the concept is simple, the multiple parameters involved make it complex, and more studies and research are required to determine the optimal parameters for the treatment of approved as well as off-label indications. At the time of this writing MAL (methyl aminolevulinate)-PDT is approved for AK, superficial/nodular basal cell carcinoma (s/n BCC) and Bowen's Disease (BD) in 22 European countries, as well as New Zealand and Australia, where it is marketed under the trade name Metvix→ (Photocure, Oslo, Norway and Galderma, Paris, France) and has recently been launched under the name Metvixia→ in USA. Levulan→ (DUSA Pharmaceuticals Inc.) is the other proprietary drug [ALA (5-aminolevulinic acid) 20% solution in an alcohol-water-surfactant vehicle] that has been FDA-approved but only for actinic keratoses in the United States and Canada (although not in European countries). Different from the US, ALA is not yet in the pharmacopeia of any European country and can be produced and commercialized only as a chemical reagent and its use is subject to the rules and specific authorizations of local ethics committees and national health regulatory authorities. PDT for AKs and the other approvedindications represent an effective treatment option, it is well tolerated and non-invasive, there is no need for anesthesia and standardized protocols exist and it has shown excellent cosmetic results [6-15]. ALA/MAL PDT has been investigated in the off-label treatment of a number of other neoplastic, infectious, inflammatory skin conditions with variable and often contrasting results and for the improvement of visible signs of photoageing. The use of ALA/MAL-PDT in these indications must follow all the rules and authorizations specified by the local Ethics Committees. In these cases

different various photosensitizing agents and different uses in delivery and incubation times, such as being combined with various parameters relating to light, are used and no standardized protocols exist.

3. PDT Action in Photorejuvenation

Photodynamic therapy (PDT) is a treatment modality using a photosensitizer, light and oxygen to cause photochemically induced selective cell death. When exposed to light with the proper wavelength, the topically applied photosensitizer or photosensitizer precursor can activate a biomolecule through electron transfer to yield free radicals or produce singlet oxygen from energy transferred from the excited sensitizer to molecular oxygen. The tissue damage is the result of the activation of reactive singlet oxygen or free radicals production; this causes cell apoptosis or necrosis, membrane, mitochondrial damage and many signaling molecules activation. These free radicals have a selective action based on the characteristic location of accumulation of ALA in the skin. Furthermore, damaged and highly proliferative epidermal cells produce more PpIX when exposed to ALA/MAL and light and, as a result of decreased barrier function, greater penetration of the sensitizing agent is allowed. We are still far from a thorough understanding of the molecular mechanism of rejuvenation with this technique: we think that PDT permits the production and release of factors as TGF-β and FGF, inducing a consequent fibroblasts' activation and collagen type I-III synthesis, moreover it reduces the expression of collagen-degrading enzymes as matrix metalloproteinases-1, -3, and -12. Afterwards PDT can achieve smart results in photorejuvenation, thanks to its skill to contrast the collagen degradation, permitting its synthesis into dermis. PDT has become one of the most often chosen treatment for premature skin aging especially due to sun exposure. A significative improvement of many photodamage signs, like fine lines and wrinkles, dyschromias (hyperpigmentation and hypopigmentation), sallowness, diffuse redness, teleangectasias, can now be achieved thanks to PDT technique, giving the patients a better aesthetic appearance of the treated area. Nowadays the patients themselves are able to notice the results obtained with PDT and they have started seeking this kind of treatment in the field of dermatologic practice. The possibility to utilize different parameters as the incubation times of the photosensitizer and the light intensity, notably lower than those exploited for oncologic lesions, permits the physicians to guarantee shorter healing times, fewer

side effects and therefore a higher patient tolerance. The three main devices currently used in inducing a cosmetic PDT effect are PDL (pulsed dye lasers) (585 nm and 595 nm), IPL (intense pulsed light) (500 - 1200 nm) devices, and narrow band blue/red-light lamps (blue light sources use the maximum absorption peak of PpIX at 410 nm, red light seeks to use one of the smaller absorption peaks of PpIX at 630 nm). ALA-PDT with a blue light source resulted in an improvement of skin elasticity and reduced skin thickening in patients with photodamaged skin [16], but for the lack of penetration depth and the interference by melanin (superficial melanin absorption), cosmetic effect of blue-light PDT, is purely photochemical and limited (e.g. no results are observed for pigmentary spot). Touma and Gilchrest [17] suggested the use of microdermoabrasion just before application of ALA for a more uniform and rapid penetration of ALA. Although IPL alone has been proved effective in the treatment of photoaging, by combining the photothermal effects of IPL with the photochemical effects of ALA-PDT the cosmetic possibilities can be expanded and an enhanced cosmetic effect has been demonstrated. Deeper penetrating visible wavelengths produced by IPL not only have enough energy to activate the photochemical process but also have long enough wavelengths to effectively reach and thermally target multiple chromophores including vessels, pigment and collagen.

Ruiz Rodriguez and colleagues [18] found that ALA-PDT using IPL as a light source (two treatments at a 1-month interval) resulted in higher levels of qualitative improvement of signs of photoaging in the skin. After combining the 5-ALA in a cream, they applied it to actinic keratoses on the face under occlusion for 4 hours. A 615-nm cutoff filter hand piece was used on the actinic keratosis areas at 40 J/cm^2 and over the remaining face at 30 - 50 J/cm^2. In the three months following the second treatment they observed complete resolution of actinic keratoses in 15 subjects and an "excellent" cosmetic result in all patients with a significant improvement in the visible signs of photoageing especially for skin texture, pigmentary changes and teleangiectasias. Pain was reported as "mild," and post-treatment erythema, edema, and crusting resolved in 10 days. Excellent results are reported by using ALA-PDT and blue light or ALA-PDT with IPL (improvement of 55% for teleangiectasias, 48% for pigmentary changes and 25% for skin texture) but with a 1-hour pre-incubation of the drug [19-21]. In this case, the use of shorter incubation times permits improved patient tolerance during treatment and, consequently, fewer adverse effects [22]. A comparative study with short-contact (30 - 60 min) ALA-PDT with IPL activation by comparing ALA-

PDT-IPL with IPL alone in thirteen patients and three months after the final treatment, showed a higher improvement on the ALA-PDTIPL treated side than on the IPL alone side with crow's feet appearance (55% vs. 28.5%), tactile skin roughness (55% vs. 29.5%), mottled hyperpigmentation (60.3% vs. 37.2%), erythema (84.6% vs. 53.8%) and AK clearance rate (78% vs. 53.6%) [23]. Similar results were reported by Dover and colleagues [24] that demonstrate the superior efficacy of IPL-mediated 5-ALA PDT over IPL alone in global photoaging scale (80% versus 50%), hyperpigmentation (95% versus 65%) fine lines (55% versus 20%) whereas tactile roughness and sallowness were found to be similar between the ALA and non-ALAexposed areas. No differences in side effects were observed. Similarly, ALA-PDT-PDL was found to result in greater improvement in photorejuvenation than PDL alone [25]. Key [26] reported significant improvements in texture and dyschromias and an improved patient tolerance treating 12 patients following 1-hour incubation by using a 585 nm PDL. Alexiades-Armenakas and Geronemus [27] demonstrate CR of 99.9% at 10 days and 90% at 4 months in treating AKs of the face and scalp treated with ALA-PDT-PDL (595 nm) and an improvement of photodamaged skin. More recently, openlabel studies and few controlled trials have suggested that MAL-PDT-red light may have therapeutic potential not only, as widely demonstrated for actinic keratoses but also in photodamage [28]. An improvement in mottled hyperpigmentation, fine lines, roughness and sallowness of the skin was observed by using MAL cream under occlusion for 3 hours before exposure to 37 J/cm^2 of red light (2 treatments with a 1-month interval), but deep wrinkles, telangiectasias, facial erythema and sebaceous gland hypertrophy did not always change. The authors reported a novel mechanism for evaluating the effect of PDT on skin thickness using echographic analysis [29]. No changes in mottled pigmentation or telangiectasias but with an improvement in fine lines, tactile roughness, and skin tightness was observed by Ruiz-Rodriguez et al. in a randomized, prospective, split-face comparison (1 hour versus 3 hours incubation time) study of 10 white, adult patients with moderate photodamage, mostly on the 3-hour time incubation side [30]. A clinical improvement with regard to texture, firmness, wrinkle depth, skin coloration, and clearance of actinic keratoses was observed in an interesting histopathologic and morphometric study that demonstrated an increase in the amount of collagen fiber statistically significant 6 months after treatment [31].

4. Our Experience

In our experience we treated 25 female with ALA-red light and we observed an improvement in telangiectasias, dyschromias and tactile roughness (CR 50%, PR 10% and no response (NR) 40%) after the first session. However during the last control, after three PDT sessions (three months after the start of the treatment), we obtained a CR in 63%, PR in 17% and NR in 20%. The skin texture was significantly improved at the last control with a marked improvement in 70%, partial improvement in 13% and no improvement in 17% (Figures 1, 2, 3 and 4). Clinically obtained results were evaluated by using Optical Coherence Tomography (OCT), a non-invasive diagnostic method which gives a histomorphology evaluation of the skin after 45 days from the last control,

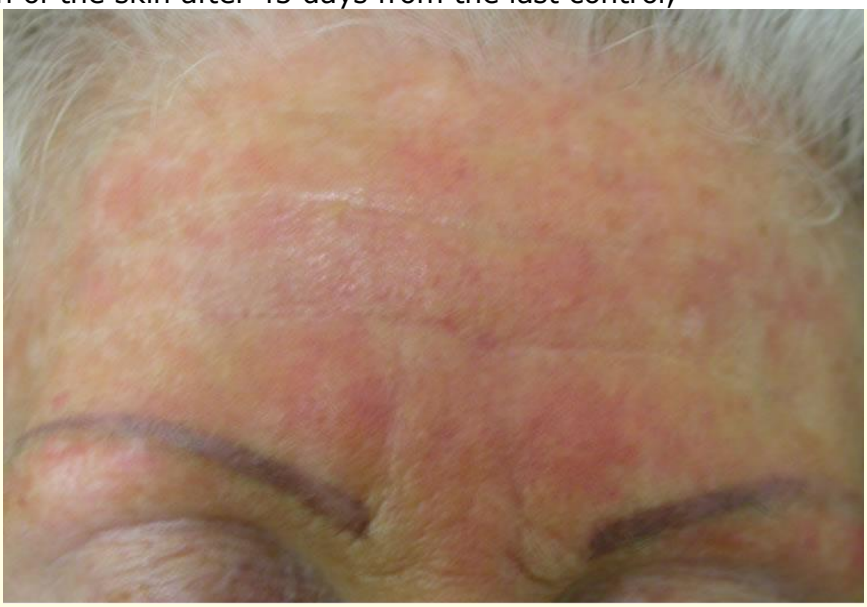


Figure 1. A forehead before PDT.

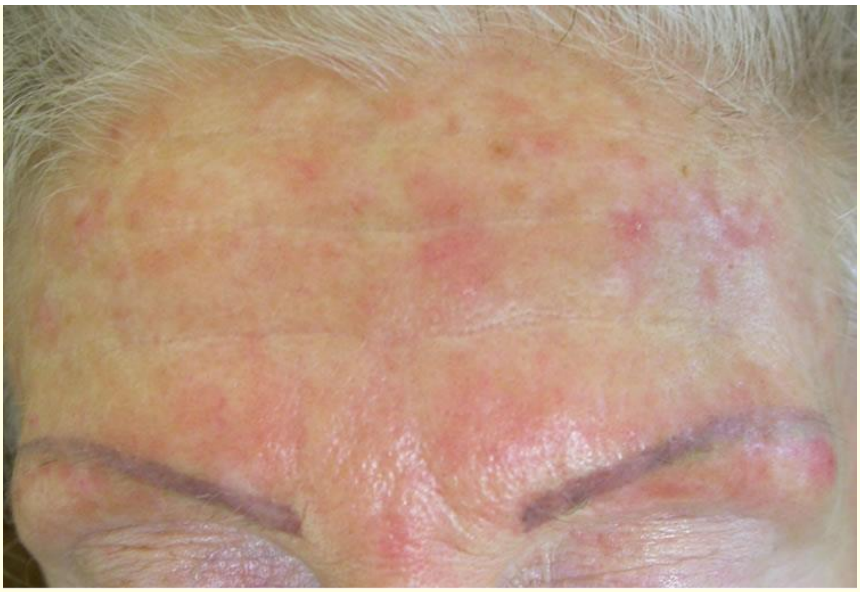
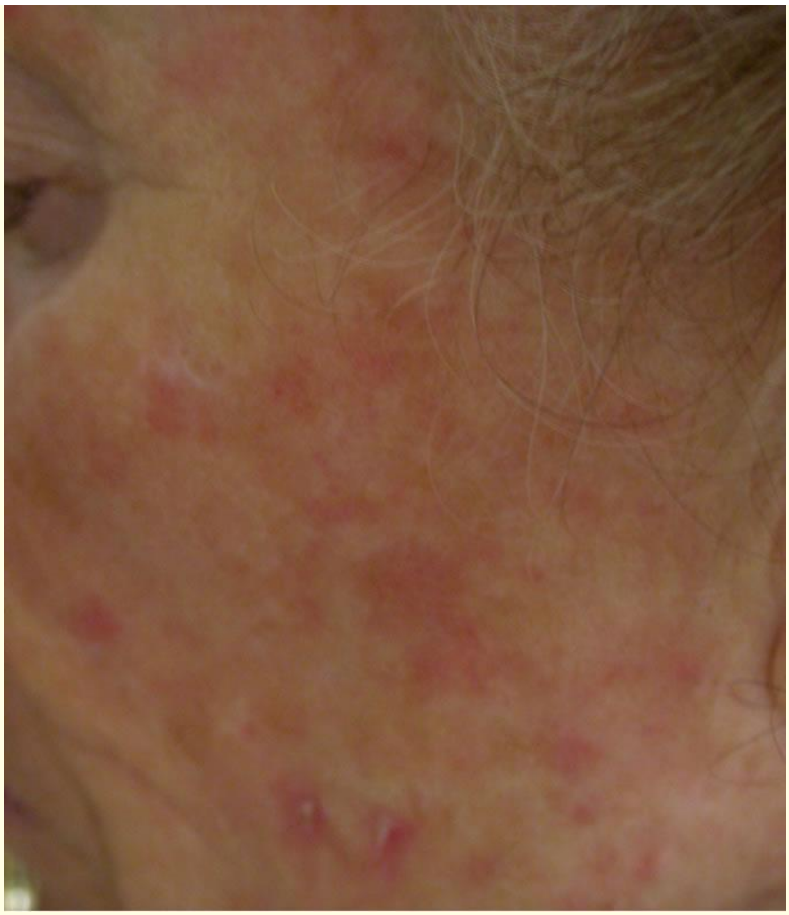


Figure 2. The same patient of **Figure 1** after 3 PDT sessions, at 2 weeks-interval; she was observed 3 months after the start of treatment. The lesion was treated with non coherent red light at wavelength of 632 nm; the lamp used(Aktilite PDT-model CL128→, PhotoCure, Oslo, Norway) had a light dose 37 J/cm^2 , light intensity 70 - 100 mW/cm^2, it illuminated areas at a distance from 50 to 80 mm.



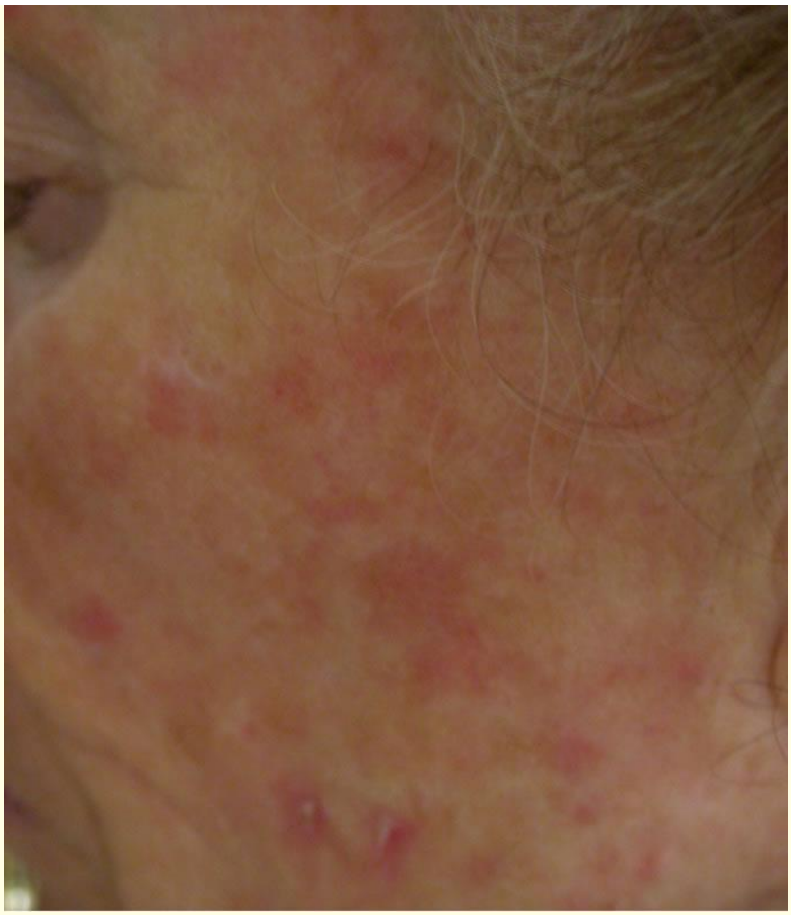


Figure 3. A cheek before PDT.

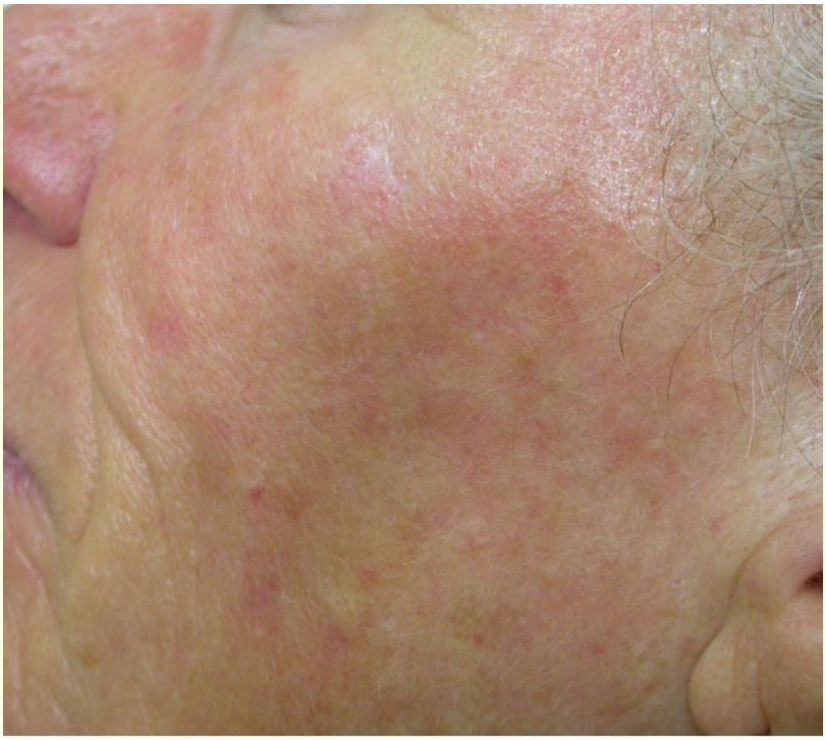


Figure 4. The same patient of **Figure 3** after 3 PDT sessions, at 2 weeks-interval; she was observed 3 months after the start of treatment. The lesion was treated with non coherent red light at wavelength of 632 nm; the lamp used(Aktilite PDT-model CL128→, PhotoCure, Oslo, Norway) had a light dose 37 J/cm^2 , light intensity 70 - 100 mW/cm^2, it illuminated areas at a distance from 50 to 80 mm.

avoiding a biopsy. We observed the undulated movement reappearance of the dermo-epidermic junction, that was linear before the start of the PDT treatment [32]. The lack of standardized protocols about the employment of PDT technique in the particular field of photorejuvenation, the presence of high number of parameters regarding the different light source used, the photosensitizers, the incubation times of the latter and others features, make our results hardly comparable with those obtained by different authors, even if all these results are very promising and encouraging. Potential long term beneficial effects depend on a proper patient selection and education. Very recently the use of 0.5% liposome-encapsulated 5-ALA spraying has been shown to be an alternative to 20% 5-ALA in a cream base in patients undergoing photorejuvenation but more studies are necessary [33].

5. Conclusions

These experiences show how the topical application of ALA/MAL acid followed by well-tolerated light sources (blue/red light, PDL, IPL), can be considered a new non-invasive procedure for the treatment, with safety and efficacy, of photodamaged skin and bridges the world of medical and cosmetic dermatologic surgery [34,35]. ALA/MAL PDT offers cosmetic benefits when used alone or combined with other therapies (chemical peelings, fillers, botulin toxin) increasing the satisfaction rate of our patients, depending on the goals of the patient [36]. Most significant advancements have been the development of short contact therapy and the synergistic photochemical and photothermal effect of IPL-PDL PDT. Other advantages are linked to its selectivity for tumoral cells, its efficacy in treating field cancerization, preventing any degenerating skin condition and the capacity to preserve normal tissues that lead to very excellent cosmetic results, thus offering a good alternative chance to standard treatment options with minimal, temporary and easily managed adverse effects [37]. Anesthesia during treatment is not necessary. It is relatively easy to adopt by any practicing dermatologist and requires no additional staff members. The prevention of the

incidence of neoplasms represents one of the most important clinical fields of interest in modern medicine and, as regards dermatology, PDT-based clinical action could play a great part in it. PDT is a promising therapy, capable to treat both signs of time and neoplastic change of damaged skin preventing new lesions by aging on field cancerization. If PDT can be useful in photorejuvenation, in the rapid and effective treatment of skin cancer and pre-tumoral conditions, and definitely in the improvement of overall skin health, thus it must be a powerful mean of preventing any degenerating skin condition. Among the therapeutic options available, it is advisable, when supported by the clinical situation of the lesions and of the patient (different signs of photoageing including, on a severely sun damaged skin, signs of neoplastic changes on an invisible field cancerization), to favour those options whose objective is the treatment of both the lesion and the surrounding field such as PDT; in any case never forget that prevention is the best medicine.

REFERENCES

1. T. C. Fischer, E. Perosino, F. Poli, et al., "Chemical Peels in Aesthetic Dermatology: An Update 2009," Journal of the European Academy of Dermatology and Venereology, Vol. 24, No. 3, 2009, pp. 281-292. doi:10.1111/j.1468-3083.2009.03409.x
2. K. Beer, "Dermal Fillers and Combinations of Fillers for Facial Rejuvenation," Dermatologic Clinics, Vol. 27, No. 4, 2009, pp. 427-432. doi:10.1016/j.det.2009.08.011
3. J. D. Carruthers, R. G. Glogau and A. Blitzer, "Advances in Facial Rejuvenation: Botulinum Toxin Type A, Hyaluronic Acid Dermal Fillers, and Combination Therapies—Consensus Recommendations," Plastic and Reconstructive Surgery, Vol. 121, No. 5, 2008, pp. 5S-30S; 31S-36S.
4. J. Carruthers and A. Carruthers, "Botulinum Toxin in Facial Rejuvenation: An Update," Dermatologic Clinics, Vol. 27, No. 4, 2009, pp. 417-425. doi:10.1016/j.det.2009.08.001
5. P. Babilas, S. Schreml, R. M. Szeimies, et al., "Intense Pulsed Light (IPL): A Review," Lasers in Surgery and Medicine, Vol. 42, No. 2, 2010, pp. 93-104. doi:10.1002/lsm.20877

6. R. Rossi, T. Lotti, P. Cappugi, et al. and GIDFE (Italian Photodermatology Group), "Guidelines for Photodynamic Therapy in Dermatology: Treatment Protocol," G Ital Dermatol Venereol, Vol. 140, 2005, pp. 637-644.
7. J. Jans, W. Schul, Y. G. Sert, et al., "Powerful Skin Cancer Protection by a CPD-Photolyase Transgene," Current Biology, Vol. 15, No. 2, 2005, pp. 105-115.doi:10.1016/j.cub.2005.01.001
8. R. Rossi, P. G. Calzavara-Pinton, A. Giannetti, et al., "Italian Guidelines and Therapeutic Algorithm for Actinic Keratoses," G. It. Dermatol, Vol. 144, 2009, pp. 713-723.
9. D. De Berker, J. M. McGregor and B. R. Hughes on Behalf of the British Association of Dermatologists, "Therapy Guidelines and Audit Subcommittee. Guidelines for the Management of Actinic Keratoses," British Journal of Dermatology, Vol. 156, No. 2, 2007, pp. 22-30. doi:10.1111/j.1365-2133.2006.07692.x
10. L. R. Braathen, R. Cerio, B. Cribier, et al., "Subcommittee of the European Dermatology Forum. Guidelines for the Management of Actinic Keratoses," 2009. http://www.euroderm.org/
11. E. Stockfleth and H. Kerl, "Guideline Subcommittee of the European Dermatology Forum. Guidelines for the Management of Actinic Keratoses," European Journal of Dermatology, Vol. 16, No. 6, 2006, pp. 599-606.
12. E. Stockfleth, C. Ferrandiz, J. J. Grob, et al. for the European Skin Academy, "Development of a Treatment Algorithm for Actinic Keratoses: A European Consensus," European Journal of Dermatology, Vol. 18, No. 6, 2008, pp. 651-659.
13. G. F. L. Hofbauer, M. Anliker, A. Arnold, et al., "Swiss Clinical Practice Guidelines for Skin Cancer in Organ Transplant Recipients," Swiss Medical Weekly, Vol. 139, 2009, pp. 407-415.
14. C. A. Morton, S. B. Brown, S. Collins, S. Ibbotson, H. Jenkinson, H. Kurwa, et al., "Guidelines for Topical Photodynamic Therapy: Report of a Workshop of the British Photodermatology Group," British Journal of Dermatology, Vol. 146, No. 4, 2002, pp. 552-567. doi:10.1046/j.1365-2133.2002.04719.x
15. E. Christensen, T. Warloe, S. Kroon, et al., "Guidelines for Practical Use of MAL-PDT in Non-Melanoma Skin Cancer," Journal of the European Academy of Dermatology and Venereology, Vol. 24, No. 5, 2010, pp. 505-512. doi:10.1111/j.1468-3083.2009.03430.x

16. M. H. Gold, "The Evolving Role of Aminolevulinic Acid Hydrochloride with Photodynamic Therapy in Photoaging," Cutis, Vol. 69, No. S6, 2002, pp. 8-13.
17. D. J. Touma and B. A. Gilchrest, "Topical Photodynamic Therapy: A New Tool in Cosmetic Dermatology," Seminars in Cutaneous Medicine and Surgery, Vol. 22, No. 2, 2003, pp. 124-130. doi:10.1053/sder.2003.50012
18. R. R. Ruiz, T. Sanz-Sanchez and S. Cordoba, "Photodynamic Photorejuvenation," Dermatologic Surgery, Vol. 28, No. 8, 2002, pp. 742-744. doi:10.1046/j.1524-4725.2002.02018.x
19. M. P. Goldman, D. Atkin and S. Kincad, "PDT-ALA in the Treatment of Actinic Damage: Real World Experience," Journal of Clinical Laser Medicine and Surgery, Vol. 14, 2002, p. 24.
20. D. K. Avram and M. P. Goldman, "Effectiveness and Safety of ALA-IPL in Treating Actinic Keratoses and Photodamage," Journal of Drugs in Dermatology, Vol. 3, 2004, pp. S36-S39.
21. P. K. Nootheti and M. P. Goldman, "Advances in Photorejuvenation and the Current Status of Photodynamic Therapy," Expert Review of Dermatology, Vol. 1, No. 1, 2006, pp. 51-61.doi:10.1586/17469872.1.1.51
22. N. S. Uebelhoer and J. S. Dover, "Photodynamic Therapy for Cosmetic Application," Dermatol Ther, Vol. 18, 2005, pp. 242-252. doi:10.1111/j.1529-8019.2005.05023.x
23. M. H. Gold, V. L. Bradshaw, M. M. Boring, et al., "Split-Face Comparison of Photodynamic Therapy with 5-Aminolevulinic Acid and Intense Pulsed Light versus Intense Pulsed Light Alone for Photodamage," Dermatologic Surgery, Vol. 32, No. 6, 2006, pp. 795-801, Discussion 801-803. doi:10.1111/j.1524-4725.2006.32163.x
24. T. S. Dover, A. C. Bhatia, B. Stewart, et al., "Topical 5-Aminolevulinic Acid Combined with Intense Pulsed Light in the Treatment of Photoaging," Archives of Dermatology, Vol. 141, No. 10, 2005, pp. 1247-1252. doi:10.1001/archderm.141.10.1247
25. D. J. Key, "Aminolevulinic Acid-Pulsed Dye Laser Photodynamic Therapy for the Treatment of Photoaging," Cosmetic Dermatology, Vol. 18, No. 1, 2005, pp. 31-36.

26. D. J. Key, "Evaluation of 585-nm Pulsed Dye Laser Activated Photodynamic Therapy (PDT) Using Topical Aminolevulinic Acid HCL 20%," Lasers in Surgery and Medicine, Vol. 15, 2003, p. 160.
27. M. R. Alexiades-Armenakas and R. G. Geronemus, "Laser Mediated Photodynamic Therapy with of Actinic Keratoses," Archives of Dermatology, Vol. 39, No. 13, 2003, pp. 113-120.
28. G. Sanclemente, L. Medina, J. F. Villa, et al., "A Prospective Split-Face Double-Blind Randomized PlaceboControlled Trial to Assess the Efficacy of Methyl Aminolevulinate + Red-Light in Patients with Facial Photodamage," Journal of the European Academy of Dermatology and Venereology, Vol. 25, No. 1, 2010, pp. 49-58. doi:10.1111/j.1468-3083.2010.03687.x
29. C. Zane, R. Capezzera, R. Sala, et al., "Clinical and Echographic Analysis of Photodynamic Therapy Using Methylaminolevulinate as Sensitizer in the Treatment of Photodamaged Facial Skin," Lasers in Surgery and Medicine, Vol. 795, 2007, pp. 203-209.doi:10.1002/lsm.20470
30. R. Ruiz-Rodríguez, L. López, D. Candelas, et al., "Photorejuvenation Using Topical 5-Methyl Aminolevulinate and Red Light," Journal of Drugs in Dermatology, Vol. 7, No. 7, 2008, pp. 633-637.
31. M. C. Issa, J. Piñeiro-Maceira, M. T. Vieira, et al., "Photorejuvenation with Topical Methyl Aminolevulinate and Red Light: A Randomized, Prospective, Clinical, Histopathologic, and Morphometric Study," Dermatologic Surgery, Vol. 36, No. 1, 2010, pp. 39-48.doi:10.1111/j.1524-4725.2009.01385.x
32. G. Buggiani, M. Troiano, R. Rossi and T. Lotti, "Photodynamic Therapy: Off-Label and Alternative Use in Dermatological Practice," Photodiagnosis Photodynamic Therapy, Vol. 5, No. 2, 2008, pp. 134-138. doi:10.1016/j.pdpdt.2008.03.001
33. E. Tierney, A. Barker, J. Ahdout, et al., "Photodynamic Therapy for the Treatment of Cutaneous Neoplasia, Inflammatory Disorders and Photoaging," Dermatologic Surgery, Vol. 35, No. 5, 2009, pp. 725-746. doi:10.1111/j.1524-4725.2009.01117.x
34. A. T. Shamban, "Current and New Treatments of Photodamaged Skin," Facial Plastic Surgery, Vol. 25, No. 5, 2009, pp. 337-346. doi:10.1055/s-0029-1243083

35. P. K. Nootheti and M. P. Goldman, "Aminolevulinic Acid-Photodynamic Therapy for Photorejuvenation," Dermatologic Clinics, Vol. 25, No. 3, 2007, pp. 35-45.doi:10.1016/j.det.2006.09.010