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Field-directed Therapy Options for Diffuse Actinic Keratoses

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INTRODUCTION

In recent years, climate change has rapidly become an international focus and with it, its economic and environmental consequences. Less attention has been given to its effect on human health. A byproduct of climate change includes higher levels of ultraviolet or UV light exposure.[1] UV light has long been associated with the development of skin cancer and pre-cancerous lesions known as actinic keratoses or solar keratoses.[1] Given these changes, providers will begin to see more malignant or pre-malignant skin lesions on their patients and will need to confidently determine the best course of treatment for them. What constitutes good treatment? Efficacy is arguably the most important factor but, when efficacy is similar across various treatment modalities, then it is time to examine other criteria such as adverse effects, tolerability, treatment accessibility, cost-effectiveness, and patient satisfaction.

BACKGROUND INFORMATION

Prolonged exposure to UV light may cause proliferation of atypical keratinocytes.[2] These UV induced changes can eventually result in lesions known as actinic keratoses or AKs, which are premalignant lesions.[2] AKs can regress or remain stable for the entirety of a patient's lifetime but can also progress into an in-situ or invasive cutaneous squamous cell carcinoma (cSCC) which is sufficient reason for early AK detection and treatment.[3] Cutaneous squamous cell carcinomas have the potential to become invasive and even metastatic.[2] Furthermore, patients presenting with multiple AKs are at 80% greater risk of developing a cSCC from one of their AKs, especially AKs in sun-exposed areas of the body.[3]

Consequently, even "pre-malignant" lesions should not be ignored. Medical providers should make identifying and treating AKs a priority since these lesions have the potential to morph into cSCCs.[2] AKs typically present as easily palpable, rough, erythematous patches in the setting of diffuse photodamage.[4] Early treatment and management of AKs benefits not only the patient but also the provider and the health care system by saving time and resources. AK screening and management is ultimately less invasive, less time consuming, and cheaper than treatment and management of skin cancer. Furthermore, treatment for premalignant lesions is easily accessible in ambulatory care settings.

These outpatient treatment options for premalignant lesions consist of lesion-directed therapies and field-directed therapies.[3] Lesion-directed therapies target isolated AKs while field-directed therapies target diffuse actinic damage, also known as field cancerization, which consists of clinical and subclinical AKs.[3] Cryotherapy with liquid nitrogen is a commonly utilized treatment for lesion-directed therapy; while surgical excision of AKs is an option, it is no longer done routinely. [2] It is important to treat AKs early, which can be difficult when a large number of lesions are present on an individual. In such cases, field-directed therapy is recommended. However, unlike lesion-directed therapy, there does not appear to be a consensus within the medical community regarding a commonly accepted field-directed therapy option.

Available field-directed therapeutic options include topical agents that need to be applied at home by the patient and in-office photodynamic therapy (PDT).[2] PDT involves application of a topical photosensitizer followed by exposure to an activating visible wavelength light source resulting in a reaction that allows for target tissue destruction .[4,2] Various PDT regimens have been studied and can differ in pre-treatment regimens, topical photosensitizer used [Aminolevulinic acid (ALA) versus Methyl Aminolevulinate (MAL)], incubation times, and light sources. Similarly, various topical agents have been studied for their effect on field cancerization. Ideally, a field-directed therapy should be efficacious with limited side effects, but providers must also consider the therapy cost, therapy accessibility, and cosmetic outcome, all of which can affect patient satisfaction.

Although lesion-directed therapies are preferable for isolated or low number of lesions, field-directed therapies are more practical and effective for multiple lesions. With the availability of newer field therapies, such as a photodynamic therapy or PDT, the question arises as to which field-directed therapy is the best option. A comparison between PDT and topical agents for their efficacy, adverse effects, and patient satisfaction in the treatment of clinical and subclinical actinic keratoses is presented. The appraisal of the available literature, on both PDT and topical field treatments, will provide clinicians with a more concise summary of the available treatment options, and ultimately, better equip them to make the most appropriate treatment choices for their patients. Gaps in current research and possible solutions for future studies will also be discussed.

EFFICACY

Often, the goal of a treatment is to heal or alleviate symptoms. Interventions or treatments used most commonly in practice are typically those found to have superior efficacy compared to other, less used, options. Currently, no mainstay of treatment for diffuse actinic damage is recognized. Current research can help shed some light on more commonly utilized field-directed therapies such as topical agents and PDT. When choosing one of these therapies, providers should instinctively look first at effectiveness, as evidenced by AK clearance rates.

PDT regimens

Piacquadio et al looked at efficacy of PDT with ALA and visible blue light and found that 89% of the individuals that had been treated with this regimen experienced 75% or more lesion clearance at their 12-week follow-up while 73% had complete lesion clearance.[5] As mentioned before, various PDT regimens are available. Much of the research in field-directed therapies focuses on one specific PDT regimen. Touma et al, another PDT-only study utilizing a different PDT regimen, revealed a 90% and 89% AK clearance rate at 1- and 2-hour incubation times respectively; seven of the ten patients available for the 5-month follow-up showed complete AK resolution, overall improvement in the skin quality, and decrease in diffuse photodamage.[4] Despite varying regimens, both of these studies were able to draw a similar conclusion that PDT is a highly efficacious method of clearing clinical and subclinical AKs.

Topical agents

The Food and Drug Administration or FDA approved PDT as a field-directed therapy of AKs in 1999.[4] Since then it has become one of the most popular treatment options for diffuse actinic damage. Before PDT, the topical agents were used; many providers still preferred this option before jumping to PDT. This preference can be attributed to factors such as insurance coverage and patient preference. 5-fluorouracil (5-FU), was the first topical agent approved for field treatment of AKs.[3] Diclofenac, imiquimod, and ingenol mebutate are other commonly used topical agents.[3] They all have different mechanisms of action that can affect efficacy and secondary outcomes. Pomerantz et al, looked at the efficacy of 5-FU and found a 73% reduction in total AK count in all the study participants including a 38% complete clearance of AKs at the

6-month follow-up.[6] The complete clearance rate is significantly lower in this study than the studies discussed earlier involving PDT. While the complete clearance rate may have been lower, the reduction in pre-malignant lesions was comparable to treatment with PDT.

PDT versus topical agents

While studies examining specific PDT regimens or individual topical agents provide insight on the effectiveness of those individual therapies, studies that included both are even more useful for determining a mainstay therapy. Kurwa et al compared PDT and topical 5-fluorouracil and found only a 2% greater reduction in field cancerization with PDT versus the topical agent.[7] Smith et al performed a similar study and their results showed AK clearance of 75% or more in 75% of the patients with PDT and the topical agent.[8] Yet, another study revealed a complete clearance rate of 80% and 93% with PDT and topical 5-FU respectively.[9] Study after study showed similar efficacy rates with PDT versus topical agents.

After analyzing the available research, it becomes clear that, while both treatments can be highly efficacious, no clear superior option becomes apparent. So, how does one proceed? Commensurate efficacies can be quite advantageous to a patient and provider, allowing other aspects of treatments and therapies to be explored, such as treatment tolerability, accessibility, and cost-effectiveness.

ADVERSE EFFECTS & TOLERABILITY

Tolerability of a treatment is indirectly related to treatment efficacy. If a patient does not tolerate a treatment well, then it is more likely that they will not comply with the full course of treatment. Poor treatment compliance results in poor treatment outcomes. Every treatment comes with its own set of adverse effects. The goal is to look at the research and determine if the adverse effects of PDT are comparable to those of topical agents and if not, how each adverse effect impacts treatment tolerability.

PDT

With PDT, patients oftentimes experience a burning sensation during the light therapy and varying amounts of erythema and edema afterwards.[3] These effects can vary with different PDT regimens. In Touma et al, lidocaine hydrochloride was applied topically to the areas that were to be treated and, while all these patients experienced pain with light exposure, none asked to discontinue treatment.[4] To further alleviate

some of the discomfort felt during PDT, patients used a handheld fan to cool the skin while under the light and/or took acetaminophen tablets prior to treatment. Many tools help make PDT a more tolerable treatment option for patients. Erythema, edema, and areas of crusting can be expected in the days following PDT but, in Touma et al, no patient had erythema, edema, crusting, or post-inflammatory hyperpigmentation at their 1-month follow-up.[4] In Piacquadio et al, erythema and edema were the most severe the first 24 hours after PDT; symptoms resolved one to four weeks after treatment without any hyperpigmentation.[5] These two studies provide evidence which supports PDT as a safe and relatively tolerable treatment for AKs. Whether PDT's tolerability is superior or that of topical agents needs exploration.

Topical agents

With topical agents, adverse effects can vary depending on the specific agent used. If applied correctly, 5-FU patients often experience erythema, inflammation, and areas of erosion or crusting on the skin.[3] Smith et al looked at tolerability of 5-FU and PDT and found significantly more erosive effect on the skin in subjects that used the 5-FU.[8] This erosion of the skin can be quite uncomfortable, and eventually caused two of the subjects to discontinue treatment with 5-FU.[8] Spontaneous resolution of adverse effects, such as erythema and crusting, occurs more rapidly after treatment with daylight (DL) PDT versus treatment with the topical agent, 5-FU.[9] This evidence holds promise for DL-PDT, but these findings may not be observed in other PDT regimens. Nonetheless, if the tolerability of PDT were better than 5-FU, then compliance would be superior to 5-FU. Since many of the patients treated with 5-FU no longer tolerated the adverse effects, they decided to discontinue the 5-FU thus halting any further benefit.

The evidence in these studies suggests that PDT is better tolerated and is associated with higher rates of compliance. These findings may correlate with the fact that PDT is a one time in-office treatment whereas topical agents require repeat at-home applications. Noncompliance is a big issue among patients and, even more so, if the treatment in question causes a significant amount of discomfort. If a provider foresees compliance being an issue, they should consider recommending PDT. PDT may be associated with better compliance because of its better tolerability. PDT requires patients to be exposed to the irritant for one day with subsequent healing while topical-only therapy will consist of daily exposure to the irritant for

weeks to months resulting in chronic discomfort. Therapies resulting in less discomfort tend to be better tolerated and accepted. So, even though adverse effects are comparable between both types of filed-directed therapies, providers may choose one treatment modality over another depending on a patient's preference, tolerance level, or compliance ability. In the end, the ability to make these choices will allow for the best clearance rates of pre-malignant skin lesions.

COSMESIS & PATIENT SATISFACTION

Treatment cosmesis can be highly important to some individuals and can have a significant impact on patient satisfaction. Oftentimes, field-directed therapies will result in skin improvement over time. This outcome is explained by the resolution of not only the premalignant cells but also the textural changes associated with them. Unfortunately, before this happens, the patient will most likely first experience a worsening in their skin while the treatment takes effect. Topical agents have a reputation for being "harsher" on the skin then PDT. In Galimberti, patients preferred PDT since they had experienced fewer adverse effects than with the topical agent, 5-FU.[9] These adverse effects can include erythema, edema, and crusting. In Serra-Guillen et al, PDT was preferred yet again. PDT was shown to have a higher rate of acceptance and patient satisfaction versus a different topical agent called imiquimod.[10] It is important for clinicians to explain these expected skin changes to their patients so that they are not deterred from necessary treatment.

ACCESSIBILITY & COST EFFECTIVENESS

Efficacy and patient satisfaction mean nothing if the treatment in question is not accessible or affordable to the patient. While both treatments can be given in an outpatient setting, topical agents are superior to PDT in terms of accessibility. Topical agents are given via a prescription to be done at home, while PDT must be done in-office, usually in a dermatology office. PDT usually requires the clinician to give a dermatology referral and hope that the patient will schedule an appointment with the dermatologist for further consultation regarding this procedure. Treatment may also be guided by cost considerations which will depend upon the patient's insurance coverage. Oftentimes, insurance companies require that a patient first try topical therapy before moving on to more expensive treatments like PDT. Fortunately, Wilson found imiquimod, a topical agent, to be a more cost-effective treatment option versus PDT.[11]

Therefore, clinicians need to be aware of treatment accessibility and cost and factor them into the treatment decision process.

STRENGTHS & LIMITATIONS OF THE STUDIES

Based on the literature, the numerous PDT regimens that can be created as well as the wide array of topical agents available for treatment of AKs, makes comparison of the two modalities difficult. One specific topical agent may have better clearance rates when compared to a specific PDT regimen but may be comparable or even worse when compared to a different PDT regimen. Most of the available literature compares specific topical agents with specific PDT regimens or evaluates only a single therapy. Studies that generalize all topical agents or all PDT regimens and then compare them to each other are limited making it difficult for providers to figure out which is a better option for their patients. Few head-to-head trials proved to be a major limitation to the examined studies. Small sample sizes were also a chief limitation of the studies and trials with larger cohorts would be beneficial for further investigation of treatments for actinic keratoses. Periodic evaluation of the available literature is necessary for the purpose of providing clinicians with guidance in determining the most appropriate field-directed therapy option for their patients.

CONCLUSION

In terms of efficacy, topical agents were not superior to PDT, and vice versa. Both treatment options were similarly effective allowing clinicians to look at other aspects related to the treatment. Adverse effects were better tolerated with PDT. The adverse effects also impacted the cosmesis factor of treatment. The studies indicate higher patient satisfaction with PDT since the adverse effects were not as uncomfortable as is often the case with topical agents. Compliance improves with better tolerability. Topical agents were superior to PDT in terms of accessibility. PDT usually requires patients to see a dermatologist since most primary care offices do not have the necessary equipment to perform the procedure. PDT seems to be a better choice if a patient's insurance will cover the costs of the procedure. The medical community would benefit from further studies involving larger sample sizes using the most common PDT regimens and topical agents.

REFERENCES

1. Bharath AK, Turner RJ. Impact of climate change on skin cancer. *J R Soc Med*. 2009.

2. Jorizzo J. Treatment of actinic keratosis. In: Corona R, ed. UpToDate. Waltham, Mass: 2018. https://www-uptodate-com.pacificpa.idm.oclc.org/contents/treatment-of-actinic-keratosis.

3. Costa C, Scalvenzi M, Ayala F, Fabbrocini G, Monfrecola G. How to treat actinic keratosis? An update. *Journal of Dermatological Case Reports*. 2015.

4. Touma D, Yaar M, Whitehead S, Konnikov N, Gilchrest BA. A Trial of Short Incubation, Broad-Area Photodynamic Therapy for Facial Actinic Keratoses and Diffuse Photodamage. *Archives of Dermatology*. 2004.

5. Piacquadio DJ, Chen DM, Farber HF, et al. Photodynamic Therapy with Aminolevulinic Acid Topical Solution and Visible Blue Light in the Treatment of Multiple Actinic Keratoses of the Face and Scalp. *Archives of Dermatology*. 2004.

6. Pomerantz H, Hogan D, Eilers D, et al. Long-term Efficacy of Topical Fluorouracil Cream, 5%, for Treating Actinic Keratosis. *JAMA Dermatology*. 2015.

7. Kurwa HA, Yong-Gee SA, Seed PT, Markey AC, Barlow RJ. A randomized paired comparison of photodynamic therapy and topical 5-fluorouracil in the treatment of actinic keratoses. Journal of the American Academy of Dermatology. 1999.

8. Smith S, Piacquadio D, Morhenn V, Atkin D, Fitzpatrick R. Short Incubation PDT Versus 5-FU in Treating Actinic Keratoses. *Journal of Drugs In Dermatology*. 2003.

9. Galimberti GN. Daylight Photodynamic Therapy Versus 5-Fluorouracil for the Treatment of Actinic Keratosis: A Case Series. *Dermatology and Therapy*. 2018.

10. Serra-Guillen C, Nagore E, Hueso L, et al. A randomized comparative study of tolerance and satisfaction in the treatment of actinic keratosis of the face and scalp between 5% imiquimod cream and photodynamic therapy with methyl aminolaevulinate. British Journal of Dermatology. 2011.

11. Wilson EC. Cost Effectiveness of Imiquimod 5% Cream Compared with Methyl Aminolevulinate-Based Photodynamic Therapy in the Treatment of Non-Hyperkeratotic, Non-Hypertrophic Actinic (Solar) Keratoses. PharmacoEconomics. 2010.