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Literature Review

The use of photodynamic therapy in actinic keratosis in comparison to cryotherapy and chemical peels

Aneesa Arshad[1]* and Mohammed Taiyyib[2]

[1]Department of Medicine, St George's University of London, United Kingdom

[2]Kings College London, United Kingdom

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***Corresponding authors:** Aneesa Arshad, Department of Medicine, St George's University of London, United Kingdom, E-mail: aneesa.arshad@outlook.com

ORCID: https://orcid.org/0000-0002-5276-3902

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Abstract

Photodynamic Therapy (PDT) is an effective treatment of actinic keratosis. 5-Aminolevulinic Acid (ALA) and Methyl Aminolevulinate (MAL) are commonly applied. However, there is a need to establish the quality of life after PDT treatment and potential conversion to squamous cell carcinomas. The objectives of the review were to compare the efficiency of PDT, the long-term reoccurrence, and cosmesis in actinic keratosis patients. Relevant studies from the year 2000 onwards involving PDT in comparison to Cryotherapy (CT) and chemical peels were collated using a combination of terms and keywords. Conflicting results were obtained when analysing PDT in comparison to CT. A conclusion could not be deducted as to whether PDT was more, less, or equivalently effective to CT However, results obtained indicated that PDT was of greater benefit in comparison to chemical peels. Additionally, in all the studies, a conclusion was made that PDT was far superior in cosmesis in comparison to conventional therapies.

Abbreviations

PDT: Photodynamic Therapy; CT: Cryotherapy; HpD: Haematoporphyrin Derivative; AK: Actinic Keratosis; TCA: Trichloroacetic Acid

Introduction

The association of a photosensitising drug with visible light to damage cancerous cells and microvasculature is known as photodynamic therapy (PDT) [1]. The scientific background for applying PDT was unclear until 1900 when Raab demonstrated the cytotoxic effects with the combination of acridine dyes and light on paramecia [2,3]. Subsequently, Von Tappeiner in 1903 highlighted the importance of oxygen in the photodynamic effect [4,5]. Haematoporphyrin derivative (HpD) is a complex of porphyrins derived from haematoporphyrin. Lipson, et al. provided the foundation of PDT as trials in 1960 were conducted using HpD for the detection of tumours [6]. In 1966, Lipson, et al. reported the use of HpD in a single patient with large, recurring breast cancer. However, despite frequent treatments, the lesion returned [7]. Dougherty treated skin tumours photodynamically in 1978 by using an argon dye laser; the first study to demonstrate complete tumour clearance following HpD injection [8]. Porfimer sodium is the purified version of HpD. It was approved in 1999 to treat and ease the symptoms of oesophageal cancer and the early stages of non-small cell lung cancer [9].

PDT targets a layer of skin, precisely and directly. The photosensitising agent will accumulate in cancerous cells and avoid the surrounding areas [1]. PDT additionally delays the need to undergo conventional therapies. This evades the side effects such as hair loss which may be associated with chemotherapy to more serious complications such as extravasation (drug enters the subcutaneous or subdermal surrounding tissues). In addition, PDT can be applied where surgery may not be applicable; for example, if a patient has lung cancer of the upper bronchi, PDT can be utilised as it does not destroy collagen-containing structures (fibrous tissues) [10]. Furthermore, scarring and lighter or darker spots appearing

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are not likely as collagen and elastin are not affected compared to conventional methods [11].

However, PDT has some drawbacks. Light may not penetrate deep enough into the layers of tissues that have cancerous cells therefore reoccurrence may arise, and multiple treatments may be necessary [12]. Another difficulty is that a certain direction of light to the targeted site is required for the treatment to be efficient. This is particularly challenging as it requires good hand coordination and can be challenging for clinicians to direct the laser correctly [13].

Following treatment, a red rash and crusts may be seen. Pain is a common side effect reported by individuals. Hyper (too much) or hypo (too little) pigmentation (skin colour) is associated with PDT [14]. The chronic effect, contact allergy (a rash caused by skin contact with a substance), is rare. Three incidents have been reported: one regarding aminolaevulinic acid exposure and two concerning methyl aminolevulinate [15].

Chlorin, derived from porphyrins through reduction, cycloaddition, or cyclization reactions, represents a distinct class of compounds. In comparison to porphyrins, chlorin demonstrates enhanced photosensitizing characteristics, with heightened absorption intensity at longer wavelengths. These photosensitizers are recognized for their robust absorption within the blue light spectrum (400 nm - 450 nm) and the red light spectrum (640 nm - 700 nm) [16]. These are widely employed in Russia for treating precancerous skin conditions like actinic keratosis and certain non-melanoma skin cancers through PDT.

Beyond their therapeutic effectiveness, they offer cosmetic benefits, minimizing scarring and preserving the skin's natural appearance. This cosmetic advantage is particularly valuable for patients concerned about the aesthetic outcome of their treatment [17].

PDT is applied as a principal treatment or added alongside surgery, radiotherapy, or chemotherapy as an adjunctive therapy. Systematic reviews conducted by Fayter, et al. [18] and Brown, et al. [19] have focused on PDT in cancerous states. However, there is still a need to establish high-quality trials that focus on endpoints such as the quality of life of a patient after photodynamic therapy and the occurrence of AK transitioning to Squamous Cell Carcinomas (SCC). Another factor to consider is that although PDT has been established for numerous years, there has been a slow approach in the use that has been applied to oncology.

Actinic Keratosis (AK)

AKs are precancerous conditions of keratinocytes that occur on sun-damaged skin.

AK has the potential to develop into metastatic SCC if left untreated; areas that are exposed and receive long-term solar radiation such as the face and hands [20]. SCCs are non-melanoma cancers that commence from the uncontrolled growth of squamous cells. They usually take years to develop and only spread to other areas of the body if they are left untreated. The annual rate of transformation is controversial with reports suggesting that the likelihood of progression is between 0.025% - 20%. Currently, there is no clinical way to determine whether the AK will lead to SCC therefore all lesions are treated regardless. Treatment options for AK include destructive therapies such as cryosurgery (CT), chemical peels (trichloroacetic acid), and PDT.

CT is the application of extreme cold produced by liquid nitrogen to destroy abnormal tissue. It has been shown highly effective in retrospective trials (99%). However, many patients prefer other treatment methods. This may be due to CT failing to provide complete assurance that all AK will be destroyed. Patients subsequently require numerous treatment sessions which can be painful.

Chemical peels are also potential agents for superficial AK layers and are used to create smooth skin by collagen remodelling, exfoliation, and wound repair. However, they may cause further damage (scarring), leading to limited clinical application. Trichloroacetic acid (TCA) is an FDA-approved treatment for superficial lesions (10% - 35%) and medium-depth lesions (50%).

Clinical trials involving PDT have applied the use of MAL and ALA as photosensitisers to treat AK due to the greater light penetration.

Aims

The aim of the literature review was to focus on the year 2000 onwards and subsequently research the development of PDT in AK. The review attempted to identify, evaluate, and summarise relevant findings of clinical research. These helped to consider the effectiveness of PDT regarding AK.

Objectives

1. The aim of the report was to achieve the following objectives:To review appropriate literature regarding photodynamic therapy in AK
2. To analyse clinical trials to gain insight into the effectiveness of photodynamic therapy in relation to AK
3. To assess the need for further research in AK and the specific endpoints that may need to be conducted to improve the research

Method

A search was conducted to complete the literature review on photodynamic therapy in actinic keratosis. The search focused on data from the year 2000 till the present day. It included results that had been obtained from the United States, Europe, and Australia. To start the data collection, research on clinical trials from several sources was obtained from the following:

1. https://clinicaltrials.gov/ct2/search - Database of U.S. National Institutes of Health Trials
2. www.ukctg.nihr.ac.uk/home - NHS: UK Scientific Trials

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3. http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial - Cancer Research: Find Clinical Trials

4. www.clinicaltrialsregister.eu/ctr-search/ - Records of Trials Conducted in EU

5. http://apps.who.int/trialsearch/ - World Health Organisation, International Clinical Trials Registry Platform

By collating relevant studies, further research was subsequently conducted using scientific databases. Keywords such as 'photodynamic therapy' and 'skin' were applied to obtain results.

To analyse data from the clinical trials, a tool to assess systematic reviews, cohort studies, and meta-analysis was applied. This was by utilising the Critical Appraisal Skills Programme (CASP) – a public establishment based in the UK. The report was structured on the set of questions that CASP provides. However, in some instances, it was not possible to apply the tool. This was due to the lack of quality or availability of the trials obtained. When this occurred, the results of the trials were individually, and critically assessed based on many factors which included: conventional treatment, duration, lesion response rate, cosmetic outcome, and patient preference.

Results

Summary of trials: PDT in comparison to Cryosurgery (CT) (Table 1)

Table 1: Trials comparing PDT and CT lesion response and reoccurrence rates.

Study	Treatment Groups	Number of patients	Total lesions	3 months' lesion response	6 months' lesion response	1-year lesion reoccurrence
Freeman, et al. [21]	MAL-PDT CT	88 89	360 421	91% 68%	NR NR	NR NR
Hauschild, et al. [22]	ALA-PDT CT	148 149	750 692	89% 77%	NR NR	11% 18%

Total lesions = Identified by medical diagnosis.
Lesion response rate = Lesions with complete Response to treatment (NR) = Not recorded.
Cosmesis = Classified on the amount of scarring, atrophy, pigmentation changes and redness.

Summary of trials: PDT in comparison to chemical peels – TCA (Table 2)

Table 2: Trials comparing PDT and TCA lesion response and reoccurrence rates.

Study	Treatment Groups	Number of patients	Total lesions	1 months' lesion response	1-year lesion response	1-year lesion reoccurrence
Holzer, et al. [23]	ALA-PDT TCA 35%	14 14	384 354	NR NR	74% 49%	NR NR
Nuzzo, et al. [24]	MAL-PDT TCA 50%	13 13	123 121	80% 66%	NR NR	5% 18%

Discussion

Freeman, et al. found a 3-month lesion response rate of 68% with CT [21]. This is less than the previously reported retrospective trials and the 3-month lesion response rate obtained with MAL-PDT. Two sessions of PDT, with a week in between, were conducted to achieve greater lesion responses. The recommendations from the EU and the FDA are conflicting with the EU suggesting one treatment session of MAL-PDT (Metvix) utilised (retreatment at 3 months if necessary) in comparison to the FDA suggesting that two sessions with a week difference are employed (Table 1). In previously documented single-session studies, a result of 69% was obtained hence suggesting that an 'over-treatment' may have occurred as more than two-thirds of the lesions were successfully managed with one session. This leads to the potential recommendation that one session of PDT should be conducted and only patients who do not show satisfactory responses re-treated. However, given the high lesion response rate after the two sessions, the retreatment period may be employed regardless as further studies have also reported excellent response rates when a similar method has been implemented. In addition to the 69% result documented in single-session studies, Tarstedt, et al. similarly obtained a lesion response rate of 70% after a single treatment but reported an outcome of 88% when patients were retreated after one week [25].

Although a retreatment period of one week may lead to effective results, it might be appropriate for patients with thicker lesions to obtain retreatment primarily. This is because thicker lesions had a larger response to CT in comparison to thin lesions which had a greater eradication with MAL-PDT. This may be due to the increased freeze time of CT for thicker lesions and subsequently deeper penetration of the skin. In comparison, thin lesions treated with MAL-PDT are more sensitive to light, and therefore penetration of superficial layers is effective but not as efficient in skin cells more than 2mm.

The lack of an adequate timeframe to follow up the lesion response rate additionally introduced bias. This is predominantly surrounding the evidence around the management of AK with PDT, as there is not an acceptable period to report any potential change of AK to SCC or the possibility of AK lesions reoccurring. A minority of AK lesions progress to SCC therefore a larger sample size and duration would be required to indicate this outcome.

Facial lesions represent the greatest challenge in terms of cosmesis. This is because they are the most common type of lesion and patients may be anxious to receive effective treatment when they develop AK in this area. Cosmesis was evaluated as 'excellent' in a greater proportion of MAL-PDT patients in comparison to CT patients – 27% more. This indicates that PDT may be of greater advantage as there is minimal damage to surrounding healthy tissue compared to CT. This is beneficial to patients as indicated in the satisfaction survey with PDT being more favoured in comparison to previous destructive treatments undertaken. However, the survey did

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not compare against CT alone, but alongside other destructive treatments previously undertaken. An improvement might be to ask patients which therapy they prefer between PDT and CT alone. This may allow a direct comparison between the two therapies.

Adverse effects are also a major consideration when opting for a treatment option. As expected with PDT, a larger proportion of adverse reactions occurred. Local reactions such as erythema and burning were most reported. However, the duration of reactions was short (one-week average) and patients opted for PDT in the satisfaction survey. This may indicate that patients are still willing to undertake PDT and the discomfort of reactions does not deter individuals from selecting it as a future treatment if required.

Hauschild, et al. conducted a single session of ALA-PDT which demonstrated a high lesion response rate of 89% in comparison to single session studies of MAL-PDT which have previously been conducted [22]. Although the response rate was slightly less than in comparison to the MAL-PDT two-session study conducted by Freeman, et al. (91%), Hauschild, et al. demonstrated that the requirement for two sessions may not be necessary when a change of photosensitiser is applied (Table 1). A long-term comparative study on AK conducted by Ko, et al. [26] supports this improvement as a lesion response rate of 56.9% with ALA-PDT and 50.7% with MAL-PDT was reported in Asian patients. However, Hauschild, et al. noted that Caucasian individuals alone were included in the study and subsequently a wider variety of populations may be required to support the evidence that a change in photosensitiser may improve lesion response rates.

Most ALA-PDT patients were rated 'excellent' in terms of cosmesis in comparison to CT. Hypopigmentation was seen in a third of CT patients which may have contributed to the low number of 'excellent' rated patients and the inferior patient satisfaction results in the survey. In contrast, hyperpigmentation was seen in a minority of patients who were treated with ALA-PDT; far less than patients experiencing hypopigmentation with CT. However, only patients who were rated excellent were asked to take part in the patient evaluation survey therefore leading to bias. An improvement may be to invite all patients who had received ALA-PDT or CT to give their opinions about their cosmetic outcomes and then assess the results accordingly.

75% of total patients observed side effects associated with MAL-PDT and CT treatment. A greater proportion of patients experienced adverse effects that were related to CT-cold exposure injuries. The duration and severity of the injuries were not recorded therefore no indication was documented of how patients were affected in the short and long term. This may be needed to allow the quality-of-life outcome to be determined.

Holzer, et al. observed a greater lesion response rate for ALA-PDT in comparison to TCA 35%. However, any severity of AK was treated; PDT is beneficial on mild-moderate layers due to light penetration and not as effective on deeper layers [23] (Table 2). This may have led to the reduced lesion response rate for ALA-PDT. Similarly, TCA 35% is FDA-approved for mild lesions. A greater concentration may be required if thicker lesions are to be treated effectively as the destructive outcome increases when concentration is increased.

Up until the 1-year review period, 7 patients were retreated with ALA-PDT. The time at which the patients were retreated was at different stages and 2 TCA patients were also retreated with ALA-PDT. A certain period for retreatment should have been implemented instead of randomly retreating patients. No lesion response rates were documented at the stages they were retreated so a comparison cannot be concluded with the final 1-year review. An improvement may be to evaluate the response rates at the stages patients were retreated as well as the reasons why the 2 TCA patients were additionally treated with ALA-PDT. The TCA patients may have been retreated with ALA-PDT due to the side effects that were experienced (scarring), nevertheless, the reasons should be highlighted for an effective analysis to be undertaken.

Researcher bias may have potentially occurred as the TCA was applied until a 'pinkness' was seen. There is no suggestion in the study that an independent verification was undertaken to check whether this result had been achieved. An additional researcher may need to verify whether the correct technique of the TCA was implemented.

Nuzzo, et al. observed a greater lesion response rate in MAL-PDT patients compared to TCA 50% [24]. A direct comparison cannot be determined between MAL-PDT and ALA-PDT as Nuzzo, et al. did not include facial aspects in the study and the retreatment time was vastly different (Table 2) Patients were retreated in both the MAL-PDT and TCA groups. A small reoccurrence rate was obtained for MAL-PDT suggesting that it was more effective at penetrating AK lesions than TCA. This can be established as a greater lesion response rate for MAL-PDT was observed when targeting thicker lesions (grade lll). However, MAL-PDT and TCA 50% are ideal for targeting lesions under 2mm and medium depth lesions respectively. A greater light dose for MAL-PDT and concentration of TCA may be required if the thicker lesions are to be successfully treated.

TCA patients had exceptionally poor results in terms of cosmesis. The mild pigmentation, which most patients experience, may lead to this. Although it was reversible, a time frame was not indicated for how long the pigmentation persisted. An improvement may be to follow up on an individual basis and note the times that the pigmentation reverses. This may allow further counselling to patients in potential future studies who undergo TCA treatment.

Conclusion

In my perspective, the utilization of Photodynamic Therapy (PDT) within the realm of oncology has undeniably encountered a sluggish path. Its potential trajectory, whether it ascends or stagnates, is contingent upon a multifaceted interplay of various determinants. These encompass the institutional apathy prevalent in hospitals towards adopting novel therapeutic approaches, the formidable initial costs associated with establishing PDT setups, and the notable

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dearth of accessible, cost-effective light sources essential for the procedure's execution. Paramount among the challenges hindering its broader acceptance is the unclear nature of outcomes discerned from randomized controlled trials when contrasted against traditional treatment modalities. Conversely, within dermatology, PDT has already attained the status of a commonplace intervention, with its prevalence anticipated to escalate further. However, the persistent appeal for improved pharmaceutical agents exhibiting heightened selectivity and diminished propensity for inducing sustained skin photosensitivity remains unsatisfactory.

The evidence is unclear whether MAL-PDT or ALA-PDT is more effective, less effective, or equal to CT for treating mild-moderate AK. Though the research suggests that PDT is an effective therapy for mild-moderate AK of the facial and scalp areas, whether it is more effective than CT on areas of the body (aside from the facial and scalp) is not conclusive.

Studies surrounding areas apart from the facial area and scalp are limited and the data obtained is minimal to provide a firm conclusion. Interestingly, in most studies researched, the facial and scalp area results are collated together, and the scalp area frequently has a poor lesion response rate. It may be of benefit to separately research the facial and scalp areas to recommend the optimal therapy for patients. However, TCA led to poor results when studied alongside PDT for facial and scalp lesions therefore leading to the recommendation that PDT is superior in terms of lesion response rates.

There are several parameters such as the review period, reoccurrence rate, optimal light dose, retreatment sessions of PDT, the site at which AK is treated, and light sources that cause conflict to achieve a unanimous decision regarding the effectiveness. I believe these various parameters would ideally need to be controlled and aligned to provide a definitive answer. The review time is diverse among the studies collated for the report and ideally, a lesion reoccurrence would need to be monitored in all the studies to assess the effectiveness of treatment in the long term. The optimal light dose may play a crucial part in the lesion response rate dependent on the number of retreatment sessions employed and the site of application. There is a lack of evidence supporting an optimal number of retreatment sessions and the time frame that should be applied. Though the EU and FDA have set out recommendations, further research may be required as different lesion response rates have been reported with various retreatment sessions and time frames. A large sample and extended time duration may be required to indicate this.

PDT appeared to have a significantly enhanced cosmesis effect in comparison to CT and TCA. However, the absence of blinding in the studies proposes that there is an ambiguity concerning the reliability of the analysis. Nonetheless, in studies that obtained patient satisfaction results, patients preferred PDT. PDT was opted for when experience of common side effects such as erythema and itching had occurred. This suggests PDT may be of use in patients who find the adverse effects of CT severe – scarring and cold exposure injuries. It may be of advantage to patients who have experienced pigmentation associated with TCA.

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St George's University of London

MTA MBBS - second author

Kings College London

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