CLINICAL RESEARCH OF PHOTODYNAMIC THERAPY WITH 5-ALA FOR CERVICAL INTRAEPITHELIAL NEOPLASMS: FROM PRELIMINARY STUDIES TO CURRENT DEVELOPMENTS

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Abstract

Non-surgical therapies are essential for reducing the progression rate of human papillomavirus-associated cervical intraepithelial neoplasia (CIN) from low-grade (CIN 1) to high-grade CIN (CIN 2/3) and subsequently to cervical cancer with minimal adverse reactions and complications in women, such as haemorrhaging, cervical stenosis, spontaneous abortion, and preterm birth.

Photodynamic therapy (PDT) has garnered considerable attention as a non-invasive approach to CIN treatment in recent years. PDT works by applying photoactive compounds, known as photosensitizers, that accumulate in target cells. Subsequent exposure of these cells to light of a specific wavelength (photoactivation) occurs. This paper aims to review the clinical development of clinical research on the effectiveness of PDT with a 5-Aminolevulinic acid (5-ALA) photosensitiser for treating CIN 1-3 from the early preliminary studies to recent reports.

Early PDT studies using lower concentrations of 5-ALA showed poor effectiveness, but recent research with a 20% concentration of 5-ALA demonstrated better outcomes. Larger studies, preferably conducted across multiple centres, are needed to establish the optimal number of PDT sessions required to eliminate HPV.

Keywords: cervical intraepithelial neoplasia, photodynamic therapy, human papillomavirus, 5-aminolevulinic acid, squamous intraepithelial lesions.

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КЛИНИЧЕСКИЕ ИССЛЕДОВАНИЯ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ С 5-АЛК ПРИ ДИСПЛАЗИИ ШЕЙКИ МАТКИ: ОТ ПИЛОТНЫХ ИССЛЕДОВАНИЙ ДО СОВРЕМЕННЫХ РАЗРАБОТОК

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Резюме

Неоперативные методы терапии имеют важное значение для снижения скорости прогрессирования дисплазий шейки матки, ассоциированных с вирусом папилломы человека (ВПЧ), от CIN 1 до CIN 2/3, а затем до рака шейки матки, при минимальных побочных эффектах и осложнениях у женщин, таких как кровотечения, сужение шейки матки, спонтанные аборты и преждевременные роды.

Фотодинамическая терапия (ФДТ) привлекла значительное внимание как неинвазивный метод лечения CIN в последние годы. ФДТ

основана на применении фотоактивных соединений, известных как фотосенсибилизаторы, которые накапливаются в целевых клетках. Затем эти клетки подвергаются воздействию света с определенной длиной волны. Цель данной работы — обзор клинического развития и исследования эффективности ФДТ с фотосенсибилизатором 5-аминолевулиновой кислоты (5-АЛК) для лечения CIN 1–3, начиная с ранних пилотных исследований и заканчивая последними отчетами.
Ранние исследования ФДТ с использованием низких концентраций 5-АЛК показали низкую эффективность, но недавние исследования с концентрацией 20% 5-АЛК продемонстрировали лучшие результаты. Для установления оптимального количества сеансов ФДТ, необходимых для устранения ВПЧ, требуются более крупные исследования, желательно проводимые в нескольких центрах.

Ключевые слова: дисплазия шейки матки, фотодинамическая терапия, вирус папилломы человека, 5-аминолевулиновая кислота, плоскоклеточное интраэпителиальное поражение.

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Introduction

Among all human cancer cases worldwide, approximately 15% to 20% are associated with viral infections, thus making oncogenic viruses recognized as significant risk factors for cancer development [1]. One of the most prominent infectious oncogenic agents worldwide is human papillomavirus (HPV) which is responsible for 31.1% of all infectious disease-induced cancer cases and the development of 99.7% of cervical cancer in women [1, 2]. Particularly, HPV types 16 and 18 are the most virulent and are responsible for about 70% of all pre-cancerous cervical lesions and cervical cancers [3]. While 90% of HPV infections are transient and get cleared up by the immune systems within 12 to 24 months of exposure, some persistent HPV strains can prompt infected cells to proliferate uncontrollably, therefore inducing precancerous or tumorous changes in the host organism [4].

Cervical cancer is a progression of a prolonged phase of pre-invasive disease known as cervical intraepithelial neoplasia (CIN). CIN is further categorized into CIN 1, 2, or 3, reflecting increasing severity based on the proportion of abnormal cells within the cervical epithelium. Although CIN is classified as a precancerous condition, only about 9% of CIN 1 lesions progress to CIN 3 over approximately 2 to 3 years [5], and only 30% of CIN 3 lesions progress to cancer in 10-25 years [6]. According to the Lower Anogenital Squamous Terminology (LAST) standardization, low-grade squamous intraepithelial lesions (LSIL or CIN 1/2) are an instantaneous expression of HPV infection, exhibiting distinct biological properties from malignant tumours and featuring a high natural regression rate, – about 60%-90% of LSIL cases undergo natural reversal within 2 years, and only 1% may advance to cervical cancer [7], whereas high-grade squamous intraepithelial lesions (HSIL or CIN 3) a more dangerous category with the risk of progression to invasive carcinoma of the cervix in the absence of appropriate treatment.

Generally, the mortality rate in underdeveloped countries from cervical cancer is 18 times higher than the wealthier Western countries due to their lack of public awareness, socioeconomic factors, no HPV vaccination, limited access to screening programs, and subsequent delayed or inadequate treatments [8].

Conventional treatment methods for CINs and HPV infection, such as radiation, chemotherapy, cryotherapy, and surgical excision using laser or loop electrosurgical excision procedures, are all invasive in their application. These invasive treatments can lead to various adverse reactions and complications, including haemorrhaging, cervical stenosis, and serious issues in subsequent pregnancies like spontaneous abortion, preterm birth, and overall fertility [9, 10]. Hence, there is a crucial need to develop alternative treatment approaches that effectively address CIN and cervical HPV infection without compromising a patient's fertility and health [11, 12].

Photodynamic therapy (PDT) stands out as a promising and highly selective therapeutic method in this context. PDT involves the use of photoactive compounds (photosensitizers) that accumulate in target cells, and its therapeutic effect is not limited to the direct destruction of these cells. The photodynamic action also includes damage to local vasculature and modulation of the immune response, making PDT a multifaceted treatment modality [13, 14]. 5-Aminolevulinic acid (5-ALA), a precursor to the potent sensitizer protoporphyrin IX (PpIX), has been utilised in PDT treatments for cervical condyloma, cervical intraepithelial neoplasia (CIN), and other diseases of the female reproductive tract. The sensitiser selectively accumulates in abnormal tissues and, upon exposure to light at specific wavelengths induced, induces cellular oxidative stress by generating reactive oxygen species that kill pre-cancerous cells [15]. PDT has found utility across various medical domains as a non-invasive, highly selective, and locally applied treatment.

Our study seeks to review the development and evolution of clinical research assessing the effectiveness of PDT with 5-ALA with some parallels with similar

photosensitisers as a therapeutic option for women diagnosed with cervical dysplasia induced by an HPV virus.

PDT-5-ALA Mode of Action

PDT consists of three essential components: a photosensitiser, an optical wavelength of light, and a reactive oxygen species [11, 15]. Early clinical trials of PDT utilized first-generation photosensitisers, such as hematoporphyrin derivative and its purified form photofrin II, demonstrating effectiveness against various cancers including brain, lung, and skin carcinomas [16-18]. However, first-generation photosensitisers were limited by their complex composition and structure, which negatively impacted tissue selectivity and the stability of photodynamic damage intensity. In contrast, second-generation photosensitisers have a clear composition and structure, with significantly improved photosensitivity, absorption spectrum, and tissue selectivity [16]. Many second-generation photosensitisers are based on the porphyrin structure, including benzoporphyrins, purpurins, texaphyrins, and protoporphyrin IX (PpIX)[16].

5-ALA, and its more hydrophobic ester derivatives, methyl aminolevulinate (MAL) and hexaminolevulinate, is a natural amino acid and a precursor of PpIX. When externally administered, 5-ALA enters normal cells and participates in the porphyrin metabolism pathway, contributing to haem synthesis. However, in cancer cells, PpIX accumulates selectively and acts as a photosensitizer due to the reduced activity of the enzyme ferrochelatase (FECH), which is responsible for converting PpIX into haem [19, 20]. Cells infected with HPV can selectively take up ALA upon exposure, leading to the accumulation of PpIX within these infected cells [21, 22]. During irradiation, specifically ultraviolet or blue light, PpIX exhibits distinct red fluorescence, simultaneously initiating the generation of cytotoxic reactive oxidative species that eliminate the cells, inhibiting viral replication through oxygen-dependent cytotoxic reactions, viral nucleic acid strand breaking, or base site disappearance [23]. Unlike typical fluorescent agents used solely for imaging, these prodrugs serve a dual purpose by labelling cancer cells for easy detection and cancer cell death, which is employed by PDT [24].

Early feasibility studies of 5-ALA-PDT in treating cervical dysplasia

Hillemanns et al. were one of the pioneers in employing 5-ALA for fluorescence-based diagnosis of CIN, revealing promising prospects for the 5-ALA-mediated PDT (5-ALA-PDT) of CIN [25, 26]. In their study, it was the topical application of 1% 5-ALA that exhibited distinctive porphyrin fluorescence specifically in CIN, while the lesser concentration of 5-ALA (0.5%) was proven ineffective due to rapid photobleaching [26].

In a retrospective analysis involving clinical data from 115 patients with CIN (53 in a control group and 62 in an experimental group treated with 5-ALA-PDT), Yi Chen et al. found that the PDT treatment achieved HPV clearance and disease reversal at significantly higher rates (79.0% and 80.6%, respectively) than the one-time CO_2 laser therapy (62.3% and 64.2%, respectively) ($p<0.05$) at the 6-month follow-up. Furthermore, the PDT therapy achieved a better therapeutic effect with no significant difference in the cure rate of different parts, indicating that 5-ALA-PDT can reach a target site without causing scarring and preserving fertility function, thus demonstrating the ability to target localized HPV infections [27].

HPV is a highly epitheliotropic virus, – it adheres to basal cells, and the released viral DNA integrates into the host cell genome [28]. This integration results in elevated protein expression levels of E6 and E7 with synergistic effects, enhancing the proliferation capacity of cells and contributing to the transformation into cancerous cells [28]. Yi Chen et al. hypothesized that eradication of HPV from a host happens through 5-ALA-PDT-induced inhibition of the expression of E6 and E7, which in turn creates conditions in which the host cells cannot support the complete life cycle of HPV [27]. However, it is worth noting that in this study both control and case groups consisted of patients only with low-grade squamous intraepithelial lesions (LSIL).

In a similar prospective study with 76 patients with persistent cervical HPV infection, a randomly allocated treatment group (39 patients) underwent three sessions of topical 5-ALA–PDT at two-week intervals, while the control group (37 patients) received no treatment [29]. After being monitored for 9 months, the treatment group exhibited an overall HPV remission rate of 76.92%, while the control group's natural remission rate was 32.4%. A statistical analysis comparing remission rates between the two groups revealed a significant difference ($p<0.01$). The findings in a comparative study between cold-knife conization and ALA–PDT treatment for CIN 2 associated with HR-HPV infection were consistent with previous research findings where Bodner et al. found negative viral detection in 73% of patients after a 3-month treatment [30].

Contrastingly, upon the investigation of the ameliorative effects of topical 5-ALA-PDT in a clinical trial involving 40 women diagnosed with CIN 2 and 3, Keefe et al. reported that locally applied 5-ALA–PDT showed non-significant effects in the treatment of cervical CIN 2 and CIN 3 [31]. Colposcopy, followed by morphological examination of cervical biopsy material at 4, 8, and 12 months after PDT, confirmed complete regression in 15 (4-month checkpoint), 13 (8-month checkpoint), and 9 patients 1 year after PDT. Three patients experienced disease progression immediately after treatment [31]. Notably, the efficacy of PDT for the irradiation of neoplastic lesions did not show dependence on the varying light

doses (50—150 J/cm^2) used for irradiation [31]. Barnett et al. reported similar results from their randomized, double-blind, placebo-controlled trial with topical 3% 5-ALA-PDT treatment against placebo (13 women each, 26 total) for the treatment of CIN [32]. Histologic examination at the 3-month post-PDT mark revealed that 33% showed no evidence of CIN 3 (31% in the placebo arm), 42% displayed CIN of the same grade observed before PDT (38% in the placebo arm), 25% presented evidence of a higher-grade CIN than before the treatment (31% in the placebo arm), thus concluding there was no significant difference in response observed between the groups receiving 5-ALA-PDT and those undergoing placebo treatment [32]. The limited success of PDT in treating CIN, as reported by these authors, might be attributed to the topical application of photosensitizers. More promising outcomes were observed with the systemic administration of photosensitizers for CIN treatment through PDT.

The non-specific, selective absorption of 5-ALA and its derivatives by cervical mucosa and urethral mucosa, coupled with the predominant location of PPIX in the epidermal layer of cervical mucosa (rather than the dermis), ensured the safety of 5-ALA-PDT treatment in addressing cervical HPV infection. The dose increase of 5-ALA did not result in an increased accumulation of 5-ALA in the cells of the cervical epithelium [25]. Notably, 5-ALA-PDT exhibits selective action on rapidly proliferating cells, resulting in a specific killing effect with little or no damage to normal tissues and cells [33]. Side effects observed in the studies observing topically applied 5-ALA mostly included local burning and vaginal discharge, which did not require treatment or pain relief [29, 30, 32, 34]. Notably, it produced minimal local scarring compared to procedures like laser or LEEP, effectively preserved cervical function, and minimised the impact on fertility. Topically applied 5-ALA's small content in normal cells does not induce photosensitivity. However, depending on the sensitizer used, when applied intravenously or orally, patients are advised to restrict sunlight exposure to their eyes and skin for up to thirty days or more after treatment, due to the significant likelihood of skin photosensitivity, despite the dye having greater affinity for tumour tissues [35, 36].

These clinical studies had common limitations, such as a small sample size, a relatively short duration for observing the curative effects, and a lack of extensive research on long-term negative conversion rates and recurrence rates.

Current clinical studies of 5-ALA-PDT in treating cervical dysplasia

The most recent studies indicated that 5-ALA-PDT is an effective treatment for LSIL with a regression rate of 84.88%-94.81% with no significantly different rates among different age groups [37, 38]. However, patients with normal vaginal microecology might elicit a significantly higher remission rate compared to those with vaginal microecological imbalance [38]. Moreover, Liyiong Gu et al. reported women older than 50 years had a higher progression rate than the <50 years old women after the PDT treatment (12.20 % and 0.46 %, respectively). It is worth noting that women above 50 years had an increased risk of spontaneous progression than women of age >50 (31.4 % and 21.98 %, respectively) [39]. Therefore, Liyiong Gu et al. recommended patients over 50 still need close follow-up monitoring.

A single-centre, prospective cohort study by L. Ma et al. compared the clinical efficacy of 5-ALA-PDT and cryotherapy for CIN2: the regression rate after PDT was significantly higher than cryotherapy (91.7% vs 81.4%) but with no difference in HPV clearance rate [40]. Moreover, the study used a 20% concentration of 5-ALA with two follow-up treatments while suggesting increasing the frequency if patients have multicentric lesions in the cervix and inflammation in the genital tract to achieve a better outcome. The 20% concentration could be more suitable since 12-20% 5-ALA reached 91% of efficacy [41, 42], compared to 30.8-63% with 5-10% 5-ALA [43, 44].

Xiaoyun Wang et al. noticed that most women with LSIL had cervical ectropion, a condition that might expose the host to various sexually transmitted diseases, including HPV infection [45]. Interestingly, Xiaoyun Wang et al. unexpectedly discovered a significant reduction in cervical erosion and a decrease in vaginal discharge in 78% of the cases following treatment, indicating the benefits of 5-ALA-PDT not only as an organ-preserving alternative but also a simultaneous treatment of LSIL and cervical ectropion [45].

The systemic review and meta-analysis of data from 45,000 women with CIN reported that the high-risk HPV was associated with a 28.4% treatment failure rate [46]. After the integration of HPV DNA into a host genome, viral oncoproteins promote the hypermethylation of CpG islands of tumour suppressor genes, consequently silencing them and allowing the progression of cervical lesions [47, 48]. Particularly, PAX1 methylation is strongly linked to the development of cervical lesions [49, 50]. As was reported by Y. Tang *et al.* during the 5-ALA-PDT study on treating HSIL, the HPV clearance and complete remission (CR) rates in the PAX1^{lm} group were 71.3% and 92.5%, respectively, which were significantly higher than the rates of 36.8% and 73.7% observed in the PAX1^{hm} group, suggesting that the PAX1 methylation status may influence the effectiveness of 5-ALA-PDT [51]. The findings imply that patients with higher PAX1 methylation levels are more likely to progress toward cervical cancer rather than experience regression, although the exact mechanisms behind this effect remain unclear.

Nonetheless, the virus clearance rate is of great importance to avoid the risk of disease remission. A systematic review and meta-analysis of randomised

clinical trials reported promising outcomes: 62.3% of patients (48 out of 77) who underwent PDT achieved complete remission at the 3-month follow-up [52]. More recent studies reported similar results, with a 64.34%-75.32% HPV remission rate at 3 months, 64.6%-88.54% at 6 months, and 81.3-81.82% at 12 months post-treatment [37, 38, 51, 53], or a 63.64% HPV remission rate following six treatment sessions [54]. These remission rates are considerably higher than the conization (57-59.1%) [55, 56]. A minimum of two years of follow-up is required to confirm the effectiveness of the treatment for HR-HPV clearance, although the complete response rate of 75% and 90% was achieved in CIN1 and CIN2/3 patients, respectively, during the one to two-year long-term effectiveness of topical PDT for CIN1 and CIN2/3 study [41].

The recent retrospective study revealed that small cervical intraepithelial lesions responded more positively to 5-ALA-PDT, while larger lesions had a higher failure rate, implying that factors such as "HSIL/ASC-H on cytological tests" and lesion characteristics were linked to the effectiveness of 5-ALA PDT [57]. Z. Qu suggested that the severity of the lesion increases with the extent of the SIL [57], and large cervical lesions may lead to micro invasion or invasion [58]. The research showed that patients with visible lesions covering less than one cervical quadrant had a higher HSIL regression rate after 5-ALA PDT [57]. Therefore, the authors expressed the importance of the use of appropriate cytological tests, endocervical curettage, and colposcopic examinations to assess the severity of HSIL, and strict criteria when selecting patients for 5-ALA PDT.

There are several potential reasons for the failure of 5-ALA PDT. First, 5-ALA may not adhere tightly to the cervical surface, resulting in insufficient absorption by some of the target cervical cells, thus failing to accumulate the photosensitizer [57]. Second, if the lesion is located near the external os of the exocervix, the LED light may have difficulty reaching the lesion due to the direct path the light travels [57]. Lastly, if the intraepithelial lesion is too deep, the 635nm red light may not penetrate effectively to activate the photosensitiser.

As far as safety is concerned, the primary side effects of 5-ALA-PDT were reported to be local discomfort, burning sensations, and increased vaginal discharge [59], or abdominal pain, increased vaginal discharge, and itching sensations, while the incidence of increased vaginal discharge was significantly lower in the PDT group compared to the cryotherapy group [40].

As 5-ALA-PDT is a tissue-preserving treatment that doesn't result in visible scarring, the preservation of the reproductive abilities of women remains a high priority. 5-ALA PDT has not caused cutaneous phototoxic reactions to the cervix, and studies on reproductive and developmental toxicity have indicated that it is relatively safe for the embryo and fetus [60]. There have been no reports of pregnancy failure resulting from PDT. Conversely, some patients were able to conceive successfully within 6 months after treatment [53], and one patient delivered a healthy baby vaginally at full term after becoming pregnant within three months post-5-ALA-PDT [38]. Out of 29 patients who attempted pregnancy after undergoing 5-ALA-PDT, 18 became pregnant, and none of the fetuses experienced death due to cervical insufficiency [34].

The main advantage of PDT with 5-ALA that was indicated by all researchers is that it clears oncogenic HPV, selectively targets epithelial tissues or CIN lesions, avoiding surgery, hospitalization, or even interference with follow-up colposcopies, and in some studies, it avoids the risk of preterm birth in later pregnancies. Additionally, the devices used for the PDT application were easily administered by the gynaecologist and removed by the subjects. In many countries, such as Germany, conization is often performed under general anaesthesia, and hospitalization and disability are significant cost drivers [61]. Pregnancy-related morbidity linked to surgical procedures is substantial, with the average incremental cost per preterm birth (all causes) estimated to be $51,600 in the United States [62]. This highlights the potential for economic advantages by reducing the number of surgical interventions in patients with cervical high-grade disease using tissue-preserving treatments like PDT.

Conclusion

Multiple clinical studies suggest that 5-ALA-PDT is particularly attractive as an alternative treatment for its minimally invasive application, high tissue selectivity, reduced risk of adverse events compared to conventional methods, and lower likelihood of severe complications. Moreover, 5-ALA PDT can shrink cervical ectropion and reduce vaginal discharge, making it a potential treatment for cervical ectropion and chronic cervicitis. These advantages make PDT a potentially effective approach for managing CIN and cervical HPV infection, particularly among young women who plan for pregnancy. Regulating vaginal microflora during PDT can improve the remission rate of HPV for patients with vaginal microecological imbalance. For patients over 50, close follow-up monitoring after treatment may be necessary.

Early studies with smaller concentrations of 5-ALA showed poor effectiveness rates; however, 5-ALA with a concentration of 20% has shown better results in recent research. Larger studies, ideally from multiple centres, are needed to determine the optimal number of PDT sessions required to eradicate HPV.

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