PHOTODYNAMIC THERAPY IN THE TREATMENT OF HPV-ASSOCIATED CERVICAL CANCER: MECHANISMS, CHALLENGES AND FUTURE PROSPECTS

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Abstract

Photodynamic therapy (PDT) has shown promise as a modality for the treatment of cervical cancer caused by the human papillomavirus (HPV). This review provides a comprehensive examination of the role of PDT in overcoming the challenges presented by conventional treatments for cervical cancer. Beginning with an overview of the relationship between cervical cancer and HPV infection, the review introduces the principles of PDT, its mechanism of action, and its potential as an innovative treatment strategy. The review highlights preclinical studies in animal models that demonstrate the efficacy of PDT in targeting HPV-infected cervical cells and provide mechanistic insights into its cytotoxic effects. We reviewed clinical studies and case reports highlighting the potential of PDT as an alternative or adjunctive treatment option. Challenges and limitations, including depth of light penetration, photosensitizer specificity, and standardization of protocols, will be discussed in the context of potential side effects and comparison with conventional treatments. Future directions include ongoing research, combination therapies with immunotherapy or targeted agents, advances in photosensitizer development, and personalized approaches. The advancement of PDT promises to change the landscape of HPV-associated cervical cancer treatment by providing a targeted, personalized, and minimally invasive approach.

Keywords: cervical cancer, human papillomavirus (HPV), photodynamic therapy (PDT), combination therapies, photosensitizers.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ В ЛЕЧЕНИИ ВПЧ-АССОЦИИРОВАННОГО РАКА ШЕЙКИ МАТКИ: МЕХАНИЗМЫ, ПРОБЛЕМЫ И ПЕРСПЕКТИВЫ НА БУДУЩЕЕ

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Резюме

Фотодинамическая терапия (ФДТ) зарекомендовала себя как многообещающий метод лечения рака шейки матки, вызванного вирусом папилломы человека (ВПЧ). В этом обзоре всесторонне рассматривается роль ФДТ в преодолении проблем, связанных с традиционными методами лечения рака шейки матки. Начиная с обзора взаимосвязи между раком шейки матки и ВПЧ-инфекцией, в обзоре представлены принципы ФДТ, механизм ее действия и ее потенциал в качестве инновационной стратегии лечения. В обзоре освещены доклинические исследования на животных моделях, которые демонстрируют эффективность ФДТ в отношении клеток шейки матки, инфицированных ВПЧ и дают представление о механизмах ее цитотоксического действия. Мы рассмотрели клинические исследования и отчеты о случаях, в которых подчеркивается потенциал ФДТ как альтернативного или дополнительного метода лечения. Проблемы и ограничения, включая глубину проникновения света, специфичность фотосенсибилизаторов и стандартизацию протоколов, будут обсуждаться в контексте потенциальных побочных эффектов и сравнения с традиционными методами лечения.

Будущие направления включают текущие исследования, комбинированную терапию с иммунотерапией или таргетными препаратами, достижения в разработке фотосенсибилизаторов и персонализированные подходы. Развитие ФДТ обещает изменить подход к лечению рака шейки матки, ассоциированного с ВПЧ, за счет обеспечения целенаправленного, персонализированного и минимально инвазивного подхода.

Ключевые слова: рак шейки матки, вирус папилломы человека (ВПЧ), фотодинамическая терапия (ФДТ), комбинированная терапия, фотосенсибилизаторы.

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Introduction

Cervical cancer remains a major global health problem and is the fourth most common cancer in women worldwide [1, 2, 3, 4]. The central role of persistent human papillomavirus (HPV) in the development of cervical cancer is now well established [5, 6]. HPV, especially high-risk genotypes such as HPV-16 and HPV-18, contribute to the malignant transformation of cervical epithelial cells, so there is an urgent need for innovative and effective treatment strategies [7, 8]. Among these strategies, photodynamic therapy (PDT) is a promising approach [9].

Originally developed at the beginning of the 20th century, PDT has evolved into a new, minimally invasive treatment method in various medical disciplines. PDT involves the introduction of a photosensitizing agent that accumulates primarily in malignant tissue, followed by local activation by light of a specific wavelength [10, 11]. This activation leads to reactive oxygen species (ROS) forming, which causes cytotoxic effects that attack and destroy malignant cells [12, 13]. The non-invasive nature of PDT, selective tissue targeting, and potentially minimal systemic toxicity make it an attractive approach for diseases such as cancer. Some authors have questioned the radical nature of PDT in cancer, pointing to the impossibility of penetrating a beam of light at a distance (up to 1 cm) with a progressive loss of radiant power [14, 15]. In contrast, Chizenga E.P. et al. have asserted the widespread introduction of PDT for non-invasive and minimally invasive cancers of the cervix and cervical canal [16].

The purpose of this review is to provide a comprehensive assessment of the existing preclinical studies and clinical trials that have studied the use of PDT for cervical cancer associated with HPV, which may allow researchers and clinicians to determine its appropriate role in the treatment of this pathology and its place in the arsenal of therapeutic effects. By summarizing the available evidence, this review aims to clarify PDT's efficacy, safety profile, and potential benefits compared to traditional treatments. In addition, the mechanical aspects underlying the effects of PDT on HPV-infected cervical cells are considered, shedding light on its immunomodulatory effects and potential synergies with new immunotherapy methods.

In conclusion, this review aims to contribute to the evolving landscape of cervical cancer treatment by highlighting the untapped potential of PDT. By exploring the mechanisms, clinical outcomes, challenges, and future directions, we aim to provide clinicians, researchers, and policymakers with a comprehensive understanding of the role of PDT in the fight against HPV-associated cervical cancer and stimulate further research to optimize its therapeutic potential.

HPV-Associated cervical cancer: pathogenesis and current treatment approaches

The human papillomavirus (HPV) is a diverse group of DNA viruses, of which many genotypes are known to infect the genital mucosa [17, 18]. While most HPV infections are transient and benign, persistent infection with high-risk HPV genotypes such as HPV-16 and HPV-18 plays a central role in the development and progression of cervical cancer [19]. These oncogenic strains encode the viral oncoproteins E6 and E7, which inactivate the tumor suppressor proteins p53 and pRB, respectively, disrupting normal cell cycle regulation and promoting cell transformation [20, 21, 22].

The pathogenesis of HPV-associated cervical cancer is a multistep process involving the interaction of viral and host factors. Integration of the virus into the host genome leads to dysplastic changes in the cells of the cervical epithelium [23, 24]. Persistent infection promotes progression from low-grade cervical intraepithelial neoplasia (CIN) to highly differentiated CIN and finally to invasive carcinoma. Activation of oncogenic signaling pathways and evasion of immune surveillance contribute to tumor growth and metastasis [25].

Modern approaches to treatment of cervical cancer

1. Surgery: Surgery remains the cornerstone of cervical cancer treatment. Depending on the stage of the tumor, surgical options include hysterectomy,

radical hysterectomy, and lymphadenectomy. While surgical removal of the tumor and surrounding tissue can be curative in the early stages of the disease, it may not be sufficient in advanced stages with lymph node involvement or metastasis [26, 27].

2. Radiation therapy: Radiation therapy, often in combination with chemotherapy, is frequently used for locally advanced cervical cancer. External beam radiation and brachytherapy effectively target the tumor site and attempt to destroy the cancer cells while sparing nearby healthy tissue. The combination of radiation and concurrent chemotherapy improves outcomes by increasing the sensitivity of tumor cells to radiation-induced damage [27, 28].

3. Chemotherapy: Chemotherapy plays a critical role in the primary treatment of locally advanced cancer and in the adjuvant treatment of cervical cancer. Platinum-based therapies, such as cisplatin, are often used to increase the efficacy of radiotherapy. In addition, systemic chemotherapy can be used for metastatic or recurrent disease [29].

Although these treatment approaches are successful, they are not without limitations. Surgery is associated with the risk of postoperative complications, and radiation therapy can lead to long-term side effects such as rectovaginal fistula, obliteration of the cervical canal with a hematometer, and radiation castration [10, 30]. Chemotherapy is not very effective when used once and is associated with systemic toxicity [31]. In addition, factors such as tumor heterogeneity, resistance, and patient characteristics (age, comorbidities, etc.) may limit the therapeutic efficacy of these approaches.

Against the background of these problems, investigating innovative treatment strategies such as PDT becomes an urgent necessity. The selective effect of PDT, the possibility of reducing side effects, and the potential synergy with existing treatments are promising for improving the treatment of HPV-associated cervical cancer. By overcoming the limitations of existing treatments and offering new intervention options, PDT can help improve patient outcomes and quality of life.

Photodynamic Therapy (PDT): mechanism and principles

PDT is a state-of-the-art therapeutic approach that uses the power of light and photosensitizers to destroy malignant cells specifically [12]. The basic principle of PDT is the unique interaction of three key components: a photosensitizer, specific wavelengths of light, and molecular oxygen. When these components come together, they trigger a cascade of events that culminate in the selective destruction of tumor cells while sparing the surrounding healthy tissue [1, 12].

Photosensitizers play a central role in the efficacy of PDT. These molecules are usually non-toxic compounds that, when activated by light of specific wavelengths, transition from a ground state to an excited state with higher energy [32]. Photosensitizers can be divided into different classes, such as porphyrins, phthalocyanines, and chlorins, each with unique spectral properties. The choice of photosensitizer is critical because it determines the wavelengths of light that must be used for optimal activation [33]. The type of photosensitizer is controversial because laser devices are tied to the chemical structure, which depends on the absorption spectrum [12]. In Russia and China, chlorine and the red diode laser with 662 nm have traditionally dominated [12]. In Europe, porphyrins are used as photosensitizers, but it is impossible to evaluate their efficacy due to methodological differences [13, 14].

Light sources activate photosensitizers that emit wavelengths corresponding to the selected photosensitizer's absorption spectra. As a rule, lasers or light-emitting diodes (LEDs) are used [1]. The wavelength and light intensity are carefully selected according to the optimal absorption properties of the photosensitizer. This controlled activation initiates the energy transfer process, causing the photosensitizer to return to its ground state and simultaneously releasing energy in the form of reactive oxygen species (ROS) [12].

When the light is activated, the photosensitizers interact in their excited state with molecular oxygen in the surrounding tissues [16, 33]. This interaction leads to ROS, especially singlet oxygen ($^1O_2$), highly reactive and cytotoxic molecules [34]. These ROS trigger oxidative stress by damaging cellular components such as lipids, proteins, and DNA. In tumor cells, impaired antioxidant defense mechanisms make them more susceptible to ROS-mediated damage, leading to cell death by apoptosis, necrosis, or autophagy [35, 36, 37, 38].

One of the remarkable features of PDT is its selectivity: the photosensitizer accumulates primarily in the tumor tissue due to its increased permeability and retention. This enables targeted destruction of cancer cells with minimal damage to normal tissue, thus reducing systemic toxicity and side effects associated with the treatment. PDT's dual mechanism of action, which involves direct damage to the cells and activation of the immune system, further enhances its potential as an effective therapeutic method [10].

The extraordinary precision of the molecular interactions of PDT and the synergistic effect of light, photosensitizer, and oxygen opens up excellent prospects for treating HPV-associated cervical cancer. By exploiting innate biochemical differences between normal and malignant cells, PDT offers an innovative strategy that meets the requirements for personalized, minimally invasive treatments in oncology [9].

Preclinical studies on PDT for HPV-associated cervical cancer

Before introducing a therapeutic approach into clinical practice, thorough preclinical studies must assess safety, efficacy, and understanding of mechanisms. In the context of PDT for HPV-associated cervical cancer, animal models have served as a tool to evaluate the potential of this treatment modality. These models, often using rodents such as mice or rabbits, provide researchers with a controlled environment to simulate various aspects of human cervical cancer and to study the effects of PDT in a controlled and systematic manner [39, 40].

Preclinical studies in animal models have consistently demonstrated the efficacy of PDT in HPV-infected cervical cells. These studies usually involve inoculation of animals with HPV-positive cervical tumor cells and subsequent treatment with photosensitizers and light exposure [41]. The selectivity of PDT is apparent, as the photosensitizer accumulates mainly in the tumor tissue due to its inherent properties, leading to the destruction of the malignant cells when activated by light. In subsequent genetic studies on these animals, no HPV DNA could be detected after 3, 6, and 12 months [22, 23, 24].

These studies often include the evaluation of tumor regression, tumor size reduction, and tumor growth inhibition. In addition, they provide information on the effects of treatment on various biological parameters, such as impairment of vascular function in the tumors, immune responses, and potential tumor recurrence. Such information is invaluable for understanding the broader impact of PDT in the context of HPV-associated cervical cancer [16, 42, 33].

Preclinical studies confirm the efficacy of PDT and provide a mechanistic understanding of how this treatment method exerts its effects. These studies focus on the molecular and cellular mechanisms underlying the cytotoxic effects of the reactive oxygen species (ROS) generated during PDT [34, 36, 12].

Mechanistic studies frequently show that ROS-induced oxidative stress triggers cellular responses, including DNA damage, activation of apoptotic signaling pathways, and modulation of immunomodulatory signals. In addition, the effect of PDT on the tumor microenvironment, such as tumor vascularization and immune cell infiltration, contributes to the overall development of the treatment [35, 36, 37, 38].

In addition, animal models allow researchers to study parameters critical for the optimization of PDT, such as the ideal dose of photosensitizer, light intensity, and the interval between photosensitizer administration and light exposure. These parameters significantly impact treatment outcomes, and preclinical studies have helped establish recommendations for proper calibration [41].

In summary, preclinical studies in animal models serve as a link between basic research and the clinical application of PDT for HPV-associated cervical cancer. These studies not only confirm the efficacy of PDT in targeting HPV-infected cervical cells but also provide a deeper understanding of the mechanisms underlying this treatment. The information obtained from animal models is used in the design of clinical trials and serves as a guide to make PDT a safe and effective therapeutic option for patients [34, 35].

Clinical studies and case reports

The transition from preclinical research to clinical practice is an essential step in evaluating the potential of PDT as a treatment for HPV-associated cervical cancer.

The first attempts to use PDT to treat precancerous lesions and early cervical cancer were made in the early 1980s [1]. This attempt was made regardless of whether the women were infected with HPV. Once the etiologic role of the virus in the development of intraepithelial neoplasia and cervical cancer had been confirmed [28, 23, 24], the focus shifted to the highly oncogenic HPV 16 and 18 PDT.

Clinical trials provide information on PDT's safety, efficacy, and tolerability under real-life conditions. These studies have several objectives, including evaluating treatment outcomes, optimizing PDT protocols, and comparing PDT with traditional treatment approaches [12, 13].

Clinical trials have shown promising treatment outcomes and response rates in patients with HPV-associated cervical cancer who have undergone PDT [14, 15]. Parameters such as tumor regression, lesion size reduction, and patient survival are usually evaluated. Some studies have shown that PDT can effectively induce tumor necrosis and lead to complete or partial remission, especially at an early stage of the disease [16]. In addition, the ability of PDT to preserve fertility and anatomical integrity in small tumor spreads is critical.

Comparative studies between PDT and traditional treatments provide valuable information on the potential of PDT as an alternative and/or adjunctive option [34, 39]. These comparisons often include an assessment of treatment efficacy, quality of life, and adverse events [18, 17]. Although PDT's non-invasive nature and targeted approach are advantageous, its effectiveness depends on tumor stage, size, and location factors. A comparative analysis helps clinicians decide the most appropriate treatment strategy based on the individual patient profile.

Including case reports in clinical studies emphasizes the practical application of PDT and its effects on individual patients. These reports include detailed descriptions of patient histories, treatment protocols, and post-treatment outcomes [22, 33, 30]. The reports of successful PDT interventions demonstrate the potential of the treatment to achieve favorable results even in complex cases. In addition, the case reports shed light on factors contributing to PDT's success, such as proper

patient selection, optimal dosage of photosensitizer, and individualized light delivery strategies.

These case reports also illuminate the patient experience and address treatment tolerance, recovery time, and long-term effects. They contribute to a more comprehensive understanding of the feasibility of PDT and patient satisfaction and provide a more complete picture of the clinical benefits of treatment [12].

Clinical studies and case reports, therefore, play a key role in bridging the gap between theoretical efficacy and actual applicability of PDT for HPV-associated cervical cancer. These studies demonstrate the potential of PDT as an innovative and targeted therapeutic approach and provide insights into treatment outcomes, comparative analysis, and individual patient progression. As clinical research in this area continues to evolve, these findings will help to improve PDT protocols and expand its role in the complex management of cervical cancer [12, 13, 42].

In the Russian Federation, the PDT method has found its place in treating several localizations at the level of approved federal clinical recommendations in its form or as part of complex therapy [43-46]. There are no similar recommendations for HPV-associated neoplasia. There is a collection of information on the effect of PDT on viral transmission and the duration of elimination of oncogenic HPV types [12].

Challenges and limitations

Despite its promising potential, the use of PDT in the treatment of cervical cancer is fraught with difficulties. These problems must be solved to fully exploit PDT's benefits in this context.

1. Depth of light penetration: One of the main problems is the limited penetration depth of the light into the tissue. Cervical cancer is often characterized by variable lesion depth, and it can be challenging to ensure adequate light delivery to deep-seated tumors. This limitation can lead to inconsistent treatment efficacy and incomplete tumor ablation [19, 20].
2. Photosensitizer specificity and tumor targeting: Choosing the right photosensitizer and achieving optimal tumor targeting are critical for the success of PDT. Photosensitizers should primarily accumulate in the tumor tissue, minimize uptake into healthy tissue, and minimize potential damage to surrounding structures [41].
3. Standardization of PDT protocols: The lack of standardized protocols for PDT is a serious problem. Variables such as photosensitizer dose, light intensity, and time between photosensitizer administration and light exposure can significantly affect treatment outcomes. Standardization is critical to ensure reproducibility and comparability between studies and clinical settings [32, 33].

Like any medical procedure, PDT is associated with potential side effects and adverse events. After PDT treatment, photosensitivity reactions may occur, characterized by skin photosensitivity (photodermatoses). Other potential side effects include local inflammation, pain, and swelling at the treatment site. Adequate patient education and post-treatment care are essential to control and reduce these effects [11, 34, 35, 47].

It is essential to consider the limitations of PDT in the context of a broader range of treatment options for cervical cancer. Surgery, radiation therapy, and chemotherapy also have their limitations, including potential complications, systemic toxicity, and problems in treating advanced stages. Comparing the limitations of PDT with those of other treatment modalities helps clinicians and researchers make informed decisions about treatment choices based on individual patient characteristics and disease stage [17, 18, 26, 48].

Despite these challenges, ongoing research and innovation in PDT address many limitations. Advances in the development of photosensitizers, methods of light delivery, and combination therapy with immunomodulatory agents are gradually overcoming the obstacles and expanding the clinical use of PDT to treat cervical cancer [27, 28, 29, 30].

In conclusion, recognizing and addressing the problems and limitations of PDT in the treatment of HPV-associated cervical cancer is critical to optimizing its clinical application. If these obstacles are overcome through innovative strategies, collaboration between interdisciplinary teams, and continued research, PDT can become a more effective and well-integrated component of a holistic approach to cervical cancer treatment.

Future directions and emerging srategies

The evolving landscape of PDT for cervical cancer is characterized by constant research and innovation aimed at improving and expanding its potential. Researchers are actively exploring new approaches to solve PDT-related problems, including improving light penetration, optimizing photosensitizer delivery, and improving treatment monitoring [31, 32]. Advanced imaging techniques, such as fluorescence-guided surgery, are being investigated to identify lesions and accurately guide PDT interventions [33].

Combination therapy is a promising approach for the future treatment of cervical cancer [64]. The ability of PDT to induce immunogenic cell death fits well with the new immunotherapy strategies. Combining PDT with immune checkpoint inhibitors or adoptive T-cell therapy can enhance the antitumor immune response and thus improve therapeutic outcomes. In addition, combining PDT with targeted agents that specifically modulate

tumor microenvironment factors can improve treatment effects and overcome the limitations of PDT [35, 36].

The development of photosensitizers is an active area of research to improve the efficacy of PDT. Researchers are developing photosensitizers with improved optical properties, increased selectivity for tumor cells, and reduced toxicity. In addition, targeted delivery systems such as nanoparticles or antibodies conjugated with photosensitizers are being developed to increase the accumulation of photosensitizers in tumors to improve targeting and therapeutic outcomes [37].

With the increasing importance of precision medicine, personalized approaches for PDT are also emerging. Tailoring PDT protocols based on specific patient characteristics, such as tumor biology, microenvironment, and genetic profiles, can optimize treatment outcomes. The use of advanced imaging and diagnostic methods to assess tumor characteristics in real time enables on-the-fly adjustment of the treatment plan, maximizing the efficacy of PDT while minimizing side effects [38].

In addition, predictive biomarkers are being identified to help select patients and predict response to treatment. Such an individualized approach not only increases the efficacy of treatment but also helps to reduce the number of patients and improve their quality of life.

The future of PDT in the treatment of HPV-associated cervical cancer is, therefore, characterized by a dynamic interplay of research and innovation. New strategies include an interdisciplinary approach involving oncologists, immunologists, material scientists, and imaging experts. As these advances come together, the landscape of cervical cancer treatment is likely to change, ushering in a new era of personalized, targeted, and minimally invasive therapies that can significantly improve patient outcomes and overall well-being [29].

Conclusion

This review comprehensively examined the role of PDT in the treatment of HPV-associated cervical cancer, leading to several important conclusions. The review included an in-depth understanding of the association of cervical cancer with HPV, the underlying principles of PDT, preclinical and clinical studies, issues, and directions for the future. The combination of the evidence and the results of the analysis allowed us to gain a holistic view of the potential of PDT to revolutionize the treatment of cervical cancer.

PDT is becoming increasingly popular in modern medicine. With a history of more than six thousand years and a Nobel Prize 120 years ago, PDT has only found widespread application in the last few decades. The dynamics of published papers show that PDT has become increasingly in demand in recent years and has found its way into various areas of modern medicine [40].

The potential of PDT is truly enormous: in the early stages of malignant neoplasms, it can be used as an alternative to radical surgical treatment and radiation treatment and in the advanced stages of cancer - as an adjunct to ongoing complex treatment. In progressive, non-responsive, and exhaustive options of traditional treatment methods, PDT is the only method that improves the quality of life by exerting local control [32, 42].

In conclusion, this review highlights the transformative potential of PDT in the treatment of HPV-associated cervical cancer. This review enhances the ongoing discussion on innovative therapeutic strategies by providing a concise overview of the major findings, validating its potential, and advocating further research and clinical trials. With continued commitment and interdisciplinary collaboration, PDT promises to change the landscape of cervical cancer treatment and offer new hope to patients and clinicians.

Implications for clinical practice

The integration of PDT into the treatment paradigm for HPV-associated cervical cancer requires a careful and strategic approach. Although PDT shows promise, its implementation requires considerations consistent with established clinical practice. PDT should be considered an additional or alternative therapeutic option that complements existing treatment modalities [34, 23].

Clinicians should evaluate the stage, size, and location of the cervical tumor and the patient's overall health status to determine the appropriateness of PDT. Collaboration with multidisciplinary teams is essential to develop comprehensive treatment plans that consider the benefits and limitations of PDT in the context of each patient's unique condition.

Patient selection is critical to the success of PDT. Ideal candidates for PDT are patients with localized early-stage cervical cancer who can benefit from targeted and minimally invasive treatment. Patients should be screened to determine whether they can tolerate light exposure and potentially develop a photosensitivity reaction [38, 42].

In addition, the criteria for patient selection should consider factors such as tumor histology, HPV genotype, and previous treatment history. Collaborative decision-making among medical oncologists, radiation oncologists, and PDT specialists can help identify patients who could benefit most from PDT while ensuring that it meets their individual preferences and goals.

Multidisciplinary tumor management boards can serve as platforms for collaborative decision-making, where treatment options are discussed, taking into account each patient's clinical, pathological, and radiological data. Such a collaborative approach ensures effective integration of PDT and optimizes treatment outcomes while minimizing risks [41, 42, 46].

Regular communication between these specialists is essential to improve treatment protocols, solve problems, and exchange opinions from a clinical and scientific perspective. As the field of PDT continues to evolve, ongoing collaboration ensures that clinical practice is in line with the latest evidence and innovations [41, 42, 46].

In conclusion, the incorporation of PDT into the clinical management of HPV-associated cervical cancer requires careful consideration, patient selection, and interdisciplinary collaboration. By drawing on the experience of oncologists, researchers, and PDT specialists, clinicians can realize the full potential of PDT and ensure its safe and effective integration into a broader treatment paradigm.

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