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Review Article

In-Vivo Photodynamic Therapy Studies in Cancer

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Abstract

The traditional surgical method for cancer treatment has not been successful in removing primary or metastatic tumors. Chemotherapy and radiation therapy methods, as well as cancer cells and healthy cells affect the process of treatment nausea, hair loss, immune system weakness, such as there are many side effects. Photodynamic therapy (PDT) is a regulator for the treatment of many malignant carcinomas that can cause immunogenic apoptosis. Despite these adversities in surgery, chemotherapy and radiation therapy, significant progress has been made in PDT research recently. This review article is aimed to present recent studies.

Keywords: Photodynamic Therapy; Cancer Treatment; Metastatic Tumors

Introduction

Photodynamic therapy (PDT) is an alternative treatment method that was first introduced in Canada in 1993 and then it was introduced in the USA, Europe, Japan and Australia; especially for the treatment of cancer [1]. PDT has been applied in treating certain types of cancer. For example, skin cancer possibly could be treated using PDT approach. It has been reported that methyl-amino levulinate photodynamic therapy (MAL-PDT) is an excellent potential for the treatment of basal cell carcinoma (BCC) [2]. PDT is an approach not only to combat the tumorous and cancerous cells but also has the capability to treat infectious diseases. For instance, the PDT could be effective in treating the fungal infection. It has been reported that the combination of 5-aminolevulinic acid PDT (ALA-PDT) could be an alternate approach for monitoring infections caused by *Trichosporon asahii* [3]. In addition, there is one study had reported that ALA-PDT is an effective and safe technique for the treatment of rosacea by controlling the clinical manifestations and reducing the symptoms [4].

PDT is based on the destruction of the target tissue by intravenous administration of a photosensitive chemical to the body by stimulating the substance with a low energy light in the target tissue and by occlusion of the vascular component in the target tissue without damaging the surrounding tissues [5].

Compared to conventional cancer therapies, PDT has many advantages such as being a non-invasive and local treatment method, being able to be given to the patient in repeatable doses, and not having any concern about resistance or overdose [6].

The applications of photodynamic therapy

The applications of the photodynamic could be various. One of the applications is to treat certain types of cancer. Zheng., *et al*. had suggested that the targeted lesion causes traumatic oxidative stress due to photosensitizing effect [7]. Photosensitizers can be excited by visible light in the presence of oxygen. One of the photosensitizers is hypericin. Hypericin is a naturally occurring photo-sensitizer synthesized by Hypericum plants. It is considered a valuable photo-sensitizer for PDT because of its strong photo-sensitizing properties, minimal dark toxicity and high single oxygen quantum yield. Hypericin is mainly located in the membranes of the endoplasmic reticulum and Golgi apparatus. Stress and reactive oxygen species (ROS) production are important features of immunogenic apoptosis. Hypericin-mediated photodynamic therapy produces

ROS-based ER stress. This ROS-based anticancer therapy may also cause the surface or secretion of damage-associated molecular patterns (DAMPs) that activate the host immune system, also called the "eat me" signal. In their study on mice, it was observed that the "eat me "signal and the "not eat me" signal were reversed after Hypericin-PDT treatment. GSH, which can reduce the disorder of this immune-associated antigen, can also reduce the immune response caused by PDT. The results of this correlation analysis suggest that the disorder of the "eat me" and "not eat me" signals may contribute to impairing the ability of Lewis lung carcinoma (LLC) cells to escape the immune crisis. This imbalance of immune homeostasis also caused a change in the number of lower regulatory T cells (Tregs) as well as the immune status of DC (dendritic cells), the release of immune-associated cytokines (NO high, IL-10 absent) and stimulation of tumor-specific IFN-γ (Interferon-γ). PDT treatment kills tumors directly with cytotoxic, affecting vascular damage and induction of immune response. However, PDT is not an effective treatment for disseminated tumors, resulting in its limited clinical efficacy. These researchers are recommended to use in combination with other treatment modalities to increase the efficacy of PDT [7].

Tang., *et al*. had suggested that nano photosensitizers are formed by encapsulating or conjugating photosensitizers known with nanomaterials [8]. Nanoparticles such as liposomes, polymers, or hollow particles are not the source of ROS. Instead, they are used to increase photosensitizer load, improve solubility, modulate pharmacokinetics, increase bioavailability and minimize the natural toxicity of drugs to vital organs. Nano photosensitizers have been used successfully to enhance the therapeutic effect of drugs such as doxorubicin. In addition to the advantageous properties of nanomaterials for PDT, some materials such as nano fullerenes, titanium dioxide (TiO_2) and zinc oxide (ZnO) nanoparticles exhibit intrinsic photosensitivity properties. Compared to small molecule photosensitizers, fullerenes have much better photostability and *in vivo* stability. These nanomaterials serve as both type-I and type-II PDT agents because of their ability to produce ROS in an oxygen-dependent and independent manners. Many photosensitizers absorb light at UV and visible wavelengths. This binds PDT to shallow or accessible tissue. Photosensitizer activation can be accomplished by converting light from one form to another or by spectrally changing light to enhance photosensitizer activation in deep tissue [8].

In a study by Elliott., *et al*. implantation of "VX2 cancer cells" was performed as a pancreatic tumor model on six rabbits [9]. The tumor mass was drawn on the ultrasound image. Verteporfin-based PDT was applied to local pancreatic cancer. The ability to predict verteporfin uptake used in photodynamic therapy was evaluated by CT perfusion. Further studies have suggested that this type of study can be used in different animal models [9].

The study results of Cheng., *et al*. showed a higher therapeutic efficacy of Oxy-PDT than conventional PDT both *in vitro* and *in vivo* [10]. *In vivo* study by direct injection into tumors showed complete tumor growth inhibition in Oxy-PDT mice treated with low photosensitizer dosage and 20-s laser irradiation, while conventional PDT showed negligible tumor inhibition. Oxy-PDT is considered to be the first PDT design capable of achieving high efficiency in hypoxic conditions. Oxy-PDT approach with self-enriching oxygen provides a simple but effective treatment option for cancer patients [10].

In a study by Huang., *et al*. the importance of the combination of PDT and nano liposomal irinotecan (L-IRI) was emphasized [11]. PDT and nano liposomal irinotecan; they cooperate mechanically with each other. Here, three cooperative pathways have been shown to clarify synergy. Firstly, PDT decreases ABCG2 expression, thereby increasing intracellular irinotecan and SN-38 levels. Secondly, Irinotecan reduces the tumoral expression of MCT-4 upregulated with PDT. Third, PDT reduces surviving expression and amplification of apoptotic and anti-proliferative effects is seen in the combination. In this study, dramatic increase in inhibition of tumor growth was observed with combination therapy. Such combination therapy demonstrates the strength of mechanistic-cooperative combinations in which it is developed and beneficial for difficult-to-treat diseases, such as pancreatic cancer. In summary, it was demonstrated that the low-dose combination of PDT and L-IRI is compared to synergistically enhanced tumor growth inhibition compared to treatment alone and is more effective than the results reported with a standard chemotherapeutics for pancreatic cancer [11].

Agostinis., *et al*. had reported that PDT consists of 3 main components which are photosensitive (PS), light and oxygen [12]. These core components of the PDT are a two-stage procedure. Firstly, after administration of a light sensitive PS, the tumor loci are irradiated with a light of appropriate wavelength. Secondly, it

can be transmitted to almost any organ in the body by means of flexible fiber optic devices.

Liu., *et al*. had reported that the photodynamic molecular beacon (PMB) consists of three elements which are photosensitizer, extinguishant) molecule and target-specific connector [13]. It is confirmed that intravertebral injection of PMB are minimally activated by the spinal cord and, when combined with intravertebral light application, do not cause any damage to this critical organ in healthy large animals such as rabbits or pigs. Immunohistology analysis after PMB-PDT indicates that not only the destruction of spinal metastases, but also PMB-PDT demonstrates the ability to disrupt the osteolytic cycle [13].

In the study of Obata., *et al*. PDT is still considered a new and promising antitumor strategy [14]. The advantages of PDT over surgery, chemotherapy, or radiotherapy reduce long-term morbidity, and PDT is one of the future treatment options for patients with residual or recurrent disease. Finally, many conventional antitumor therapies run the risk of inducing immunosuppression. PDT-induced immunogenic cell death associated with induction of a strong local inflammatory reaction offers excellent local antitumor activity and the ability to transform into a therapeutic procedure that enhances the immune response for the effective destruction of metastases. The interdisciplinary uniqueness of PDT is a source of inspiration to experts in physics, chemistry, biology and medicine, and its further development and new applications can be limited only by enormous imagination. In this study, new photosensitizer called Phthalocyanine (Pc) was used in Murine melanoma [14].

In a study on nude mice by Shemesh., *et al*. indocyanine green (ICG), photosensitizer was used as a non-toxic organic near-infrared (NIR) [15]. It is a water-soluble, anionic tricarbocyanine dye and commonly used in many medical imaging and diagnostic applications used. Selective and localized PDT has been shown to provide tumor destruction *in vivo* while preventing non-cancer tissue damage in the triple negative breast cancer xenograft murine model. This study minimizes unwanted side effects and toxicities and the application of liposomal indocyanine green based PDT (LPICG-PDT) for localized and effective treatment of triple negative breast cancer has shown positive and promising results [15].

5-Aminolevulinic acid (5-ALA) for PDT is a potent photosensitizer and precursor of protoporphyrin IX (PphIX). Upon red light irradiation, PphIX is highly toxic and can produce reactive singlet oxygen which, at the end of the interaction, leads to cell apoptosis or necrosis. Folic acid receptor-mediated endocytosis with multifunctional hollow mesoporous silica nanoparticles as the nanocarrier, cellular uptake of 5-ALA and protoporphyrin IX (PphIX) deposition significantly increased [16].

In the study of Pereira., *et al*. dendritic galactose units and conjugated porphyrin were used as PDT agents *in vitro* and *in vivo* [17]. The potential of PDT with four dendritic galactose units and conjugated porphyrin (PorGal8) has been shown to induce galectin-1 expression primarily in bladder cancer cells, and then it causes changes in ROS formation and cell skeleton of cancer cells. PorGal8 by PDT stimulates tumor contraction. In the study of Pereira., *et al*. a xenograft tumor model was developed with UM-UC-3luc + human bladder cancer cells in the dorsum (containing high levels of galectin-1 protein) for vivo efficacy of PorGal8. PDT-based PorGal8 has been shown to be very effective from the preferential accumulation of PS in the tumor and its activation after irradiation of the target tissue, furthermore it has been suggested that PDT can have indirect effects on the cellular and molecular components of the tumor [17].

Combination therapies approaches for PDT

Standard of care is defined as treatment that is accepted by medical experts as a proper treatment for a certain type of disease and that is widely used by healthcare professionals. The therapy using PDT is considered as a treatment in treating diseases including certain types of cancer. Basically, the PDT could be divided into two main types which are topical or non-topical PDT approaches. Topical photodynamic therapy (PDT) is an effective treatment for superficial non-melanoma skin cancers [18]. For instance, 5-aminolevulinic acid-based photodynamic therapy (ALA-PDT) is a non-invasive therapy that was used in treating cancer topically. It has been reported that ALA-PDT is effective in inducing the oxidative stress which could lead to immediate mitochondrial dysfunction, and finally resulted in a caspase-independent cell death in PC12 and CL1-0 cells [19]. In addition, the cells that were treated with 5-ALA-PDT and metformin exhibited condensation of nuclear chromatin and the presence of autophagosomes, indicate the apoptosis and autophagy are occurring during the following combined treatment with 5-ALA-PDT and metformin [20]. Moreover, it has been reported that 5-aminolevulinic acid (ALA) and methyl amino levulinate (MAL) PDT appear to be effective in the treatment of nodular basal cell carcinoma and superficial basal cell carcinoma [18].

One of the examples of PDT approach via non-topical route is using the porfimer sodium. It is the sodium salt of a mixture of oligomers formed by ether and ester linkages of up to eight porphyrin units with photodynamic activity which it was absorbed selectively by tumor cells, porfimer produces oxygen radicals after activation by 630 nm wavelength laser light, resulting in tumor cell cytotoxicity [21]. It has been reported that porfimer sodium is effective in treating human non-small cell lung cancer tumors to a depth of 6 - 10 mm [22].

Conclusion

In conclusion, the PDT approach is very effective in treating certain types of cancer. The PDT technique will be involving the light and a photosensitizer used in an oxygen dependent process which initiate the oxidative stress, inflammation and cell death. The specific wavelength of the light will be activating the photosensitizers, which will cause the cytotoxicity effect on the cancer cells. One of the advantages of PDT approach, the repeated treatment will not cause any resistance to the treatment. The optimal light is very crucial in order to achieve the most effective PDT approach. However, the research on PDT is still a hope as an adjunct technique in cancer treatment.

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