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REVIEW ARTICLE

Photodynamic combinational therapy in cancer treatment

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Summary

Photodynamic therapy (PDT) has attracted widespread attention in recent years as a non-invasive and highly selective approach for cancer treatment. PDT involves the activation of a photosensitizer by an appropriate wavelength of light, generating transient levels of reactive oxygen species (ROS). However, the utilization of PDT against deep tumors has been greatly limited by insufficient luminous flux and the occurrence of peripheral tissue damage. Therefore, experts have begun to explore whether the combination of PDT with other treatments can improve its efficacy. In this review, we have collected articles about experiments (in vitro and in vivo) and clinical research on photodynamic combination therapies in recent years, roughly divided into four parts corresponding to PDT combined with chemotherapy, radiotherapy, immunotherapy and other therapies, to compare the therapeutic effects of the combination therapy and monotherapy. The results showed that photodynamic combination treatments, in general, perform better than single treatment modalities. Thus, the increased therapeutic effects, reduced side effects and coordination treatment effects of PDT are worth of further exploration.

Key words: *combination therapy, curative effect, malignant tumor, photodynamic therapy*

Introduction

PDT, as a local treatment, has attracted increasing attention in recent years. The principle of this approach is the use of a light-sensitive material (photosensitizer) with a difference in affinity between tumor tissue and normal tissue [1], resulting in a higher photosensitizer concentration in the former than in the latter. Under laser irradiation, the photosensitized tissue can produce singlet oxygen and free radicals to damage cells, thereby interfering with the growth of tumor cells and leading to their death [2]. Currently, PDT is widely used in the treatment of cancers, such as oropharyngeal cancer, esophageal cancer and cutaneous carcinoma. However, the weakness of laser penetration [3] and the toxicity of photosensitizers can affect the application of PDT in clinical tumor treatment [4,5]. To improve the therapeutic effect of PDT, increasing numbers of attempts have been made to combine PDT with other traditional cancer therapies, including chemotherapy, radiotherapy, immunotherapy, and enzyme inhibitors. In this article, we summarize the recent experimental and clinical research progress on photodynamic combination therapies in cancer treatment.

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Anti-tumor mechanism of PDT

Under laser irradiation, the selective use of photosensitizer can influence biochemical functions, causing the oxygen molecules that exist in tumor tissue to form ROS, which then exert toxic effects leading to necrosis and apoptosis of tumor cells [6,7].

Microvascular injury, thrombosis, vascular embolization, and lesions in tumor tissue can be induced by light irradiation at the peak concentration of the photosensitizer. These vascular lesions would eventually lead to tumor ischemia and necrosis to a degree related to the photosensitizer concentrations in the vascular endothelial cells of the tumor [8,9].

The strong inflammatory reaction provoked by PDT will stimulate the proliferation of the immunocytes such as neutrophils, macrophages and lymphocytes. These cells can rapidly infiltrate into the tumor tissue to elicit specific immune responses against tumor cells [10-13]. Gollnick [14] found that the amount of tumor antigen induced by PDT is sufficient to generate an anti-tumor immune response. Homogenate, a tumor antigen made from tumor tissue by using PDT to inoculate BALB/c mice, can significantly restrain the growth of cancer cells without the help of any immunological adjuvant, indicating that PDT can independently induce a strong anti-tumor immune response.

PDT in combination with chemotherapy

Chemotherapy, one of the main methods for the treatment of tumors, is widely used to treat a wide variety of tumors. The anti-tumor mechanism of chemotherapeutic drugs is generally believed to involve binding to the DNA of tumor cells to inhibit the process of cell division and thereby prevent DNA replication, eventually leading to the death of the cancer cells [15-17]. Although these drugs can kill cancer cells to some extent, chemotherapy also has severe side effects on the whole body because of the non-specificity of the drugs and is susceptible to drug resistance, which limits its clinical application. To overcome theadverse effects and resistance to improve the therapeutic effect, many attempts have been made to combine PDT with chemotherapy. Some better effects of PDT combined with chemotherapy are shown conclusively in Figure 1.

PDT combined with chemotherapy may result in a synergistic anti-tumor effect and reduce the therapeutic dose of the chemotherapeutic drugs. Numerous studies [18-22] have demonstrated that combining PDT with chemotherapy can increase

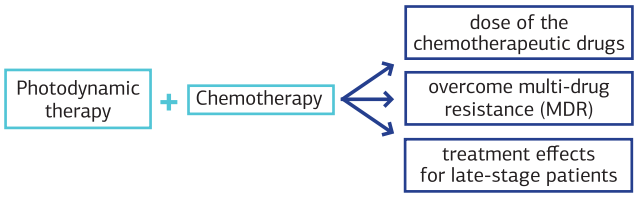

Figure 1. Effects of PDT in combination with chemotherapy.

the therapeutic effect, although the mechanisms behind this enhancement remain unknown. Bano [23] found that the combination of doxorubicin (DOX) with nickel oxide nanoparticles (NOPs) in the form of NOP-DOX@BSA-FA (a potential PDT agent) resulted in higher rate of cell death than the use of NOPs alone. Casaba [24] showed that low-dose treatment with adriamycin (ADM) before PDT could induce a significant increase in the lipid peroxidation (LPO) product, malondialdehyde, whereas a high-dose regimen did not alter the LPO concentration. The relative stabilization of hydroperoxides and other ROS generated during the PDT process could partly explain the increase in LPO caused by pretreatment with a low dose of ADM. LPO is the oxidative degradation of lipids. Free radicals remove electrons from the lipids in cell membranes, resulting in cell damage. LPO is a good indicator of cell damage by free radicals in chemotherapy. Xiaojun Wang [25] found that using the 1O2-responsive nano-carrier NOP-DOX@BSA-FA as a delivery system in PDT combination chemotherapy enables DOX to easily reach tumor sites to effectively kill cancer cells and thereby decreases the side effects of chemotherapy on the body. Husain's study [26] suggested that the genotoxicity of cisplatin can be significantly reduced and blunted in epidermal keratinocytes by PDT using riboflavin as a photosensitizer.

Combining PDT with chemotherapy may overcome multi-drug resistance (MDR) produced during tumor treatment. In general, MDR is mainly associated with the overexpression of P-glycoprotein on the surface of tumor cells and thus can be induced by a short-term application of chemotherapeutic drugs. Khdara [27] found that methylene blue-mediated PDT combined with adriamycin exhibited strong cytotoxicity against drug-resistant tumor cells because a high concentration of DOX was present in the resistant cells after PDT. At the same time, the decline in the expression of P-glycoprotein and the mass accumulation of ROS in the tissue eventually result in necrosis or apoptosis of drug-resistant tumor cells.

Photodynamic combination therapy has some advantages in improving treatment effects for

late-stage patients. The majority of cancer patients are diagnosed at late stages with advanced tumors for which curative surgery is impractical. These patients can choose only palliative treatment to improve their quality of life and survival time. Wentrup [28] studied 68 patients with hilar nonresectable cholangiocarcinoma (NCC) treated with either PDT plus chemotherapy (PDT-C) or PDT monotherapy (PDT-M). The mean survival time was 374 days in the PDT-M group (n=35) and 520 days in the PDT-C group (n=33, p=0.021). The study indicated that the combined treatment group had better outcomes than the solo group. Kimura [29] chose 12 patients (8 male, 4 female) with advanced non-small cell lung carcinomas who were contraindicated for operations to undergo PDT combined with chemotherapy for local control of the intraluminal lesions. The median stenosis rates before and after treatment were 60% and 15% ($p<0.05$), respectively. The data demonstrated that PDT combined with chemotherapy could improve the quality of life and relieve bronchial obstruction in patients with advanced non-small cell lung cancer.

PDT combined with radiotherapy

Local tumor radiotherapy with X-rays is one of the effective anti-tumor methods. Approximately 60-70% of patients with malignant tumors need to receive radiation treatment. In general, the therapeutic rate of radiotherapy alone in patients with early skin cancer, cervical cancer, or lymphoma and nasopharyngeal carcinoma (NPC) can be as high as more than 90%. The 5-year survival rate for patients with early esophageal cancer, rectal cancer, or head and neck cancer who receive radiotherapy alone can reach more than 50%. In addition, palliative radiotherapy for patients with advanced cancer can alleviate the symptoms, relieve pain and increase survival time. However, the nonspecific nature of radiotherapy can lead to varying degrees of damage to normal tissues in the radiation field. Moreover, hypoxic cells inside tumor tissues may exhibit resistance to radiotherapy [30]. Hence, more studies are still required to find new approaches to enhance the tumor sensitivity to radiotherapy, improve its efficiency and shorten the time of radiotherapy or reduce the radiation dose. Some promising results can be found in Figure 2.

PDT combined radiotherapy for patients with advanced tumors can significantly improve the quality of life, alleviate the symptoms, relieve pain, and prolong survival [31]. Yi-shan Wang [32] investigated the effect of PDT combined with radiotherapy in 90 cases (32 cases of gastric cancer, 12 cases of esophageal cancer, 24 cases of rectal cancer, 8 cases of bladder cancer, 6 cases of cervical cancer, and 8 cases of superficial tumors) of surgical failure or patients for whom surgery was not indicated and had cavity or superficial middle-late malignant tumors. The results showed that PDT combined with intensity-modulated radiotherapy (IMRT) clearly alleviated symptoms, thereby improving the quality of life of patients with middle- and advanced-stage malignant tumors, especially for cavity viscera patients. In addition, combination therapy improves palliative care for patients with malignant tumors for whom radiation and chemotherapy have failed and who have obstructive symptoms.

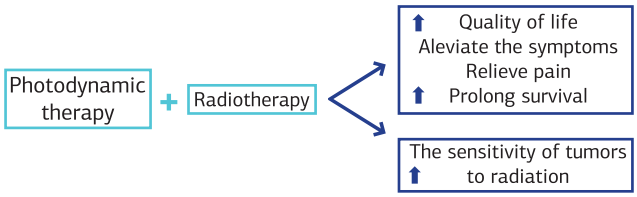

Figure 2. Effects of PDT in combination with radiotherapy.

PDT has high efficiency, low toxicity, and selectivity in the treatment of tumors, though its mechanisms differ from those of radiotherapy. Hence, there is no crossresistance between these two treatment methods, which is a favorable foundation for combination therapy. Studies [33,34] have shown that PDT combined with radiotherapy can increase the sensitivity of tumors to radiation and improve the effectiveness of treatment. At the same time, it can also shorten the exposure time or reduce the radiation dose. Sazgarnia [35] demonstrated that mitoxantrone (MX), a photosensitizer used in PDT, is also a radiotherapy sensitization agent. The adverse effects of radiotherapy were partially reduced, with no reduction in the efficacy of treatment when MX was used as a sensitizer, followed by combination treatment with ionizing radiation and PDT.

PDT combined with immunotherapy

The immune response caused by PDT plays a vital role in preventing metastasis and recurrence of the tumor. The mechanism of these processes is complex and involves almost all aspects of the immune system. Therefore, every point of the immune system may become a target for the treatment. By designing corresponding PDT agents specific to the immune target, it is possible to enhance the anti-tumor immune effect of PDT and reduce the side effect of immune response inhibition.

PDT-generated lysates can activate dendritic cells (DCs) and T cells to express IL-12, thus enhancing the host anti-tumor immune response. Gollnick [14] proposed that PDT-generated tumor cell lysates were potent vaccines, which would be more effective than other forms of whole tumor vaccines. Mladen Korbelik [36] identified PDT-treated SCCVII cells derived from head and neck squamous cell carcinoma, which can be used for the vaccination of SCCVII tumor-bearing mice, and the administration of calreticulin to the cells before injection into mice could produce improved therapeutic effects. However, recent data from clinical trials indicate that vaccination rarely yields significant benefits for cancer patients in terms of tumor progression and long-term survival [37,38]. Yuanhong Zheng [39] found that tumor cells adapted to the immune pressure and exhibited enhanced tumorigenic and stemlike phenotypes after treatment with PDT-mediated vaccination.

PDT combined with monoclonal antibodies (MAbs) can improve the specificity of photosensitizers and reduce their undesired side effects. Conventional photosensitizers are mostly non-specific and usually cause damage to normal tissues. To solve this problem, the combination of PDT with MAbs is now being studied. Hisataka Kobayashi [40-43] used a photosensitizer conjugated to MAbs targeting epidermal growth factor receptors (EGFRs), which led to deeper tissue penetration and specific targeting and thus resulted in eradication of the tumor. When combined with checkpoint inhibitors (PD-L1/PD1), PDT mediates the regression of both lightirradiated primary tumors and non-irradiated distant tumors by inducing a strong tumor-specific immune response [44].

The serum of animals treated with PDT exhibits adaptive immunity, which could induce an immune response that suppresses the growth of homologous transplantation tumors in animals [45,46].

PDT combined with an immunological adjuvant represents a novel modality: laser immunotherapy (LIT). Indocyanine green (ICG, a light-absorbing dye), glycated chitosan (GC, a new immune adjuvant) and a near-infrared laser are the main components of LIT. LIT is a novel modality extended from PDT to induce personalized tumor-specific immunity. Recent experimental studies [47,48] show that ICG and GC in combination with PDT produce better therapeutic effects than PDT alone. Moreover, the immune stimulation ability of GC is stronger than that of several other common immune adjuvants.

Combining PDT with an immunological adjuvant can also increase the effectiveness of PDT. The cell walls of mycobacterium extract (MCWE) is a nonspecific immune activation agent. Korbelik [49] found that PDT combined with MCWE can clearly increase the activity of immune cells. Complement activation agents also have potential for PDT combination therapy. The combination of PDT with complement activation agents, such as the local application of yeast polysaccharide to a tumor or the systemic application of streptokinase, can enhance the therapeutic effect of PDT and reduce tumor recurrence [50].

Currently, the preparation and application of DC vaccines has become one of the most exciting developments in cancer immunotherapy. DCs are considered the most powerful professional antigen-presenting cells (APCs), which are specialized in the uptake, transport, processing and presentation of antigens to T cells. DCs can promote the activity and development of native T cells [51,52]. Jie Ji [53] found that DC vaccines generated in apoptotic squamous carcinoma cells (SCCs) induced by ALA-mediated PDT can inhibit the growth of SCCs in mice. The results indicated that immunogenic apoptotic cells can activate anti-tumor adaptive immunity and lead to DC vaccine-based cancer immunotherapy.

Several effects of PDT combined with immunotherapy found recently are summarised in Figure 3.

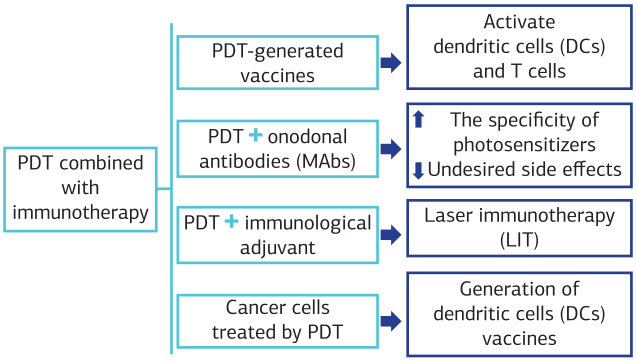

Figure 3. Effects of PDT in combination with immunotherapy.

PDT combined with other therapy

PDT combined with enzyme inhibitors, such as Dickkopf 3 (Dkk-3) [54], a Wnt signaling inhibitor, glycolytic inhibitors 2-DG and 3-bromopyruvate (3-BP) [55] and EGF-SubA, a kind of GRP78-targeting subtilase cytotoxin [56], can block metabolic cycles at any stage to enhance the effect of PDT, and PDT combined with photothermal therapy can release vibrational energy (heat) to kill the targeted cells. Combining the two phototherapy techniques can reduce side effects and improve selectivity [57,58].

Discussion

Chemotherapy, radiotherapy, immunotherapy, and surgery, as the basic methods for cancer treatment, have been widely used to treat various tumors and have achieved modest to excellent results. However, problems still exist, such as the toxic side effects and tolerance of chemotherapeutic drugs, the radioactive damage induced by radiotherapy, and the weak efficacy of immunotherapy, which have limited the therapeutic effects of cancer treatment and reduced the patient quality of-life. Hence, a new way to mitigate these problems must be found.

PDT, as a non-invasive treatment method of tumors, is more specific to its target and causes less damage to the surrounding normal tissues than its alternatives. Direct toxicity to tumor cells, damage to tumor blood vessels, and anti-tumor immunological effects are the main mechanisms of its beneficial effects.

In this article, we summarized the results of combinational PDT in recent years. Better effects can be obtained by combining PDT with other conventional treatment modalities. PDT combined with chemotherapy can reduce the dose of chemotherapeutic drugs, overcome the MDR of tumor cells, increase the survival rate and improve the quality of life significantly. In addition, PDT combined with radiotherapy can meaningfully improve the quality of life and increase tumor sensitivity to radiotherapy. With the help of anti-tumor immune agents, PDT can reach local primary tumors to inhibit resistance, even fighting metastasis and preventing tumor recurrence. The activation process may be associated with the PDT dose, the strength of the inflammatory response, and the release of the target cell antigen in response to PDT and may also be involved in the positive regulation of immune cells. Promoting the expression of tumor-specific antigens induced by PDT, in combination with the use of PD1/PDL1, has been suggested to aid in the development of novel vaccines for the prevention and treatment of cancers.

Despite the better anti-tumor effect observed for the combination of PDT and other therapies, PDT still has some limitations: The first and most severe problem is that experiments and clinical studies on photodynamic combinational therapy are scarce and cannot provide reliable evidence for clinical application. More animal studies and clinical trials are needed to remedy the lack of sufficient valid studies in this field. Second, more studies are required for comprehensive illumination of the mechanisms of the improved therapeutic effects of PDT combination therapy. Third, the weak penetration of PDT has not been solved, which limits the application scope of combined treatment. More studies should be performed to identify the most effective photosensitizers and light source technologies.

In summary, our study suggests that combining PDT with other therapies might offer a significant survival benefit by reducing side effects, improving quality of life, and increasing the anti-tumor effects. As discussed earlier, combinations of PDT with radiotherapy, chemotherapy and immune agents will provide new opportunities for tumor treatment.

Conflict of interests

The authors declare no conflict of interests.

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