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REVIEW

A Comprehensive Review on Photodynamic Therapy (PDT) and Photothermal Therapy (PTT) for Cancer Treatment

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SUMMARY

Cancer is a group of diseases characterized by uncontrolled and abnormal cell growth, leading to serious health consequences. Although various approaches are available for treating cancer, including chemotherapy, surgery, radiation, and immunotherapy, the severe adverse effects of these approaches limit their clinical effectiveness. New cancer treatment strategies including phototherapy uses light to treat cancer, which has attracted wide interest in the oncology research community. There are two types of phototherapy: photodynamic therapy (PDT) and phototherapy (PTT). PDT requires the administration of a photosensitizing agent and light exposure at a particular wavelength. On the other hand, PTT uses a photothermal agent that activates and kills cancer cells at a longer wavelength of light; hence, it is less energetic and, therefore, less harmful to other cells and tissues. PTT is gaining tremendous popularity because of its limited side-effects. A significant downside of PDT is that the photosensitizing drug stays in the body for a long time, which renders the patients extremely sensitive to light exposure. PDT is useful for the treatment of lining organs as they are can be easily reached by the light source. Although PDT is helpful for treating lining organs, its potential side-effects have been reported in the treatment of skin mouth esophagus and lung cancer, among others. Therefore, PTT remains a good alternative for cancer treatment.

Keywords: Cancer; photodynamic therapy; photosensitizing agent; photothermal agent; photothermal therapy.

Introduction

Cancer is a disease of uncontrolled cell division caused by gene damage that regulates the cell growth and cell division. Cancer is initiated with a localized disease, but then it spreads to distant locations in the body (metastasis), which makes cancer incurable. Cancer ranks second as the world's leading cause of death. Every year, more than 10 million people are diagnosed with cancer.[1-3] There are various treatment strategies available to combat cancer, depending on its intensity and type. For instance, surgery helps to remove tumors or cancer mass. Chemotherapy uses drugs to kill targeted cancer cells. Radiation therapy, bone marrow transplant, immunotherapy, hormone therapy, targeted drug therapy, and cryoablation are some of the other treatment options available to treat cancer. Although these treatments have been found to be effective in several cases, they also lead to severe side-effects. Therefore, there is an urgent need to find the best suitable treatment for cancer that has better potency and no or minimum side-effects. Phototherapy (PTT) is a modern cancer-care technique. PTT is a less-invasive and potentially useful alternative for cancer treatment. PTT is performed via activation of photosensitizing agents using pulsed laser irradiation at near-infrared (NIR) region to generate heat for the

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thermal ablation of cancer tumors with a limited penetration into the surrounding healthy tissues. Unlike PTT, photodynamic treatment (PDT) primarily uses photosensitizers (PSs) that are activated with light of a sufficient wavelength to transform the molecular oxygen into cytotoxic reactive oxygen species (ROS), such as a singlet oxygen, which, in effect, kills the cancer cells through oxidative stress, eventually causing cell death. A huge demerit of PDT is that the photosensitizing drug remains in the body for a long time, which makes the patient extremely sensitive to light.[4,5] Advances in phototherapy, including the use of nanomaterials such as carbon nanotube, graphene, gold nanoparticles, and quantum dots, provides advantages of targeted therapy, deep penetration, specific phototherapy, wide exposure area, and extended exposure time. PDT and PTT combination is also fast emerging for its synergistic effects to aid as an adjuvant treatment strategy along with chemotherapy and radiation.

Photodynamic Treatment (PDT)

Light has been used for therapy since the past 3000 years.[6,7] Ancient Egyptian, Indian, and Chinese cultures used light to cure numerous conditions, including psoriasis, rickets, vitiligo, and skin cancer.[8] Niels Finsen invented PDT in the 19th century. More than 100 years ago, scientists discovered that combining light and chemicals can induce cell death.[9] PDT comprises two components, a PS and a light source (usually in the red spectral zone, as red light penetrates deeper into the tissue), for cancer diagnosis. The benefit of PDT is that it can be repeated multiple times without producing any immunosuppressive and myelosuppressive effects and that it can be administered even after radiotherapy, chemotherapy, or surgery.

Photosensitizers

An optimal PS agent should be a single pure compound that allows quality assurance research with low production costs and reasonable stability. An ideal PS agent should have a high absorption peak in the range of 600 to 800 nm (red to dark red) as photon absorption with a wavelength >800 nm does not have adequate energy to excite oxygen to its single state and achieve significant yield. For example, chlorines, bacteriochlorins, and phthalocyanine can provide improvement in tumor regulation. In addition, penetration of a dark-red light into the tissues with suitable wavelength agents helps in reducing toxicity and in rapid removal from healthy tissues, thereby decreasing the phototoxic side-effects.[10] Since the delay between drug administration and light irradiation is usually long, the sensitizer provides ample time to disperse from the healthy tissues. It is hence proposed that the tumor response is often more reliable when light is delivered at a shorter intermediate drug-light. Simultaneously, PS is already present in the arteries, which can result in significant vascular damage.[11]

Some past studies have suggested that a marked inflammatory response and necrotic cell death after illumination is essential for the immune-stimulating role of PDT.[12] On the other hand, it has been suggested that PSs that induce more apoptosis and that less inflammation is appropriate for applications such as for brain tumors, where swelling is undesirable. The first PS used for cancer therapy was a water-soluble porphyrin mixture called the hematoporphyrin derivative (HPD), a refined porfimer sodium form, which later came to be known as photofrin.[13-14] Some PSs have been used to treat cancer (Table 1).

Mechanism of Action

PS can deliver through various means, such as via topical and intravenous injections. However, the change in biodistribution over a period of time gets affected; another way to control the impact of PDT is the time of light exposure. The light absorption (photons), the sensitizer, is converted into a short-lived, excited single-state form from its ground state (a single state) to the long-lived electronically excited state (a triplet state). This new triple-state responds in two ways. First, it reacts directly to the substrate, such as the cell membrane or a molecule, and transfers the atom of hydrogen into radicals. When these radicals interact with oxygen, oxygenated products (type I reaction) are formed. Alternatively, the triplet-state form can directly transfer its energy to oxygen, thus converting the singlet oxygen into a highly ROS (type II reaction). While nearly all effects of PDT drugs are oxygen-dependent, photosensitization typically does not occur in the tissue's anoxia region. Past *in vivo* studies have shown that induction by clamping of tissue hypoxia eliminates the porphyrin's PDT effects.[15]

The types mentioned are formed through specific mechanisms I and II, which are performed simultaneously,[15] which in turn depends on the type of sensitizer used and the substrate and oxygen concentration. These factors rely on the substrate sensitizer's binding affinity. Types I and II reactions occur simultaneously. The ratio between Types I and II reactions depends on the type of sensitizer, the substrate, the oxygen concentration, and the binding affinity of the substrate sensi-

Table 1 Photosensitizers used in PDT

Sensitizer	Trade name	Cancer type	Wavelength
HpD (partially purified), porfimer sodium	Photofrin	Endobronchial, oesophageal, bladder, gastric cancers, cervical, and brain tumors.	630 nm
BPD-MA	Verteporfin	Basal-cell carcinoma	689nm
m-THPC	Foscan	Neck and head tumors, prostate and pancreatic tumors.	652nm
5-ALA	Levulan	Head and neck, Basal- cell carcinoma gynaecological tumours.	635nm
5-ALA-methylesther	Metvix	Basal-cell carcinoma	635 nm
5-ALA benzylesther	Benzvix	Gastrointestinal carcinoma	635 nm
5-ALA hexylesther	Hexvix	Diagnosis of bladder tumors	375–400 nm
SnET2	Purlytin	Basal-cell carcinoma, cutaneous metastatic breast cancer, basal-cell carcinoma, Kaposi's sarcoma, prostate cancer	664 nm
Boronated protoporphyrin	BOPP	Brain tumors	630 nm
HPPH	Photochlor	Basal-cell carcinoma	665 nm
Taporfin sodium	Talaporfin	Solid tumors from diverse origins	664 nm

HPD: hematoporphyrin derivative; BPD-MA: benzoporphyrin derivative-monoacid ring A; mTHPC, meta-tetrahydroxyphenylchlorin; 5-ALA, 5-aminolevulinic acid; SnET2: tin ethyl etiopurpurin; HPPH: 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide- alpha.

tizer. PDT influenced only the cells near the ROS production site (such as the PS location sites), owing to the short half-life and the high reactivity of ROS.

Single oxygen has a half-life of <0.04 μs in the biological systems. Thus, the action radius of a single oxygen is <0.02 μm of photo-damage, and the cytotoxicity is multifactorial and linked to the sensitizer size, its extracellular or intracellular position, total administered dosage, the total dose of light exposure, light fluidity, availability of oxygen, and the time between the drug administration. These factors are all interrelated. The PDT[14] mechanism is summarized in Figures 1 and 2.

Effect of PDT on Tumor

PDT mediates tumor destruction in 3 main ways. First, PDT-generated ROS directly destroy tumor cells and damage the tumor-associated vasculature, leading to tumor infarction. PDT eventually activates the immune response to tumor cells. The three forms can also impact each other. The long-term tumor control involves a combination of all these components.[16]

The German scientist Friedrich Meyer-Betz became the first one to treat humans with porphyrins in 1913. He tested his skin for the symptoms of applying 200 mg hematoporphyrin. In the skin areas exposed to light, swelling and pain were recorded.[17] In 1975, Thomas Dougherty and colleagues reported that the administration of the derivative hematoporphyrin and red light in mice led to total breast tumor destruction. In the same year, J. F. Kelly and colleagues reported that hematoporphyrin light activation could abolish bladder cancer in mice.[18,19]

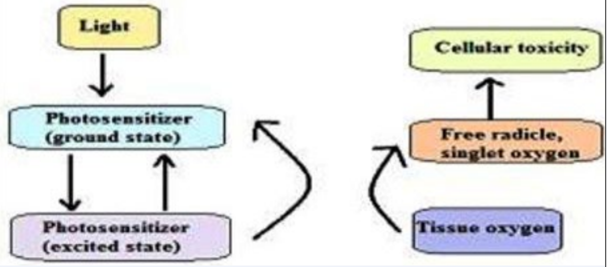

Fig. 1. Mechanism involved in PDT.

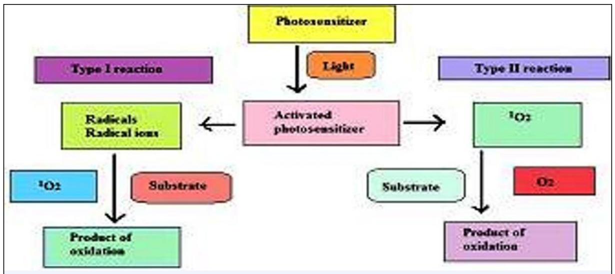

Fig. 2. Type I and type II reaction in PDT.

Limitations of PDT

PDT only treats the area where the light source is accessible, hence this treatment is mainly suitable for the lining organs, where the light source can reach, considering that light cannot travel very far through the body tissues. PDT cannot be used to identify large cancers and cancers that spread to the majority of locations. The types of PS used in PDT remain in the body for longer, which makes the patient more sensitive to light for a short while. Hence, caution should be undertaken after the PS has been inserted into the body.[20-24]

Phototherapy Therapy (PTT)

Since the 18th century, thermal treatments for cancer cells were known. Hyperthermia is the elevation of temperature above the physiological levels, typically to values of 40–45°C. The main goal of hyperthermia is to create an environment that facilitates eradication of tumors and spares the normal tissues involved in cancer treatment. Hyperthermia achieves this by instigating direct cytotoxic effects and physiologic effects. Clinically, hyperthermia can function synergistically with both radiation and chemotherapy. Cancer cells get subjected to permanent damage during hyperthermia as a result of degradation of the cell membrane and protein denaturation. However, this therapy often affects the normal tissues. Incorporating laser radiation treatment into cancer therapy can facilitate applicability of photothermal treatment for more selective cancer treatment.

As a consequence, laser-induced hyperthermia seems helpful for the treatment of retinal or choroidal tumors. The significant downside of this treatment is the need for a high-power laser to destroy the tumor cells. Meanwhile, a PTT with a photothermal agent has been proposed selectively for heating. A biocompatible photothermal agent with a high absorption coefficient, an NIR light source, and an NIR region is the primary requirement for PTT. The temperature increase in the PTT depends on the absorption of the NIR wavelength and the light-excitation coefficient. PTT alone or in combination may kill cancer cells in either the primary tumor or in tumor at the early metastasis stage. However, with the following methods, PTT offers an essential advantage in reducing metastasis in several cancer types:

1. **Direct removal of cancer cells with PTT:** NIR laser can penetrate soft tissues up to 2 cm. PTT on NIR-laser irradiation causes ablation of the primary tumors or lymph node metastasis;[25-29] it may also damage or destroy primary tumor cancer cells. It also kills the cells that trigger tumors and stem cells responsible for causing cancer, thereby preventing their metastasis to another organ.[30-32]
2. **Imaging Guide:** The image guidance offers details for an improved therapeutic regimen with PTT for the safety and efficacy of photothermal ablation.[33] Multimodal imaging (such as X-rays, computed tomography [CT], photoacoustic imaging, and magnetic resonance imaging) may be applied to assess the position of metastasis of the lymph node and to refine the therapeutic regimens throughout PTT. The current technique is limited to mapping lymph node metastasis, which is unusual in metastasis imaging of the brain, liver, and lung deep tissues. X-ray CT and photoacoustic imaging include image-guided PTT metastasis of cancer.[34-35] Using nanorods of bismuth sulfide (B2S3), Zhao et al. recently developed a theranostic framework for multimodal imaging-guided cancer metastasis. Such nanorods can be used to track their real-time distribution in the tumor sites for CT contrast agents for angiography and organic imaging. For instance, Bi2S3 nanorods can ablate the primary tumor with a Near infrared (NIR laser and thereby prevent further lung metastases. Li et al. developed copper-labeled copper sulfide nanoparticles and used it in combination with PTT for metastatic breast cancer radiotherapy. The use of PTT in radiotherapy prevents tumor development and increases the survival rate of the treated patients.[36]
3. **Combination of PTT in chemotherapy:** Chemotherapy is commonly used to treat cancer with metastasis.[37] Recently, scientists observed the synergistic effects in cancer metastasis, with the application of combined PTT and chemotherapy. Gold nanostructure and doxorubicin (DOX) have been used in chemotherapy, mainly for treatment of cancer . DOX used in chemotherapy as an anticancer drug and gold nanoclusters or nanorods as the photothermal agent in PTT, provide a synergistic combination therapy. Recently, gold nanorods primed for combination therapy in metastatic breast cancer were wrapped with DOX-loaded DNA after NIR radiation, this combination therapy with gold nanoparticles and doxorubicin nanoparticles significantly inhibited the growth of breast tumor and lung metastasis.[38] Moreover, DOX-powered mesoporous magnetic gold nanoclusters for the combination of PTT in breast cancer metastasis chemotherapy were prepared by Qian et al. Nanoclusters can be effectively applied to target tumor

sites in breast cancer model 4T1 by using an extra-magnetic field. The use of combination therapy effectively prevents pulmonary and mediastinal metastases, which contributes to animal survival.[39]

4. **Gold nanostructure as photothermal agents in cancer treatment:** Gold nanoparticles have been used owing to their simplicity in preparation, bioconjugation, nontoxicity, and inert nature.[23] Gold nanoparticles are useful as imaging agents, heat-absorbents, and therapeutic agents. Gold hyperthermic-based nanoparticles have shown promising outcomes in animal research, and the study on their applicability in early clinical trials are underway. Gold nanoparticles possess unique optical properties that are useful in photothermal and ultrasensitive detection. As light falls on gold nanoparticles at a particular wavelength, the conduction band on the surface of the gold nanoparticles oscillates with one another, producing a phenomenon known as the surface plasmon resonance. This phenomenon heats the light, which is emitted by gold nanoparticle. The wavelength of light at which particles disperse and light energy is absorbed depends on the shape, size, and composition of nanoparticles. Changing the size and shape of gold nanoparticles can also alter the peak, which is tunable in the NIR region, which penetrates the tissues more effectively than other light regions.[40] Gold nanostructure diagram is depicted in Figure 3.
5. **Advantages of gold nanoparticles in the treatment of cancer**: It can be administered in specific areas so that the chances of nonspecific distribution is reduced. It can penetrate deep into the biological tissues. By creating gold nanoparticles, it enables the delivery of drugs through passive transportation (i.e., it improves permeation and retention effect) and is safe to excrete via the urinary system.[41]

Gold Nanospheres

It is possible to synthesize gold nanosphere of size 2-100 nm (in diameter) via reduction of HAuCl4 using specific-reducing agents. Citrate is commonly used as a reductive agent. The size of the nanosphere can be modified by adding citrate/gold in 1:1 ratio. Several methods have been investigated for the synthesis of gold nanoparticles using various reducing agents.[42] Pitsilides et al. used light-absorbing microparticles and nanoparticles for the treatment of cancer cells, including iron oxide microparticles and gold nanospheres. In the presence of gold nanospheres, the radiation of lymphocytes with laser (20 ns) increases the plasma membrane permeability, which results in cell death.[43]

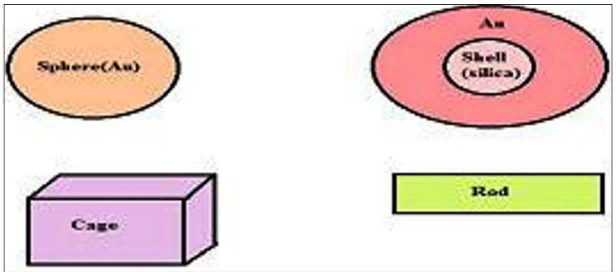

Fig. 3. Gold nanosphere, nanoshell, nanorod, nanocage.

Gold Nanorods

Gold nanorods are synthesized using a template method based on the electrochemical gold deposition in nanoporous polycarbonate or alumina template membrane pores.[44] The nanorod length is managed by depositing gold in the membrane pores. The downside of this approach is that it generates only a small amount of nanorods. Narrow absorption band and a higher two-photon luminescence than nanospheres and nanoshells are the characteristics of gold nanorods. Hence, two-photon luminescence method provides a reliable, label-free approach for three-dimensional (3D) cancer diagnostics.[45]

Gold Nanoshell

Gold nanoshell consists of an inner layer of silica and an outer layer of gold. Gold nanoshells are prepared by producing *in situ* gold nanoparticles with the core-shell cells acting as thermo-sensitive templates.[46] Silica cores are prepared from ethanol by reducing tetraethyl orthosilicate. The plating of silica nanoparticles in gold is achieved in an aqueous environment using the method of seed production. This tiny nanosphere is connected to the silica core and is used as an amine-finished silane liner molecule, which allows the extra gold to be reduced to a full shell. The diameter of the gold nanoshell depends on the silica core diameter, and its thickness can be regulated by the amount of gold accumulated on the core surface.[47] West and colleagues used gold nanoshells to operate on PTT in both dark-field imaging and in the treatment of HER-2-positive breast cancer cells, SKBr3. The researchers conjugated gold nanoshells with the antibody. Nanoshells with a laser NIR at 80 mW/cm^2 destroyed the targeted tumor cells for 7 min while the cells without nanoshells remained unaffected. In the region of laser exposure, cell damage was restricted, indicating a high localized thermal effect.[48]

Gold Nanocages

Truncated silver nanotubes and aqueous HAuCl4 are used as galvanic substitutes to produce gold nanocage. With regulated morphologies, silver nanostructures can be formed via polyol reduction, where ethylene glycol reduces AgNO3 to form silver atoms, and then nanocrystals or seeds. The combination of silver atom and seed produces nanostructure by manipulating the crystalline structures of silver seed in the presence of vinylpyrrolidone, a polymer that can selectively bind to the surface. Silver nanostructures can be used as a sacrificial template often converted by galvanic substitution reaction into gold nanostructures with hollow interiors. The wall thickness and the size of the gold nanocages can be controlled by changing the molar ratio of silver to $HAuCl_4$.[49]

Xia and colleagues used PTT gold nanocaps to treat breast cancer. For targeting purposes, an average edge length of 65±7 nm and an overall absorption target of 800 nm of gold nanocage was combined with a monoclonal antibody (Anti-HER2). Flow cytometry was used to measure the number of gold nanocages immobilized per cell and the photothermal effect. Laser irradiation parameters (such as pulsed NIR laser), including optimum nanocage dose and laser power density and irradiation time, were calculated.[50] These gold nanoparticles showed excellent success in treating cancer. Table 2 indicates the differences between the features of PDT and PTT.

Selection of PDT and PTT for Cancer Type

As PDT is mainly based on drugs that makes cells light sensitive by producing reactive oxygen which further kills cancer cells. Recent studies showed that, PDT and PTT has diversified clinical wide spread applications for treatment of skin, head and neck cancer and also found very much useful in esophageal cancer which much useful compared to he reported treatments.

Moreover, through some studies are undertaken on PTT, the results of clinical trials are not promising compared to PDT. So, PDT treatment against cancer is considered as the best option till date.

Related Research

Phototheranostic Therapy

Phototheranostics means simultaneous diagnosis and phototherapy by using light. In this therapy method, therapy phototheranostic agent is used for diagnostic imaging as well as for killing diseased cells. In this treatment phototheranostic agents upon systemic administration, targets the disease site where it shows illumination that helps to image tissue.

Irradiating light further shows activation of phototheranostic agent which can kills targeting tissues (e.g., Tumor).

Hyperthermia

Hyperthermia is used in treatment of cancer where tissues are exposed to higher temperature. When other cancer therapies combine with hyperthermia it shows synergistic effect. Like In combination of radiation, Immunotherapy, PDT, PTT with hyperthermia. Rational behind this is hyperthermia increases blood flow to the affected area which doubles the perfusion rate and improves delivery of chemotherapeutics/ Phototheranostic agent. It also increases oxygen supply to the cancer cells and thus increases chances of more damage by radiation therapy. In magnetic hyperthermia, magnetic nanoparticles show transformation of electromagnetic energy from an external high-frequency field to heat.

Conclusion

Phototherapy is a promising approach for the treatment of cancer. The elements, advantages, and disadvantages of PDT and PTT are summarized based on our analysis, with a tendency toward favoring PTT. Despite that multiple therapies are available to address the drawbacks of conventional medicine in cancer treatment, PTT has emerged as a promising treatment option. PTT can be used as an imager and for specific targeting. PTT can be

Table 2 Difference between Photodynamic and Photothermal treatment

PDT	PTT
Photosensitizers use as photodynamic agents such as porfimer sodium,Taporfin sodium Boronated protoporphyrin	Phothermal agents such as gold nanoshell, nonorods, nanocages, nanosphere.
It show low penetration into biological tissue	It can deeply penetrate into biological tissue.
PDT is useful for lining organ or problems on or just under the skin.	It can be used to treat different types of cancer.
PDT can't be used to treat cancers that have spread too many places	It can be used to treat metastasis cancer.
The drugs used in PDT leave people very sensitive to light for some time	No sensitivity problem

used alone or in conjunction with other therapies, especially chemotherapy. In animal research, a photothermal agent such as gold nanoparticles have demonstrated hyperthermia, and early clinical research is currently ongoing to study its effects. The major advantage of using PTT is that it can be administered to the targeted site while minimizing nonspecific distribution. Each approach involved in PTT shows promising results.

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