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Advancements in Targeted Drug Delivery System for Photodynamic Therapy in Cancer Treatment

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Abstract

Cancer is a life-threatening disease that claims the lives of 3.4 million people each year around the world. Smoking, being overweight or obese, eating processed meat, radiation, family history, stress, environmental variables, and chance are all factors that contribute to cancer. Surgical excision of solid tumors, radiation therapy, and chemotherapy are the first-line treatments for cancer. The fundamental clinical failure of chemotherapy in cancer treatment is systemic delivery of the free drug, because only a little amount of the drug reaches the tumor site. The majority of chemotherapy Active Pharmaceutical Ingredients (APIs) are extremely cytotoxic to both cancer and normal cells. As a result, focusing on the tumor vasculatures is critical for tumor treatment. Encapsulation of anti-cancer medications within the liposomal system provides secure platforms for the delivery of these drugs in this context.

Keywords: Photosensitizer • Liposomes • Photodynamic • Therapy (PDT) • Nano formulation

Introduction

Cancer is a deadly disease that claims the lives of 3.4 million people worldwide [1]. Cancer risk rises dramatically as people get older, and several malignancies are more common in developed countries. Cancer is caused by a variety of factors, including smoking [2], being overweight or obese, eating processed meat, radiation, family history, stress and environmental factors [3]. The first-line therapy for cancer treatment includes surgery to remove solid tumors, radiation therapy, and chemotherapy [4]. Photodynamic Therapy (PDT) is an alternative approach and it has proved its efficiency in the cancer treatment. PDT widely extended its application in medical field especially in cancer treatment. It is an ablative treatment that kills cancer cells by photosensitizing the tumor with a specific wavelength of visible light [5]. In this review, we are going to see about the different mechanism of Photodynamic therapy with respect to different types of cancer.

Literature Review

History of PDT

Ancient Egyptian, Chinese, and Indian civilizations employed light in combination with reactive chemicals to cure vitiligo, psoriasis, and skin cancer about 3000 years ago [6]. PDT was approved for clinical usage by the US Food and Drug Administration (FDA) 25 years ago, although it is still underutilized in clinical trials [5]. Photodynamic Therapy (PDT) has been widely employed in anti-tumor and anti-infection therapies since porfimer sodium was licensed as the first Photosensitizer (PS) for the treatment of bladder cancer in 1993. This review summarizes the biological and physicochemical features of the drug's clinical application status and prospects.

Concept of PDT

Photodynamic Therapy (PDT), along with Photo Thermal Treatment (PTT) and magnetic hyperthermia, is one of a group of medical methods that uses the response of sensitive chemicals or nanostructures to external stimuli [7]. It is a type of non-ionizing radiation therapy that produces singlet oxygen by combining a photosensitizer with light. When a Photosensitive Photosensitizer (PS) absorbs a photon, it is excited from its ground state level (S_0) to the singlet excited state, which is a more energetic state (S_1). At least two excited states can exist in a photosensitive species: A single and a triplet [8]. Singlet oxygen has anti-cancer properties by causing tumor cells to die in apoptotic, necrotic, or autophagic ways [9]. The harmful effects of the created highly reactive ROS (such as $1O_2$, H_2O_2, O_2, OH) are mediated by irreversible oxidation of the cellular and

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subcellular organelles, which results in apoptosis or necrosis, which leads to cell death.

ROS can also trigger autophagy through a variety of pathways, resulting in cytoprotective and cell-killing effects [10].

The development of free radicles from the transfer of a hydrogen atom to an electron between the excited photosensitizer and substrates results in the production of ROS such as superoxide and hydroxyl radicles in the first process [11]. The efficiency of PDT is influenced by a number of factors. The kind and dose of PS, the mode of administration, the intensity of light employed, the type of tumor, and the concentration of dissolved cytoplasmic oxygen are all factors to consider.

PDT in oncology

For decades, scientists have studied the mechanism of PDT-mediated anticancer action. The majority of photosensitizers used in cancer therapy have a tetrapyrrole structure, which is comparable to that of hemoglobin's protoporphyrin [5]. The fundamental benefit of PDT is that it is a very selective approach for destroying undesired cells and tissues. PDT activates an anticancer immune response in addition to killing the targeted cells and damaging the tumor-associated vasculature [12]. Scientists created a PDT nano-platform based on singlet oxygen responsive micelles for interactively triggered photosensitizer administration that improves anticancer PDT efficacy [9]. However, PDT Nano platforms are still in the early stages of translation and will require more thorough clinical trials before they can be used in the clinic.

Liposome mediated PDT

Liposomes were the first approved class of therapeutic NPs for cancer treatment when they were discovered in 1965[13]. Liposomal compositions are less toxic and have superior pharmacological characteristics than medicines alone. Although they appear to be the top choice for medication delivery systems for a variety of disorders, more research into dosage regimens in terms of dose and duration is needed [14]. To improve liposome pharmacokinetics and their capacity to pass through target membranes, reaching high concentrations inside cells while minimizing toxicity and improving therapy efficacy, ligands can be added to promote efficiency and specifically target injured cells [15]. Liposome qualities are determined by a variety of factors, including lipid content, number of lipid bilayers, size, surface charge, and manufacturing process [16]. The tumor vasculature must be targeted for effective treatment. This can be accomplished by disrupting angiogenesis with antiangiogenic agents (e.g., Axitinib (Inlyta®), Bevacizumab (Avastin®), and Cabozantinib (Cometriq®) or shutting down the existing tumor blood flow with vascular targeting agents (e.g., 5,6-dimethylxanthenone-4-acetic acid (flavonoid derivative) and Combretastatin an as a result, finding a suitably regulated anticancer dosage to control this disease is in great demand, as it is estimated to be responsible for 13.2 million deaths by 2030. The creation of liposomal vesicles has resulted in both regulated and targeted medication delivery (disease-specific localization). Because surgical resection, radiation therapy, and chemotherapy are the first-line treatments for cancer, this characteristic is particularly beneficial in cancer treatment. Chemotherapy must be administered systemically in some malignant conditions. The majority of APIs used in chemotherapy have been found to be extremely cytotoxic to both cancerous and non-cancerous cells. As a result, they are subjected to several adverse effects and restrictions, as the free medicine is injected straight into the circulatory system.

The chemotherapeutic chemical is then taken up by cancer and normal tissues, causing significant toxicity in several body organs like the heart, kidneys, liver, and others [17]. Phosphatidylcholine (zwitterionic), phosphatidylglycerol (negatively charged), phosphatidic acid, phosphatidylethanolamine (zwitterionic), and phosphatidylserine are the most well-known lipids employed in liposomal formulations (negatively charged). Because they interact with the negatively charged deoxyribonucleic acid, positively charged lipids (e.g., N-[1-(2,3-dioleyloxy) propyl]-N,N,N-triethylammonium (DOTMA) and 1,2-dioleoyl-3-trimethylammoniopropane (DOTAP)) are commonly utilized for gene transport (DNA) [18]. Different types of Liposomes are used for the delivery of drug. The different structures. Liposomes containing anionic phospholipids, for example, have a quicker endocytosis rate, which increases their intracellular uptake. Liposomes containing fusogenic lipids are also capable of fusing and penetrating the cancer cell membrane. The mechanisms of liposome cellular internalization were studied in a recent study.

It's worth noting that proteins in the circulation bind to liposomes given systemically, forming a protein corona that interacts with immunoglobulins, complement proteins, and phagocytes in the bloodstream. This would boost the synthesis of cytokines in the tumor microenvironment, resulting in adaptive antitumor immunity. Furthermore, liposome interaction with serum proteins (particularly opsonins) is critical for the quick clearance of liposomes by phagocytes in the blood, liver, and spleen [19].

Discussion

Nano-formulation of PDT for different types of cancer

Lung cancer: With over 2.1 million diagnoses and 1.8 million deaths in 2018, lung cancer is the most common disease worldwide. Surgery is the first line of treatment for lung tumors that are detected early.

However, due to uncontrolled invasion and metastases, surgery is difficult in late-stage lung cancer [20]. Because of the patient's advanced age, significantly compromised lung function, and other comorbidities, more than 20% of early-diagnosed lung malignancies are inoperable. Lung cancer therapy now includes stereotactic body radiation, cryotherapy, and systemic chemotherapy [21]. PDT was first utilized in 1982 to achieve tumor necrosis and airway reopening in Non-Small Cell Lung Cancer (NSCLC). In comparison to other

existing therapy techniques, PDT is thought to be more targeted and lesion-oriented, resulting in less collateral damage and fewer consequences. When patients with early central lung cancer were unable to have surgery to improve their overall quality of life, PDT was tested. In a short retrospective study, PDT was found to be well-tolerated and effective as part of a multi-modal treatment for non-small cell lung cancer (NSCLC). In patients with Carcinoma *in situ* (CIS) and Micro-Invasive Cancer (MIC) of the central airways, hexyloxyethyl devinylpyropheophorbide-PDT was shown to achieve high rates of chemotherapeutic efficacy that lasted for months in a Phase trial. In lung cancer, two ongoing clinical trials are evaluating the safety and efficacy of novel photosensitizers. In one trial, the water-soluble palladium-bacteriochlorophyll WST11 is being studied for its safety and efficacy in obstructive NSCLC (EudraCT ID: 2009-011895-31). WST11 was more effective than prior photosensitizers and had fewer adverse effects due to its quick clearance. Maziak and colleagues conducted a systematic review that thoroughly documented the use of PDT on NSCLC and its drawbacks. PDT may be particularly effective for tiny and superficial airway lesions of less than 1 cm in length, according to the researchers.

PDT has been successfully utilized to treat individuals with early-stage lung cancer who are not candidates for surgery. At 20.2 months, 54 patients with lung cancer who received porfimer sodium-mediated PDT demonstrated an 85 percent total response rate with a 6.5 percent local failure rate in phase II research. Based on outcomes with Photofrin® in 2003, the American College of Chest Physicians suggested that PDT be used exclusively for lesions less than 1 cm in diameter. PDT provides various advantages over traditional lung cancer therapy options, including being less invasive than surgical resection, being more target-specific, having little adverse effects on surrounding healthy tissues, having minor systemic side effects, and being cost-effective. PDT is simple to use, can be done in an outpatient setting, and can be done numerous times on the same area without leaving scars after healing.

Chemotherapies and radiotherapies are both harmful, however the photosensitizer and visible light source are not. Other cancer therapies, such as radiotherapy, chemotherapy, and photo thermal therapy, can be used in conjunction with PDT. PDT, like other lung cancer treatments, has its own set of restrictions. PDT is primarily used to treat localized cancer and cannot be utilized to treat cancer that has spread to other parts of the body. Coughing, uncomfortable breathing, and shortness of breath are all transitory adverse effects of PDT for lung cancer. A drug-light interval is the time between photosensitizer delivery and laser light irradiation. Another drawback of PDT is the 24-96-hour drug-light interval. It is necessary to create efficient photosensitizers that can more precisely target cancer cells, as well as methods for delivering light that can penetrate big or deep tumors tissue.

Breast cancer: Breast cancer is one of the most lethal diseases in women, and it can spread to crucial organs such as the lungs and bones. In her lifetime, one out of every eight women will be diagnosed with breast cancer. Scientists have used targeted PDT to treat HER2 positive breast cancer cells using conjugates of antibody-phthalocyanine-gold nanoparticles. In combination with PDT and PTT, gold nanorods coated with SiO_2 and loaded with Ce6 photosensitizer caused a high cytotoxic impact on MCF-7 breast cancer cells. These results proved that hybrid nanomaterial worked far better compared to the single nanomaterial. Ali ashkbar and group used curcumin as a photosensitizer which has the ability to decrease the inflammation and it is known for anticancer properties. They prepared silica-coated Fe_3O_4 magnetic nanoparticles which were loaded with Curcumin (CUR), as a natural photosensitizer, were injected to the tumor site and CW diode lasers at 450 nm for PDT and at 808 nm for PTT were irradiated on the tumor area for the simultaneous production of hyperthermia and singlet oxygen to improve the treatment process. This *in vivo* studies result concluded that the NC+PDT+PTT strategy might hold a promising substitute for chemotherapy to treat triple-negative breast cancers. Also, Thermosensitive liposome mediated can also be used for treating breast cancer. In this method, Liposomal formulation can be made with DPPC, SoyPC, Chol or SPE-PEG 2000 along with the photosensitizer (PS) ICG. The light intensity for the activation of the photosensitizer is 14 J/Sq.cm. Scientists when treated this with triple negative breast cancer (MDA-MB-468 and HCC-1806 cells) results shows that there is significant cytotoxicity compared to the free PSs. Zwitterion liposomes also made with oly-(12-methacryloyloxy)-dodecyl phosphoryl-choline DSPC. PS used in this study is Methylene Blue (MB) which is a promising anticancer agent. These results also showed the enhanced cytotoxicity effects on breast cancer cells (4T1 cells) with improved safety. These multimodal/ combinatorial systems are anticipated to be promising prospects for improving cancer PDT effectivenes.

Skin cancer: The most frequent type of skin cancer in Caucasians is non-melanoma skin cancer (NMSC). For the treatment of certain kinds of Basal Cell Carcinoma (BCC), Bowen's Disease (BD), and actinic keratoses, Photodynamic Therapy (PDT) is gaining favor (AK). Different types of PDT that is, Topical PDT, Systemic PDT, Daylight PDT and Prophylactic PDT has been used.

Topical PDT: 5-aminolevulinic acid (ALA) and methyl aminolaevulinate are the most regularly utilized topical photosensitizers (MAL). MAL is lipophilic, which means it has a higher penetration and selectivity for target cells than ALA. Protoporphyrin IX absorbs more light in the blue zone, at a wavelength of 410 nm. In practice, however, PDT light sources in the red area often use 630 nm, which allows for improved tissue penetration. MAL is typically applied for 3 hours prior to exposure to the light source, while ALA is often permitted for 14–18 hours, however shorter intervals have been seen.

Systemic PDT: Systemic PDT involves intravenous photosensitizers which allows the deeper penetration of tumors, an important limitation of topical PDT. Porfimer-sodium was the first systemic photosensitizer to be approved, and it's used to treat lung and esophageal cancers. Photofrin®'s half-life (21.5 days) causes widespread photosensitivity for several weeks, resulting in poor patient tolerance and increased severity of adverse skin reactions.

Prophylactic PDT: In mouse investigations, both topical and systemic PDT were found to be beneficial in the prevention of NMSC. In hairless mice exposed to ultraviolet UV radiation, scientists explored the prevention of carcinogenesis with weekly topical ALA-PDT. Despite the delay in tumor formation, the ALA-treated group had a higher rate of big tumors (>4 mm). More recently, it was discovered that preventive treatment with topical hexyl aminolevulinate (HAL 2%, 6%, and 20%) or MAL (20%) delayed UV-induced SCC in hairless mice by 264 and 269 days, respectively.

Daylight PDT: Non-hyperkeratotic actinic keratoses can be treated in the field using daylight-mediated MAL-PDT. Because the red or blue wavelengths required to activate porphyrins are present in daylight, this simplified technique is effective. The non-inferiority of daylight PDT was proven in a major European multi-centre phase III, randomised, intra-individual trial. The results of daylight PDT were unaffected by weather conditions. Researchers demonstrated considerably higher efficacy for face AKs treated with MAL daylight-PDT in a randomised multi-centre Nordic research. For all patients (9.4 Jcm^2), response rates were shown to be independent of the overall mean effective daylight dosage. Smaller studies have also backed daylight PDT. In a prospective single-center trial, grade I (mild) AKs had clearance rates of 87 percent compared to 91 percent with cPDT. Surprisingly, clearance increased dramatically with each 5°C increase in ambient temperature, possibly due to increased PpIX synthesis within cells.

Colorectal cancer: With more than a million new cases expected each year, Colorectal Cancer (CRC) has become the fourth most commonly diagnosed and third most lethal cancer. Adenocarcinomas that arise from the mucosal epithelial cells of the surrounding colon surface account for more than 90% of CRCs. After receiving a succession of genetic or epigenetic changes, certain mucosal epithelial cells convert into malignant uncontrolled polyps, resulting in cancer. PDT is a tumor-selective, minimally invasive CRC therapy that treats CRC tumors using visible light and a Photoactivable Photosensitizer (PS). To demolish sick tissues, the PS is applied topically or systemically to the cancer location. The PS produces extremely deadly Reactive Oxygen Species (ROS) after being exposed to a specific wavelength of light, which are capable of initiating oxidative cell damage and triggering cell death by necrosis, apoptosis, and autophagy. Pthalocyanine, porphyrin derivatives, mesosubstituted derivatives, chlorin, and hypericin are some of the most often utilized PSs for CRC PDT.

First-generation PSs: PDT began in the 19th century with the discovery of first-generation PSs, Hematoporphyrins (Hp). The first PS to be clinically approved for PDT was a hematoporphyrin derivative produced after the purification of Hp. Photofrin, a commercial type of Hematoporphyrin Derivative (HpD), has been extensively studied in PDT treatment of lung, brain, laryngeal, cutaneous, gastric, and esophageal malignancies. Photofrin's PDT effects and antitumor effectiveness were studied in patients with advanced CRC. Photofrin use in CRC has also been shown to be an effective PS PDT antitumor therapy in several additional investigations.

Second-generation PSs: Second Generation PSs have a greater wavelength absorption in the red and near-infrared regions of the spectrum (650–800 nm), which allows them to penetrate deeper into tissues. In addition, as compared to first-generation PSs, photosensitivity, stability, and tissue selectivity have all been greatly enhanced. Porphyrin or porphyrin-based macrocyclic structures such as benzoporphyrins, purpurins, texaphyrins, phthalocyanines, naphthalocyanines, and protoporphyrin IX form the majority of second-generation PSs. 5-aminolevulinic acid (ALA), a precursor of porphyrin, is a commonly used second-generation PS that has been thoroughly explored over the years and has shown significant potential in PDT and photodiagnosis for CRC treatment.

Third-generation PSs: Nanotechnology as a fundamental tool for PDT in CRC is an important research avenue for overcoming some of the disadvantages associated with second-generation PSs and improving selective cellular localization in afflicted tumors. Third-generation PSs are often made up of second-generation PSs that have been attached to or encapsulated by nanocarriers such as nanoparticles, liposomes, or micelle carriers in order to improve NP-PS uptake and accumulation by malignant tissues. Active targeting agents like as antibodies, biomarkers, or ligands can be added to the NPs to help them bind to receptors that are overexpressed on the surfaces of cancer cells. In comparison to the first and second-generation PSs, this new generation of PSs has a longer absorption spectra and improved properties such as increased biocompatibility, enhanced cancer targeting capabilities, and increased levels of ROS production.

The use of NPs in CRC PDT treatment has the potential to overcome many of the limitations of standard PSs while also increasing their bioavailability. Organic nanocarriers such as liposomes, lipid NPs, and polymeric NPs, as well as inorganic NPs such as silver, gold, quantum dots, and silica nanoparticles, have been used as PS carriers in CRC PDT. Liposomes are organic NPs with an aqueous core surrounded by phospholipid bilayers that can encapsulate PS for effective distribution. They also have various benefits, including biocompatibility and biodegradability, as well as a high loading capacity for carrying PSs. They also protect PSs from environmental causes and early deterioration. Inorganic NPs were shown to be beneficial in CRC PDT. Noble metallic NPs, such as gold NPs (AuNPs), have high surface-to-volume ratios and are easily tunable, making them suitable for antibody functionalization. They are also low in toxicity and have little negative effects. Furthermore, gold NPs have inherent physicochemical features such as Surface Plasmon Resonance (SPR), which could transfer heat or harmful radicals

into tumor tissues during PDT irradiation. PEGylated gold NPs are also biocompatible with the biological system, allowing them to collect passively within tumors *via* the EPR effect. The most prevalent ways for mediating the targeted delivery of PSs to tumors using NPs are passive and active targeting strategies.

The major liposomal composition used in colorectal cancer treatment is HSPC/DSPE/Cholesterol and the size is approximately 130 nm. The ingredient used is DOX which has the potential to stabilize DNA-topoisomerase II in a way that could prevent the DNA double helix resealing and thus stop the cell replication process.

Conclusion

PDT has been shown to be effective for specific forms of Non melanoma cancer cells with great cosmetic results and the ability to treat in the field. It is also effective in the treatment of lung cancer with minimal invasion procedure. PDT is more effective when it is formulated with nanoparticles. Nano formulated liposomes makes the procedure more effective and stabilized. For nodular BCC (Basal Cell Carcinoma), PDT should be used with caution. Prophylactic PDT and field treatment for specialized patient populations like organ transplant recipients are both promising advancements. PDT's involvement in NMSC management may be expanded in the future when procedures with daylight PDT, enhanced photosensitizer distribution to target tissues, new generation photosensitizers, and innovative light sources are improved. Because the use of PDT or PTT alone for cancer treatment has limits, a combination of these techniques with the simultaneous use of nanoparticles and phytochemicals was considered a viable strategy. In fact, in the current study, we used Fe_3O_4/SiO_2 nanocarriers to encapsulate curcumin as a photosensitizer reagent for the treatment of breast cancer *in vivo*. PDT+nanoparticles+liposome will give the best results and it helps us to overcome the disadvantages in chemotherapy/ surgical procedures.

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