Chapter 10

Photodynamic Therapy, a Potential Therapy for Improve Cancer Management

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Additional information is available at the end of the chapter

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Abstract

Cancer is a mass of abnormal and detrimental cells in a given part of the body. The main elucidated cause is the uncontrolled growth and proliferation of those cells after the corruption of the physiological processes responsible for normal development and functioning. The advantage of adjuvant therapy, therapy done after surgery, is to prevent the occurring of symptoms and not necessarily to make sure of the integrity of mechanisms that are crucial in preventing abnormal cell proliferation such cell cycle regulation, cell death, which include autophagy, necrosis, and apoptosis. The understanding of dysregulated cell death mechanisms combined with suitable alternative cancer therapies could lead to novel treatment modalities for cancer. Currently, breast cancer is the leading occurring cancer in sub-Saharan women after that of the cervix. This potentially curable condition kills more than half of the diagnosed group, which consists mainly of females aged between 35 and 49 years and with 77% being in stages III and IV. The social economic status of populations coupled with the limited access to proper control strategies and infrastructures in sub-Saharan regions accentuate the burden of the disease. Photodynamic therapy (PDT) has shown great potential in treating breast cancer and even greater therapeutic outcomes can be obtained when combining PDT with other therapies such as immunotherapy or nanomedicine.

Keywords: cancer, breast cancer, current treatment, photodynamic therapy, photosensitizers, photochemical reactions, cell death immunotherapy, nanomedicine

1. Introduction

The unregulated growth and proliferation of abnormal cells to form solid or liquid tumor in a given part of the body is referred as cancer. Currently, the condition denotes a collection

of related diseases with more than 100 types of cancer have been identified and named after the organs or tissues of origin [1]. Carcinoma is a common category that affects the inner and outer surfaces of the body and the subcategories include basal cell, squamous cell, transitional cell and adenocarcinoma. Sarcoma affects the cells in bones and smooth tissues, leukemia and lymphoma that of the blood and lymphocytes, respectively [1]. Due to the nature of the condition, the detection has to be as early as possible, followed by appropriate managerial approach based on the type of cancer to insure the survival of cancer patients. Early detection and treatment have increased the lifespan of patients diagnosed with cancers, and the survival rate is thrice higher than that observed in postponed intervention scenarios [2, 3]. Cancer has become a major health problem and foremost cause of death, claiming more than 8.8 million deaths in 2015, and 8.2 million deaths with 14 million new cases been diagnosed in 2012 [4–6]. The lifestyle plays a decisive role in determining cancer incidence and mortality rates, for example, the consumption of tobacco alone is one of the deadliest causes and accounts for 22% of the global cancer related deaths [5]. In developing countries, about a quarter of the incidence rate is infection-dependent, such as Hepatitis and Human Papilloma Virus (HPV) are known to facilitate carcinogenesis. While more than 90% of proper facilities and services for cancer management are reportedly available in the developed parts of the globe, less than 30% of those are in the low and middle countries. It has been established that the cancer mortality rate is proportionate to the regional dietary behavior and a third of the global cancer related deaths could be avoided as it is associated with obesity, high both tobacco and alcohol consumption, both low vegetable and fruit consumption, and physical inactivity [7, 8].

When a cancer develops and originates from the lobular or ductal tissues in the breast, it is commonly known as breast cancer, one of the most deadly cancers and the most common womanlike cancers globally [9, 10]. This carcinoma can be either recurrent, metastatic, invasive (or not) and seldom originates in the connective tissues of muscles, fat and blood vessels. A well developed breast is a tear-shaped milk producing gland and breast cancer is classified according to level of differentiation, from well differentiated in normal breast to moderately and poorly differentiated glands in breast cancer. Additionally, the size of the tumor, the possible invasion to lymph nodes in the armpits and metastatic ability help oncologists to stage breast cancer from the small ductal/lobular precancerous stage (stage 0) to medium sized in breast and lymph nodal regions (stage 1–3) and large metastatic phase (stage 4), the latter is usually associated with worse prognosis [10, 11]. Better prediction of prognosis is facilitated by the presence or not of certain receptors and the human epidermal growth factor receptor-2 (HER2) together with hormone receptors (HR, estrogen and progesterone) are usually considered. The luminal A type (HR+/HER2-) of breast cancer has the best prognosis, the luminal B type (HR+/HER2+) and the HER2-enriched type (HR−/HER2+) have moderate prognosis and the worst scenario is observed with the triple negative type (HR−/HER2+) [12–15].

The management approach of any kind of breast cancer mainly depends on the stage and the predicted prognosis; with the more hostile treatments administrated to patients, whose conditions have predicted poor prognosis and elevated probability of recurrence after intervention. Although the occasional and circumscribed effectiveness, surgery remains the main treatment modality for breast cancer, including entire (mastectomy), partial (quadrantectomy) or minute (lumpectomy) removal of the breast. The multidisciplinary approach is often preferred and

necessitates the accompaniment of chemotherapy or radiation therapy, or both for improved results [16]. Generally, hormone-blocking agents act as effectors for treatment of luminal (HR+) types and immune-modulators are favored for certain metastatic and late-staged breast cancer [17–19].

Photodynamic therapy is an unconventional treatment modality for neoplastic conditions and a promising treatment for recurrent cancers, depending on photochemical reactions and subsequent damage, and leading to cancer cell death [20, 21]. Experimental data from a diverse pool of research reports proved Photodynamic therapy to be a good treatment option for numerous cancers, offering reduced long-term mobility, very limited side-effects, better cancer-specificity over surgery, chemotherapy or radiotherapy [20, 22–23]. The radiotherapy causes loss of oxygen while oxygen is required during the Photodynamic therapy, therefore the two approaches should not be considered for a combined therapy. Furthermore, combination with conventional chemotherapeutic agents should be avoided as it would forfeit the cancer control and selectivity benefits of Photodynamic therapy. A superior targeting and eradication of breast cancer cells was achieved with photodynamic therapy, which is appealing and leaving normal-like cells such as breast epithelium and fibroblast unaffected, thus satisfying a safe usage norms. This emphasizes the edge of photodynamic therapy over other therapeutic methods; limited to none side-effects to patients. Photosensitivity is the usually side-effect observed and involves skin redness, tingling or burning sensation up to 24 hours post Photodynamic therapy, which can only treat tumors where light can reach and [21–25].

2. Fundamentals of photodynamic therapy

Photodynamic therapy was discovered more than a century ago and now is a minimally invasive and clinically approved therapeutic modality for neoplastic conditions. It involves the administration of photochemotherapeutic agents, known as photosensitizers, followed by the irradiation of the agents at a wavelength that matches their absorption properties. When this occurs in the presence of molecular oxygen, a sequence of reactions that lead to the tumor microvasculature damage, cytotoxicity and subsequent tumor cell death (**Figure 1**) [21, 26, 27]. Photosensitizers have evolved over time and are nontoxic, light absorbing dyes, able to undergo photochemical changes and transitions between the ground state and first or higher excited states. The deactivation can happen by heat-release (nonradioactive decay), emission as fluorescence or undergoing intersystem crossing (ISC). Ideal photosensitizers are readily able to be excited by appropriate photons, available in simple chemical formulation, easily synthesized from their precursors, stable and soluble in physiological environments, easily delivered into the body (injection or other means), and excreted from the body upon completion of therapy. They have high singlet oxygen quantum yield with strong absorption in the red region of the visible spectrum (680–800 nm) and high extinction coefficient, and effective accumulation in tumor tissues and low dark toxicity [28].

The third generation of photosensitizers are currently being developed from conjugating previous ones with organic and inorganic polymers, immunologic agents and nanoparticles. The first generation of photosensitizers include the members of Photofrin and hematoporphyrin

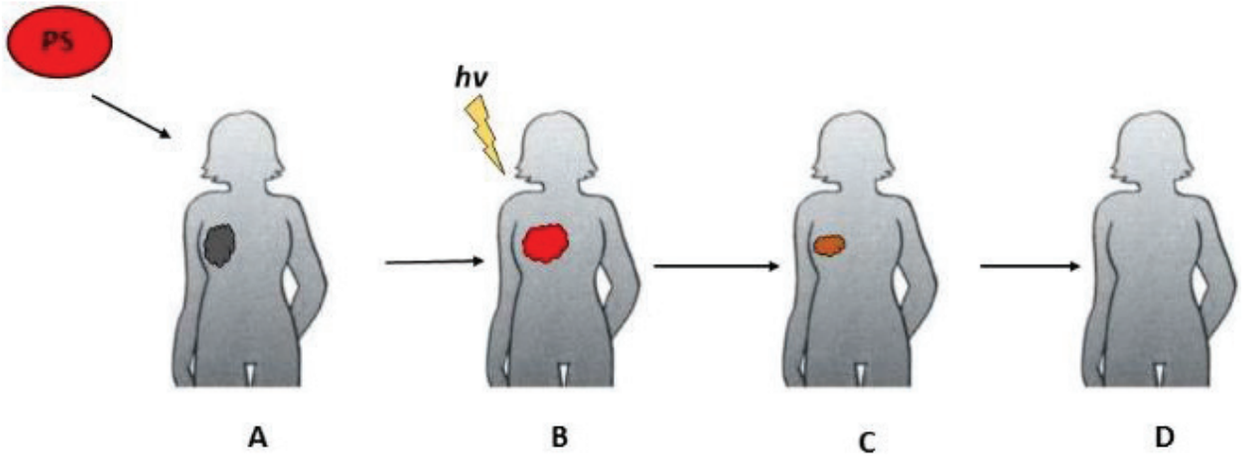

Figure 1. Elementary chronological events during photodynamic therapy. (A) Intravenous administration of photosensitizer(PS) to cancer patient. (B) Irradiation and activation of photosensitizer, which is localized in the cancer site. (C) Induction of cancer destruction mechanisms. (D)cancer-free patient after successful photodynamic therapy.

derivatives. They are complex mixtures of simple macrostructured hematoporphyrin and absorb light weakly at 630 nm, which resulted in their limited photodynamic effects. They were mostly used for surface tumors as at this wavelength of 630 nm the tissue penetration of light cannot exceed 4 mm and the major inconvenient was the extended light sensitivity period after the treatment. However, members of the first generation were efficient in generation of singlet oxygen per photon absorbed and met the standard for approval usage for clinical trials [28–31]. The development of second generation photosensitizers aimed to overcome the shortcomings of their predecessors naming low absorption in the near infrared region of the visible spectrum, prolonged light sensitivity and skin photo toxicity, and synthesizing method. From the porphyrin, many second generations were developed and included metatetra (hydroxyphenyl) porphyrin (m-THPP), 5,10,15,20-tetrakis(4-sulfanatophenyl)-21H,23H-porphyrn (TTPS4), 1,5-aminolevulinic acid (ALA) and numerous derivatives, the chlorin family derivatives, pheophorbides, bacteriopheophorides, texaphyrins, phthalocyanines. The members of the phthalocyanine family have great photodynamic actions and intersystem crossing capabilities due to the incorporation and formation of metal complexes in their core areas [32–36]. Some non-porphyrinoid photosensitizers exhibit photodynamic activity and include the anthraquinones, phenothizanies, xanthenes, cyanines and curcuminoids [37–39]. The development of third generation of photosensitizers is motivated by the fact that solubility remains poor with second generation photosensitizers, especially in aqueous environments at physiological condition, thus preventing intravenous delivery into the bloodstream. Currently, the research endeavors focus on developing delivery systems to facilitate the transportation to the target areas and to achieve greater selectivity and specificity of the third generation photosensitizers in order to increase their cellular uptake [40].

Light plays pivotal role for the successful activation of photosensitizers and subsequent outcomes of photodynamic cancer therapy. In ancient Egyptian, Indian, Greek and Chinese civilizations, light had a long track record in medical applications and the most usage being the remarkable efficacy in treat skin conditions [41]. Current applications use specific light

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sources to irradiate targeted tumor tissues. The optical power, wavelength matching the absorption spectrum of used photosensitizers and the depth of tissue penetration are among the priorities to be considered. The best tissue penetration of light is achieved in the therapeutic window, and most currently used photosensitizers absorb light maximally around that region of the spectrum, which is also known as the near infrared region (**Figure 2**) [42, 43]. Various types of light sources exist and the most commonly used in Photodynamic therapy applications are lasers, filtered lamps and light emitting diodes (LEDs). Lasers were the first to be utilized and offer high power coherent light in a narrow wavelength bandwidth but high manufactured skills and high cost are associated with them. Filtered lamps are the second and also the most flexible as they can be adapted, allowing their filters to be changed according to the properties of photosensitizers used but require an endoscope, which limits the efficiency, especially when using optical fibers. The most recent, LEDs are commonly used in Photodynamic applications and offer enhanced optical power [44, 45].

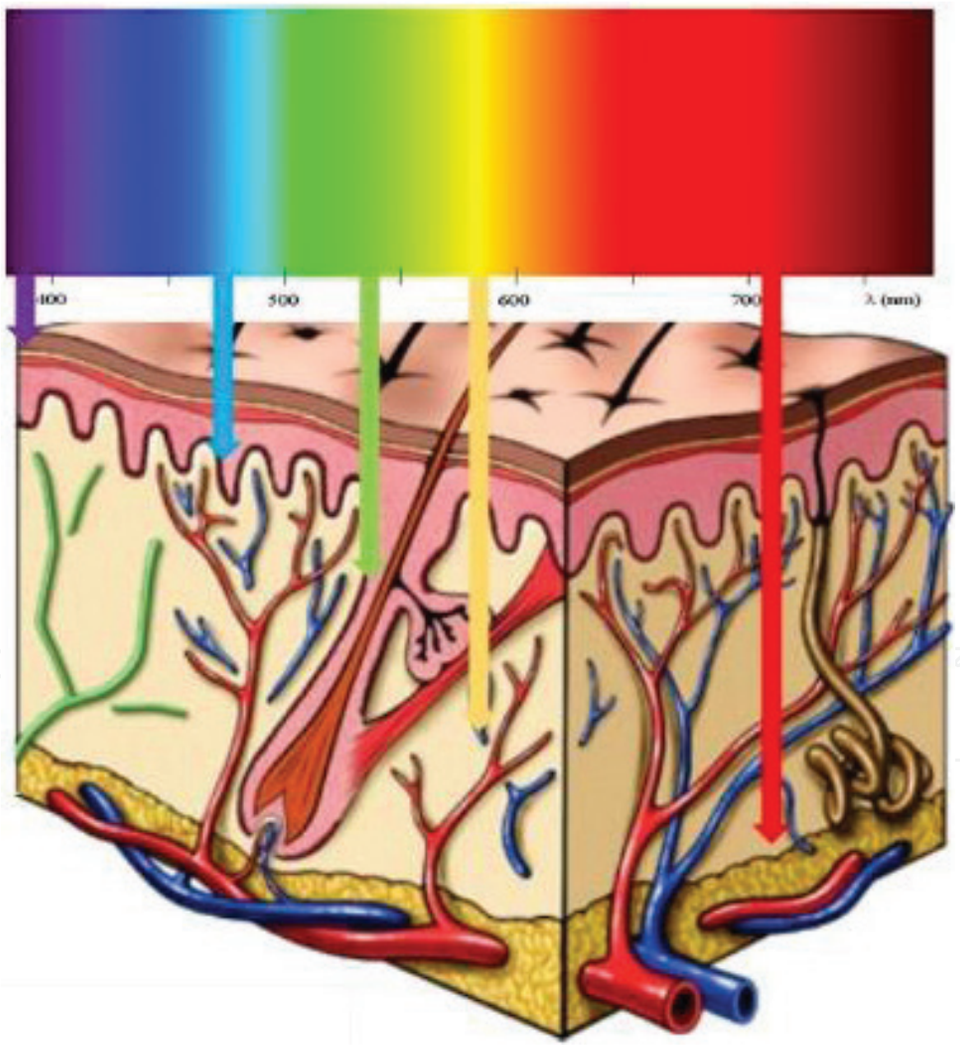

Figure 2. Light wave length and tissue penetration. Light penetration is proportional to the length of the wavelength used, the longer the wavelength, the deeper light penetrates into tissues.

The final objective of a photosensitizer is to successful transfer energy to molecular oxygen ($^3O_2$) or direct transfer of energy and production of reactive oxygen species. In photodynamic reactions, one of the most cytotoxic agent is the singlet oxygen ($^1O_2$), produced after the active interaction with a triplet state photosensitizer, and can be determined by measuring the weak near infrared luminescence of $^1O_2$, possible in both cells *in vitro* and tissues *in vivo*. In all of the cases, the treatment efficacy and cell eradication correlate strongly with the cumulative $^1O_2$ luminescence [46]. The amount of different forms of oxygen present in targeted tissues appear as an important factor to be considered for prognosis. The efficacy of Photodynamic therapy depends on the interaction of light, photosensitizers and oxygen, all in appropriate dose, and three dosimetry methods have emerged including explicit dosimetry to measure different treatment parameters and predict the outcomes, implicit dosimetry to measure biological intermediates and damage (photo bleaching) and adjust to effective dosage, and direct dosimetry to measure the critical photobiological toxins and avoid limitations seen with the previous two [46, 47].

2.1. Mechanisms of photodynamic therapy

Photodynamic therapy involves the use of light exposures to excite a photosensitizer from the ground state (PS) to the singlet excited state ($^1PS^*$). The stability of the photosensitizer in the excited state determines the occurrence of the intersystem crossing to the triplet and long-lived excited state ($^3PS^*$). Many physical pathways may be involved during intersystem crossing, converting the excited singlet state to the long-lived and excited triplet state photosensitizer. The triplet state has the ability to undergo photochemical processes and interact with triplet state molecules such as molecular oxygen. At this point, two possible photoreactions are envisaged, type I or type II reactions, involving molecular oxygen (**Figure 3**). In a type I reaction, electrons are transferred from the excited triplet state photosensitizer to molecular oxygen, when in the presence of a suitable reducing agent, to produce reactive oxygen species such as superoxide anion, hydrogen peroxide, hydroxyl radical and hydroxide ions [9].

The second reaction, Type II, energy or electrons from the excited triplet state photosensitizer are directly transferred to molecular oxygen ($^3O_2$), promoting it to an excited state singlet oxygen ($^1O_2$). Energy transfer to $^3O_2$ can occur only if both photosensitizer and oxygen (Triplet ground state) are in the same triplet state. Both type I and type II reactions generate reactive oxygen species, which are responsible for the cytodamage observed during Photodynamic therapy and type II reactions occur more frequently in photodynamic reactions (**Figure 4**) [9].

2.2. Photodynamic therapy, a localized therapy

Photosensitizers are tumor-localizing nontoxic agent, they selectively accumulate in neoplastic tissues, making Photodynamic therapy a restricted therapy. The irradiation of tumor tissues with visible light in the presence of oxygen, activates photosensitizers to generation reactive oxygen species into the tumor cells and thus induces tumor death and tissue destruction, preventing side-effects to health tissues [47]. Although the photosensitizers will effectively localize in all tumors, Photodynamic therapy is more suitable for localized diseases as

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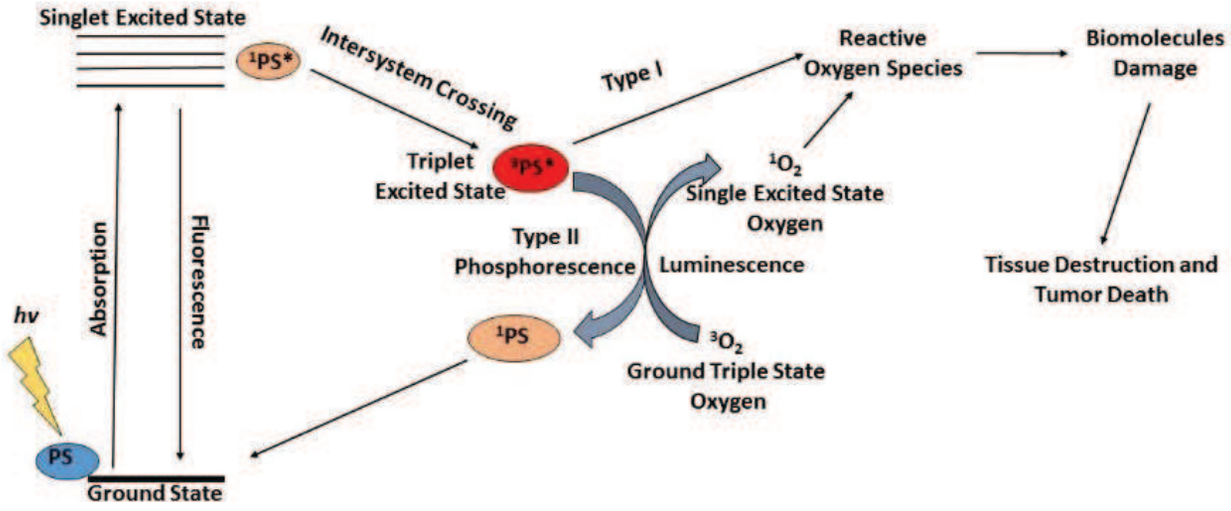

Figure 3. Schematic representation of type I and type II photoreactions following photo dynamic therapy (Jablonski Diagram). When the photosensitizer(PS) absorb a photon of light, it is elevated from the ground to the singlet excited state, it can either return back to the initial ground state by fluorescence or undergo intersystem crossing into the long triplet excited state. The photosensitizer in the triplet excitable state can transfer energy to an oxygen molecule forming reactive oxygen species (type I) or to the highly reactive triplet state (type II). There active oxygen species are responsible for the subsequent damage to biomolecules(nucleic acids, lipids and proteins) and the resulting cell death events.

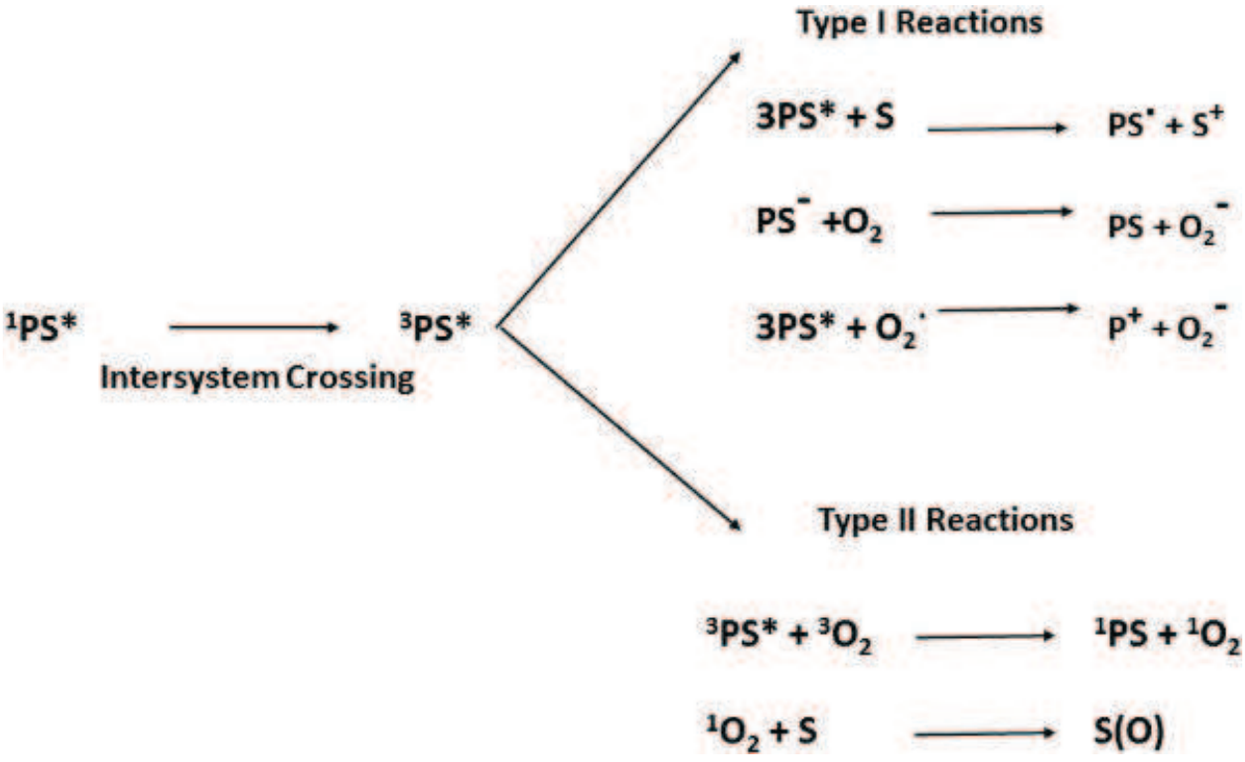

Figure 4. Possible photochemical reactions of photosensitizer (PS) in the triple excited state.

the irradiation is more feasible and efficient than in metastatic diseases. Most photosensitizers interconnect with tumor cells though their numerous low density lipoprotein receptors, facilitating the uptake of photosensitizers. Once inside the cells, the photosensitizers tend to

selective accumulate in some organelles, include in the mitochondria, lysosomes and those near the nuclear areas. Mitochondria are consistent and preferential sites of accumulation of photosensitizers and the efficiency of Photodynamic therapy is not always affect by differential localization patterns between various cells. However, all Photodynamic therapy-treated cells exhibit significant mitochondrial disruption, leading to decreased mitochondrial activity and adenosine triphosphate production. Most cationic photosensitizers have stronger water solubility properties and localize in mitochondria, yielding enhanced photodynamic activities [48, 49]. Most of the photosensitizers that localize in mitochondria of certain kind of cancer cells, including breast cancer cells, show relatively high co-localization level in near nuclear areas such as endoplasmic reticulum, and are believed to be good candidates for photodiagnosis and photodynamic therapy [50, 51]. Reduced mitochondrial oxygen consumption, decreased mitochondrial membrane potential and inhibited activity of complexes (I to IV) are all often seen after photodynamic therapy-mediated by mitochondrial localizing photosensitizers, which have apoptosis-inducing capabilities [52, 49–51]. Some lysosomal-localizing photosensitizers are hydrophilic and show excellent tumor destruction, they are usually associated with the induction of both apoptotic and necrotic responses following photodynamic therapy [53–55].

2.3. Photodynamic therapy and the induction of cell death

Cellular uptake of the photosensitizers can assist in predicting the mode of cell death as reactive oxygen species accumulated first in the organelles where photosensitizers are localized [56]. Photosensitizers that favorably localize in mitochondria seem to have the predisposition of inducing apoptosis. Damage to mitochondria following photodynamic actions, would lead to mitochondrial leakage and apoptotic response as mitochondria are well known to play critical roles in most apoptotic pathways [57, 58]. Apoptosis is a highly regulated and programmed cell death response that comprises interdependent and synchronized pathways [58, 59]. Photodamage-mediated permeabilized mitochondrial membranes induce leakage of apoptogenic proteins, such as cytochrome C. In return, the released apoptogenic proteins activate the caspase mediated apoptotic pathway [60, 61]. Photodamage may also lead to the induction of other apoptotic pathways [62, 63].

With high dose of photodynamic therapy, cellular components that are essential for the induction of an apoptotic response, become damaged in the process leading to a necrotic type of response [64]. Necrosis is a cell death response associated with the pathological processes and irreversible cellular injury [65]. Sometimes, necrosis is accompanied by an inflammatory reaction accompanies, which is caused by the direct release of intracellular components into the cell environment [66]. Successful induction of the necrotic cell death response after photodynamic therapy had been reported, especially as a result of photosensitizers accumulating maximally in the plasma membranes [67]. Photosensitizers that localize in plasma membranes showed co-localization in mitochondria and slightly in lysosomes, and the observed post treatment changes at different incubation intervals included cell membrane damage, initiated cell repair, irreversible damage, induction of apoptotic-like response, and cell cycle S phase arrest [68].

Autophagy is a cytoprotective and recycling mechanism responsible to deal with cellular organelles and cytoplasmic components after damage. The main effector of this function is the autophagosome, a temporally doubled membrane structure, with the ability to engulf cell debris and fuse with lysosomes for complete degradation of its contents [69]. Photosensitizers that localize in mitochondria and endoplasmic reticulum stimulate a prosurvival autophagic response while the lysosomal-localized photosensitizers trigger an inhibitory autophagy response [55, 70]. Furthermore, low doses of photodynamic therapy lead to the induction of a cytoprotective autophagic mechanism, and autophagic cell death mechanism is induced with the high doses [71]. When an apoptotic response is undergoing, the autophagic cell death complements it and when absent, autophagy stands as the main cell death mechanism induced after photodynamic therapy [72, 73]. Such observation indicates that photodynamic treatment gives a concurrent occurrence of various cellular responses, which all depend on the treatment parameters (types of photosensitizers, cellular localization, dose, light sources, dose, and incubation time).

2.4. Cancer recurrence and photodynamic therapy

After remaining undetected for a period following treatment, cancer can recur and according to the localization; a local, regional or distant recurrence needs to be dealt with. Surgery and other conventional cancer treatments are not suitable for advanced stage and metastatic tumors, and leaving room for development of drug-resistant cancer, which is often associated with cancer stem cells [74]. Cancer stem cells are normal stem cells, with special ability to give rise to all types of cells found in a particular cancer sample, so making them able to generate tumors through the stem cell processes of self-renewal and differentiation [75, 76]. The development of treatment modalities that target both primary and secondary and cancer stem cells becomes more than required, due to the selectivity of photosensitizers, Photodynamic therapy appears as a promising therapy for drug-resistant cancer stem cells with the photosensitizer-targeted delivery to cancer and particularly cancer stem cells [77]. For this reason, the capabilities of photosensitizers are being upgraded with prospective approaches based on nanoscience and nanotechnology for conjugating nanoparticles to photosensitizers to achieve nano-photosensitzers targeted delivery in the photodynamic treatment of cancer and cancer stem cells [78]. The use of nanoparticles makes it able to explore the poor lymphatic drainage and ensure that the photosensitizers is much more easily retained in cancer-like tissues than in normal tissues, a phenomena known as enhanced permeability and retention effect [79]. The conjugation of anticancer photosensitizers and water-dispersible nanoparticles with specific affinity for cancer stem cells yields a systemic self-deliverable photodynamic therapy, which maintains the pharmacological efficacy while improving the safety and delivery profiles [78, 80]. The nanocarriers are known to achieve both passive and active targeting delivery, which is an additional benefit to increase the therapeutic effects and reduce the side-effects [81]. With such development, the burden of enduring several drugs as currently accomplished in clinical treatment will be alleviated with the development of multifunctional nanocarriers. Another potential active targeting delivery approach will be conjugation with monoclonal antibodies specific to cancer and cancer stem cells. Multifunctional carriers of

antibodies targeted against HER2 or estrogen or any other steroid hormone receptors that are overexpressed in breast cancer and cancer stem cells could be exploited to achieve better targeting, uptake and therapeutic outcomes both *in vivo* and *in vitro*. Multifunctional drug delivery carriers containing antibodies tend to show enhanced eradication of cancer and cancer stem cells, prospect targeting drug delivery systems depend on the discovery of cancer stem cell interacting mediators [81–83].

Novel types of targeted cancer therapy like the multifunctional complexes-mediated photodynamic therapy are currently being considered along with other treatments including cancer vaccines, oncolytic virotherapy and immunotherapy [84–85]. The transcription factors that regulate cell mobility, invasion and migration during metastatic tumor stages of breast cancer are becoming attractive and constitute essential molecular targets for future treatment modalities [86, 87]. Hormone receptors remain the most currently used markers in clinical trials and the usage of breast cancer markers BRCA1 and BRCA2 is increasing as seen by numerous report studies [88, 89]. Most of the preclinical studies are performed with cell lines derived from breast cancers, and MCF-7, T-47D and MDA-MB-231 are among the most commonly used [90].

3. Conclusion

Cancer, an uncontrolled cell proliferation condition, has become a major health challenge and global killer. The incidence and related treatment facilities are unfortunately determined by the lifestyles and geographic locations of cancer patients. Breast cancer is a common carcinoma that affects the tear-shaped milk glands in women and its classification is been facilitated by the presence or not of certain receptors (HER-2 and HR), which are also to predict the prognosis. Photodynamic therapy is a promising cancer treatment and offers better specific targeting of cancer and limited side-effects, when compared to conventional therapy. Mitochondria, lysosomes and perinuclear areas are reported as the most frequent localization sites for third generations of photosensitizers. The treatment efficiency depends upon the successful light-activation and intersystem conversion into the excited triplet state, only then photosensitizers interact with molecular oxygen to produce reactive oxygen species, toxins responsible for cytodestruction and cell death. If required, Photodynamic can be repeated but the contribution of nanoparticles in combination therapy for cancer and particularly breast cancer, has permitted the successful delivery of therapeutic agents to the targeted tumor site and enhancement of therapeutic effects. When conjugated, they facilitate the delivery of hydrophobic drugs into biological environments, ensure the preservation of the pharmacologic properties of the drugs, and enhance selective targeting to cancer cells through their large surfaces, which can be functionalized with a various kind of components. The use of photodynamic therapy offers controlled conditions with high selectivity to cancer, hence reducing the undesired side-effects seen with conventional treatments. Whether used as main or adjuvant therapy, the aim of combination cancer therapy using photodynamic therapy is to selectively and completely eradicate cancer by targeting and killing both cancer and cancer stem cells.

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Conflict of interest

The authors report no conflict of interest in this work.

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