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TOPIC HIGHLIGHT

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Breast cancer as photodynamic therapy target: Enhanced therapeutic efficiency by overview of tumor complexity

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Abstract

Photodynamic therapy is a minimally invasive and clinically approved procedure for eliminating selected malignant cells with specific light activation of a photosensitizer agent. Whereas interstitial and intra-operative approaches have been investigated for the ablation of a broad range of superficial or bulky solid tumors such as breast cancer, the majority of approved photodynamic therapy protocols are for the treatment of superficial lesions of skin and luminal organs. This review article will discuss recent progress in research focused mainly on assessing the efficacies of various photosensitizers used in photodynamic therapy, as well as the combinatory strategies of various therapeutic modalities for improving treatments of parenchymal and/or stromal tissues of breast cancer solid tumors. Cytotoxic agents are used in cancer treatments for their effect on rapidly proliferating cancer cells. However, such therapeutics often lack specificity, which can lead to toxicity and undesirable side effects. Many approaches are designed to target tumors. Selective therapies can be established by focusing on distinctive intracellular (receptors, apoptotic pathways, multidrug resistance system, nitric oxide-mediated stress) and environmental (glucose, pH) differences between tumor and healthy tissue. A rational design of effective combination regimens for breast cancer treatment involves a better understanding of the mechanisms and molecular interactions of cytotoxic agents that underlie drug resistance and sensitivity.

Key words: Photodynamic therapy; Breast cancer; Tumor microenvironment; Treatment combination; Synergism

Core tip: Breast cancer is the most common cancer in women worldwide. However, effective therapies that reduce the high mortality rate and improve patient quality of life are still unavilable. In recent years, the use of photodynamic therapy has been exmined for use in breast cancer treatment. Photodynamic therapy provides a new and promising antitumor strategy that could be implemented, alone or in combination with other approved or experimental therapeutic approaches, to a wide range of applications.

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PHOTODYNAMIC THERAPY (PDT) ON SOLID TUMORS: FOCUS ON BREAST CANCER

PDT is one of the clinically approved and minimally

invasive alternate methods for treatment of various cancers, such as bladder, esophagus, respiratory tract and gynecologic cancers. PDT eliminates tumor cells by the combined use of of nontoxic photosensitizers (PS) and light[1]. Light activation of a PS results in energy transfer cascades that ultimately yield cytotoxic reactive oxygen species, which can then render cell death[2]. Antitumor effects of PDT derive from three interrelated mechanisms: direct cytotoxic effects on tumor cells, indirect damage to the tumor vasculature, and induction of an inflammatory response that can activate systemic immunity[3].

The photosensitizer is considered to be a critical element. In general, for solid tumor PDT, an ideal PS should meet at least some of the following criteria: a commercially available pure chemical, low dark toxicity but strong photocytotoxicity, good selectivity towards tumor cells, longer wavelength allowing deeper light penetration, rapid removal from the body, and multiple administration routes (oral, intravenous, intratumoral or inhalational). Although some PSs satisfy all or some of these criteria, there are currently only a few PDT photosensitizers that have received official approval around the world. Photofrin (630 nm; Axcan Pharma, Inc.), Levulan (prodrug of protoporphyrin IX, 630 nm; DUSA Pharmaceuticals, Inc.), Metvix (prodrug of protoporphyrin IX, 630 nm; PhotoCure ASA), Foscan (652 nm; Biolitec AG), Laserphyrin (664 nm; Meiji Seika Kaisha, Ltd.), and Visudyne (693 nm; Novartis Pharmaceuticals). Several second generation PSs (e.g., HPPH, 665 nm; SnEt2, 665 nm; LuTex, 732 nm) have been investigated in many preclinical and clinical trials for various solid tumors, and in particular SnEt2[4,5] and LuTex[5] are clinically applied in the US for breast cancer[3]. These photosensitizers show the selectivity towards tumor cells and are ideal for cellular- and vascular-targeted PDT, and interference with cytoprotective molecular responses is of growing interest. Any interactions between PDT and PDT-sensitizing agents is confined to the illuminated area, thus, eliminating any potential systemic toxicity.

The majority of approved PDT protocols are for the treatment of superficial lesions of skin and luminal organs, such as actinic keratosis and Barrett's esophagus, whereas interstitial and intra-operative approaches have been investigated for the ablation of a broad range of superficial or bulky solid tumors located in the head and neck, brain, breast, lung, gastrointestinal, and genitourinary regions[2]. Although Bbreast cancer is the most common cancer in women's cancer in the worldwide,. The effective ttherapies that would not only effective in both reduce reducing the high mortality rate and associated with the disease, but also improve improving patient the quality of life patients with breast cancer are still searching forhave not yet been achieved.

In recent years possibilities of PDT has recently been examined for useing in breast cancer treatment, though are analyzed, and theits full-potential range of potential applications alone or in combination with other approved or experimental therapeutic approaches nedded to behas yet to be explored defined.

This article reviews article will discuss recent progress in researches focused mainly on concerning the efficaciesy's assessing of different various photosensitizers used in photodynamic therapyPDT, as well as the combinatorialy strategies of various therapeutic modalities with non-overlapping toxicities, in order to improve the therapeutic index of treatments of parenchymal and/or stromal tissues of in breast cancer solid tumors. Any interactions between PDT and PDT-sensitizing agents will be confined to the illuminated area. Therefore, the potentiated toxicity of the combinations is not systemic

PDT COMBINED WITH CONVENTIONAL BREAST CANCER THERAPIES

Most women with breast cancer undergo some type of surgery as the main strategy for tumor removal, including breast-conserving surgery or mastectomy (removal of breast). The breast can be reconstructed at the same time as the surgery or later on. Radiotherapy or systemic therapy is commonly given as adjuvant treatment after surgery[6]. Radiotherapy involves the external (sometimes internal) application of high-energy rays (ionizing rays) to destroy cancer cells, which is typically accompanied by short-term side effects such as swelling and heaviness in the breast, sunburn-like skin changes in the treated area, and fatigue[6]. In addition, synergistic treatments offer favorable outcomes, such as increasing the efficacy, decreasing the dosage, avoiding toxicity, and minimizing the development of drug resistance[7].

In recent years, researchers have become increasingly interested in combining antitumor therapies in order to improve the patient outcome and to avoid, at least in part, unwanted side effects. In this context, there are reports indicating that some PSs can act as radiosensitizers[8,9]. With regard to breast cancer, several *in vitro* studies have shown a synergism between PDT and ionizing radiation in killing cells. The combined application of nontoxic doses of indocyanine green[10], rhodamine 123 and its platinum complex[11], zinc phthalocyanine and meso-tetrahydroxyphenylchlorine[12] with light proved to be very effective and resulted in a nearly complete reduction of survival. These reports suggest that treatment of tumors with a combination of PS-mediated PDT and ionizing radiation could be superior to their individual use. The interaction of PDT and ionizing radiation could enhance the therapeutic effect, thus reducing the dose of radiation dose and potential side effects.

Systemic therapy, better known as chemotherapy, is a treatment with cancer-killing drugs that are given intravenously or by mouth. The drugs travel through the bloodstream to reach cancer cells in most parts of the body. There are several situations in which chemotherapy may be recommended in breast cancer patients: after surgery (adjuvant chemotherapy), before surgery (neoadjuvant chemotherapy) or for advanced breast cancer. In most

cases (especially adjuvant and neoadjuvant treatment), chemotherapy is most effective when combinations of more than one drug are used. Although many combinations are currently being used, there is no clear indication that any particular combination is more effective. The most common chemotherapeutics used for early breast cancer include the taxanes (such as docetaxel and paclitaxel) and the anthracyclines (epirubicin and doxorubicin). These may be used in combination with other drugs, such as cyclophosphamide and fluorouracil. Platinum agents (cisplatin, carboplatin) have also been useful for treating women with breast cancer. The type and amount of drug(s), as well as the length of chemotherapy treatment, determine the extent of side effects, which include nausea and vomiting, mouth sores, easy bruising, hair loss, change in appetite, increased chance of infections, low blood cell counts, bleeding and fatigue[6].

Recently, the effect of PDT combined with traditional chemotherapy for the treatment of breast cancer has been studied. Low doses of cisplatin *in vitro*, which are unlikely to cause severe side effects, are more effective when appropriately combined with indocyanine green-based PDT[13]. Additionally, another *in vitro* study showed that the combination of meso-tetrahydroxyphenylchlorine-mediated PDT and the chemotherapeutic 5-fluoro-2-deoxyuridine resulted in a lower cell survival than single-mode treatment[14]. Benzoporphyrin derivative monoacid ring A-based PDT enhanced the antitumor effects of doxorubicin on breast cancer *in vivo*, which was associated with the cooperative regulation of extrinsic apoptotic pathways and the inhibition of tumor angiogenesis[15]. However, the mechanisms involving the interatctions between chemotherapeutic drugs and PSs, as well how they can be combined to increase cell killing while reducing side effects, needs to be examined in more detail.

We recently reported that the pre-clinical chemotherapeutic drug β-lapachone interacts with methyl aminolevulinic acid-PDT in breast cancer *in vitro*. However, we also demonstrated that the application scheme of both therapies have relevance on the outcome. Synergism was observed when chemotherapy was applied 24 h after PDT, due to the photodynamic induction of NQO1, the principal determinant of β-lapachone cytotoxicity. The combination of PDT followed by β-lapachone treatment is a potentially promising modality for the treatment of cancer[16].

When treating cancer, cytotoxic agents are intended to exert their effect on rapidly proliferating cancer cells. However, cancer therapeutics often lack specificity, which can lead to toxicity and undesirable side effects. Many approaches have been designed to target tumors. Selective therapies can be established by focusing on distinctive intracellular and environmental differences between the tumor and healthy tissue. Additionally, a strategy to treat breast cancer involves the combination of drugs. The molecular interactions with cytotoxic agents, combined with increasing knowledge of the mechanisms underlying drug resistance and sensitivity, allow for the rational design of effective combination regimens for the treatment of patients[17]. In this sense, combinations of PDT and tumor-targeted strategies will be reviewed.

PDT AND BREAST CANCER RECEPTOR-TARGETED AGENTS

The overexpression of many receptors in breast cancer cells, such as estradiol receptors, the human epidermal growth factor receptor 2, gonadotropin-releasing hormon receptors, and tisular factor VII receptors, is strongly associated with increased disease recurrence and a poor prognosis[18]. Thus, therapies have been developed to target removal of ligands or inhibit their activation[6]. As these receptors represent a potential site for directing receptor-mediated cellular uptake, photodynamic researchers utilized them as vehicles to selectively deliver photosensitizing agents. Thus, the overexpression of receptors in breast cancer was harnessed synergistically with the tumor-migrating effect of several PSs to selectively deliver target molecule-PS conjugates into breast tumor cells, and preferentially kill the tumor cells upon exposure to red light[19–32] (Table 1). Developments in these specific types of receptor-targeting approaches highlight their potential advantages in the discovery of more effective cancer photochemotherapy agents.

PDT COMBINED WITH ANTI-APOPTOTIC STRATEGIES

PDT leads to the generation of cytotoxic oxygen species that appear to stimulate several different signaling pathways, some of which lead to cell death, and some that mediate cell survival. In this context, we observed that methyl-5-aminolevulinic acid-mediated PDT resulted in overexpression of survivin[33], a member of the inhibitor of apoptosis family that inversely correlates with patient prognosis and whose role in resistance to anti-cancer therapies is a subject of intensive investigation. We demonstrated a specific role for survivin in modulating the PDT-mediated apoptotic response. Silencing survivin expression increased apoptotic indices and cytotoxicity exhibited by PDT on metastatic breast human cancer cells. In contrast, the overexpression of survivin increased cell viability and reduced cell death. Expression of another antiapoptotic protein, Bcl-2, was suppressed by genistein, and PDT with hypericin may represent a mutual therapeutic combination favoring apoptosis[34]. The combination of genistein and PDT may therefore achieve a higher therapeutic outcome in human breast adenocarcinoma cell lines previously identified as PDT-resistant.

PDT AND MULTIDRUG-RESISTANCE (MDR) INHIBITORS

One of the principal requirements of successful PDT is sufficient intracellular accumulation of the photosensi-

Table 1 Receptor-targeted photodynamic therapy on breast cancer cells

Targeted receptor	Photosensitizer	Result	Ref.
Estradiol receptor	Tetraphenylporphyrin	High-affinity conjugate protein binding	James *et al*[19]
Estradiol receptor	Tetraphenylporphyrin	High-affinity conjugate cell binding	Swamy *et al*[20]
Estradiol receptor	Pyropheophorbide a	Conjugate-selective cell death	Fernandez Gacio *et al*[21]
Estradiol receptor	Pyropheophorbide a	Conjugate-selective cell death	El-Akra *et al*[22]
Estradiol receptor	Pyropheophorbide a	High conjugate internalization	Sadler *et al*[23]
Estradiol receptor	Chlorin e6-dimethyl ester	Conjugate-selective cell death	Swamy *et al*[24]
Human epidermal growth factor receptor	Verteporfin and pyropheophorbide a	Conjugate-selective but less phototoxic	Savellano *et al*[25]
Human epidermal growth factor receptor	Verteporfin and pyropheophorbide a	Conjugate-selective cell death	Bhatti *et al*[26]
Human epidermal growth factor receptor	Zinc phthalocyanine (plus nanoparticules)	Conjugate-selective cell death	Stuchinskaya *et al*[27]
Human epidermal growth factor receptor	Sn-(IV) chlorin e6 monoethylenediamine	Conjugate-selective cell death	Gijsens *et al*[32]
Tisular factor (factor VII receptor)	Verteporfin	Conjugate-selective cell death	Hu *et al*[28]
Tisular factor (factor VII receptor)	Chlorin e6	Conjugate-selective cell death	Duanmu *et al*[29]
Gonadotropin-releasing hormone receptor	Zinc phthalocyanine	Conjugate-selective cell death	Xu *et al*[30]
Gonadotropin-releasing hormone receptor	Protoporphyrin IX	Conjugate-selective cell death	Rahimipour *et al*[31]

tizer drug. Mechanisms of anticancer drug elimination (or MDR) by tumor cells are mostly linked to the elevated expression and activity of drug efflux transporters that constitute a dominant impediment to curative cancer chemotherapy. Hence, novel strategies that overcome MDR modalities are considered a major goal of cancer research. The ATP-binding cassette protein ABCG2 (breast cancer resistance protein) effluxes some of the PSs used in PDT, and thus, has been associated with photodynamic resistance. It was reported from *in vitro* and *in vivo* experiments, that the tyrosine kinase inhibitor imatinib mesylate blocked ABCG2 function and enhanced the efficacy of PDT by increasing intracellular PS levels, and may therefore enhance the efficacy and selectivity of clinical PDT on breast cancer[35].

ABCG2 is a putative cancer stem cell marker. Cancer stem cells, also known as tumor-initiating cells, are a small group of cancer cells involved in drug resistance, metastasis, and relapse of cancers and tumor-drug resistance[36]. Hence, it is of importance to develop PSs that are not subtrates of ABCG2, or design strategies to avoid ABCG2-mediated antitumor therapy resistance[37]. Recently, ABCG2 was implicated in a mechanism that targets and kills cancer cells with an MDR phenotype. The MDR mediates extracellular vesicles (EVs) rich in ABCG2 in attached breast cancer cells that highly concentrate chemotherapeutics, thereby sequestering them away from their intracellular targets. The authors showed that the accumulation of photosensitive cytotoxic drugs, such as imidazoacridinones (IAs) and topotecan, damaged EV membranes and resulted in tumor cell lysis. Furthermore, the accumulation of IAs in lysosomes killed MDR cells by organeller upture upon photosensitization. Therefore, a synergistic and cytotoxic effect resulting in MDR reversal is elicited by combining targeted lysis of IA-loaded EVs and lysosomes. In contrast, a selective photocytotoxic effect exerted by topotecan is achieved by accumulation in EVs of MDR cells. Thus, MDR modalities can be converted into a pharmacological, lethal Trojan horse to selectively eradicate MDR cancer cells by ABCG2-dependent drug sequestration within EVs[38].

PDT AND NITRIC OXIDE (NO) SCAVENGERS

Photodynamic intervention generates reactive oxygen species that can destroy tumor cells. NO produced by photosensitized cells could be pro-carcinogenic by inhibiting apoptosis. It was shown that NO from chemical donor or activated macrophages made breast tumor cells sensitized by 5-aminolevulinic acid-generated protoporphyrin IX more resistant to photo killing by providing substantial protection against apoptosis[39,40]. Additionally, it was demostrated that PDT-treated breast cancer cells acquired the ability to upregulate inducible-nitric oxide synthase (iNOS) expression[41]. In this sense, apoptotic cell killing was strongly enhanced by iNOS inhibition or knockdown and a NO scavenger[42]. These findings strongly indicate that stress-elicited NO in PDT-treated breast tumors could compromise therapeutic efficacy and suggest that NOS-based pharmacologic interventions could prevent this.

PDT AND (BREAST) TUMOR MICROENVIRONMENT (TME) INTERVENTION

The TME is a well-defined ecosystem comprised of parenchymal (tumor) and stromal (non-tumor) populations that coexist and establish interspecific interactions, which contribute to malignancy[43]. The TME of solid neoplasias is very different from those of normal tissues. The implementation of interstitial and estimation of PDT dosimetry relies on the complexity of the solid tumor. Moreover, the TME should be studied if stromal cells affected by photodynamic regimes extinguish the tumor ecosystem by destroying their network within tumor cells. In this sense, we have recently reviewed the term "Ecological Photodynamic Therapy" to emphasize the need to modulate PDT application regimens to exploit their effect on interspecific relationships and thus achieve complete tumor eradication[43].

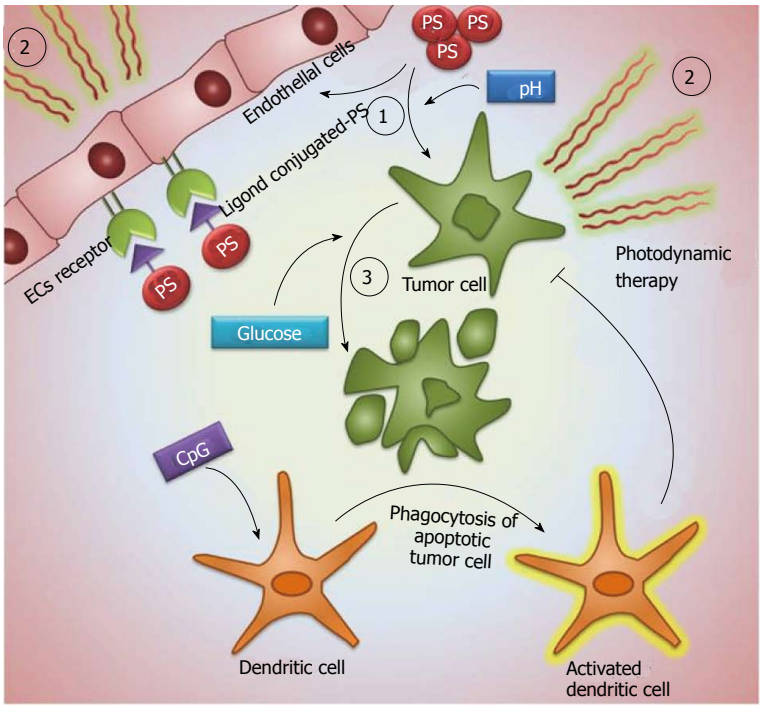

Figure 1 Photodynamic therapy (PDT) combined with tumor microenvironment intervention on breast cancer. PDT is one of the alternative methods for breast cancer treatment and involves: (1) administration of a photosensitizer (PS), which is internalized into either tumor cells or surrounding vasculature; (2) local irradiation at a wavelength corresponding to the absorbance peak of the PS; and (3) light activation of the PS, which promotes cell death mainly by apoptosis. Because of the benefits of improving PDT outcome, researchers have developed strategies to target the vasculature surrounding breast tumor cells by conjugating the PS with endothelial cell (EC)-specific ligands. Immunoactivation of dendritic cells using CpG increases phagocytosis of PDT-killed tumor cells and leads to their maturation and activation, thereby promoting an antitumor immune response. Regarding abiotic environmental factors, it was shown that photodynamic therapy sensitivity is reduced in glucose-deprived cells, and that a lower extracellular pH leads to increased PS uptake, reinforcing the photodynamic response.

Endothelial cells (ECs) are the stromal population whose principal function is to supply the TME with oxygen, hormones, nutrients, circulating cells and other fluids. A mutualistic interaction has been observed between ECs and tumor cells within TME: ECs provide nutrients and tumors cells develop a paracrine stimulation to finally sustain the angiogenic endothelial process[43]; angiogenesis refers to the growth of blood vessels from pre-existing ones[44]. Therefore, researchers have developed strategies to target the vasculature surrounding breast tumor cells. A novel and effective ligand-targeted PDT for breast cancer was synthesized by conjugating factor VII (fVII), a natural ligand with high affinity and specificity for tisular factor, with the PSs veterporfin[28] or chlorin e6[29] (Figure 1). The rationale for targeting tisular factor is based on its overexpression in breast cancer and its selective expression in pathologic neovascular ECs in cancer. fVII-targeted PDT improves the selectivity and efficacy of PDT for the treatment of breast cancer and induces apoptosis and necrosis as the underlining mechanisms of action. Moreover, fVII-targeted PDT was effective and safe for treatment of chemoresistant breast tumors *in vivo*, presumably by simultaneously targeting both the tumour neovasculature and chemoresistant cancer cells[28,29]. Strategies to favor the vascular effect of PDT by targeting tumor vasculature are constantly evaluated. Recently, PSs conjugated to a peptidase-resistent peptide that targets neuropilins overexpressed in tumor angiogenic vessels were developed. Intravenously injected peptidase-conjugated PSs selectively accumulate in vascular cells with no degradation in plasma[45] (Figure 1). This finding provides useful information for the future design of stable, targeted molecules to improve the outcome of PDT-treatment.

Treatment with PDT alone is often non-curative due to tumor-induced immune cell dysfunction and immune suppression. This phenomenon has motivated a new approach of combining immunostimulants with PDT to enhance anti-tumor immunity. Thus, verteporfin-mediated PDT was combined with an immunomodulation approach using CpG oligodeoxynucleotide for the treatment of metastatic breast cancer *in vivo*. CpG primes immature dendritic cells via toll-like receptor 9 to phagocytose PDT-killed tumor cells, leading to dendritic cell maturation and activation. Peritumoral injection of CpG after PDT in mice gave improved local tumor control and a survival advantage compared to either treatment alone (Figure 1). In conclusion, CpG may be a valuable dendritic cell-targeted immunoadjuvant to combine with PDT[46].

With regard to the TME, in addition to the cellular or biotic factors that modulate the photodynamic response, abiotic components also have a strong influence on PDT outcome. In this sense, the effect of chronic hypoglycemia on sensitivity to aminolaevulinic acid-induced PDT *in vitro* was studied in human breast cancer cells. It was shown that photodynamic therapy sensitivity was reduced in glucose-deprived cells[47] (Figure 1). Additionally, tumors, due to their abnormal vasculature, are characterized by a more acidic environment compared to their surrounding normal tissues. The low pH can enhance the lipophilicity of several PSs, such as hematoporphyrin IX[48]. It has been shown that increasing the lipophilicity of a drug leads to increased tumor uptake[48] (Figure 1). As a result, it is possible to find a concentration gradient of the drug within the breast TME between the tumor tissue and the normal surrounding tissue. By injecting glucose, it is possible to further selectively reduce the extracellular pH value of tumors[49], and to make tumor cells more sensitive to PDT treatment[47]. This will, in

turn, increase the pH gradient between tumor and normal tissue and finally result in an increased concentration gradient for drugs that becomes more lipophilic at low pH values. If the low tumor pH explains the selective localization of such drugs, the clinical outcome of PDT can be improved by combining it with glucose injections. It is therefore neccesary to characterize the interactions and biotic and abiotic components of the TME in order to achieve the disruption of ecological networks which finally can lead to the destruction of the ecosystem.

CONCLUSION

Despite major advances in the knowledge and treatment, breast cancer remains an enormous problem in terms of morbidity and mortality. It is expected the pharmaceutical industry and research institutes will continue to launch numerous clinical trials to evaluate applications of PDT in conjunction with, or as a replacement for, traditional methods for treating solid tumors.

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