



Nanocarrier-Assisted Laser-Driven Photodynamic/Chemo Therapy for Breast Cancer: A Narrative Review

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Abstract

Introduction: Efficacy of conjugated photodynamic therapy (PDT)/chemotherapy in the treatment of breast cancer is summarized in this review. Alternative chemo drugs (CDs) and photosensitizers (PSs) are irradiated with lasers at various wavelengths to verify the toxicity of photo-stimulated compounds.

Methods: The conducted studies on conjugated photodynamic and chemotherapy treatment of breast cancer across three phases (in vitro, in vivo and clinical) from 2014 to 2025 are summarized in this review. Articles on laser-activated therapies are evaluated, and irrelevant studies have been omitted. The records are sorted based on CD/PS typ laser irradiation wavelength, and energy.

Results: Synergic PDT+chemotherapy is a promising method for breast cancer treatment according to in vitro, in vivo and clinical studies. Nevertheless, the clinical translation of the conjugated approach still meets unresolved issues, including long-term safety, limited selectivity, and biodistribution challenges.

Conclusion: The hybrid treatment exhibits superior advantages in tumor shrinkage, high selectivity, inhibition of malignant cells, overcoming drug resistance, and metastasis control. Furthermore, the conjugate treatments mitigate the side effects of high-dosage chemotherapy.

Keywords: PDT, CD, PS, Chemotherapy, Breast cancer, In vivo, In vitro, Clinical, Nanocarrier

Introduction

Despite advances in treatment, the high mortality rate associated with breast cancer among women remains a global concern. However, novel hybrid therapeutic approaches show promise for improving treatment outcomes.¹ Photodynamic therapy (PDT) has significant potential to enhance therapeutic efficacy and improve patients' quality of life, particularly in the treatment of triple-negative breast cancer (TNBC).²

Many photosensitizers exhibit significant inhibitory characteristics in favor of the angiogenic activities of the chemoresistant cells. As a consequence, hybrid treatment of phototherapy+ chemotherapy provides superior outcomes compared with either therapy alone.³ Furthermore, synergic efficacy of selective PDT leads to the reduction of chemotherapeutic agent dosage and the mitigation of systemic side effects on the surrounding healthy tissues.⁴ The cancerous tumor tissue with a dense extracellular matrix absorbs more PS content, which leads to dye accumulation within the corresponding micro-cavities and larger spectral shifts detected by laser-induced fluorescence (LIF) spectroscopy. These spectral markers can be applied to discriminate between normal and cancerous breast tissue.⁵

Furthermore, certain chemotherapeutic agents, such

as irinotecan, gemcitabine (GEM), navelbine (NVB), bleomycin (BLM), doxorubicin (DOX), paclitaxel (PTX), and capecitabine (CAP), notably exhibit fluorescent properties that may act as supportive markers for real-time imaging during integrated chemotherapy and PDT.⁶⁻⁸ Treatment response is traceable by LIF spectroscopy based on the uptake of fluorescent chemo-medications or fluorescent chemodrugs+ nanoparticle conjugates by malignant cells.^{9,10}

Numerous pre-clinical studies have investigated the efficacy of combined chemotherapy and PDT for the treatment of malignant breast cells, employing both in vitro and in vivo models. Conjugated PDT with chemotherapy promotes malignant cell destruction through dual mechanisms: the elevated ROS generation from PDT and the cytotoxic effects of chemotherapeutic agents.¹¹ In some cases, additional therapeutic modalities such as immunotherapy, sonodynamic therapy, hormonotherapy, or photothermal therapy have been combined with PDT.¹²⁻¹⁵ Moreover, nanoparticles serve as carriers that improve the therapeutic consequences of the compounds in favor of efficient drug delivery, enhanced targeting, and controlled toxicity.^{16,17} In conjunction with photocatalytic therapy (PCT), nanocomposites can also facilitate drug release

during photo-biomodulation (PBM) processes as the reactive oxygen species (ROS)-responsive agents.¹⁸

Several clinical trials have been conducted to evaluate the advantages of PDT in the treatment of breast cancer, particularly in cases involving disease recurrence or metastasis.¹⁹ The key preferences include localized tumor targeting and confined toxicity, enabling differentiating healthy/malignant tissues while promoting necrosis/apoptosis sequences through photochemical and photobiological mechanisms.²⁰

On the other side, the combination of photothermal therapy (PTT) and PDT offers enhanced tumor necrosis with fewer side effects and reduced mortality. In addition, the magnetic resonance imaging (MRI) and computed tomography (CT)-assisted PDT/PTT, as well as optical coherence tomography (OCT)-guided PDT, may further improve the treatment capacity.²¹ The combinational therapy of PDT+ chemotherapy is promising at the clinical level for improving the life expectancy.²² PDT is also recognized as an effective follow-up treatment after procedures such as surgery or chemotherapy without any therapeutic interfering effects.²³

Methods

The Google Scholar and PubMed databases were searched for studies published between 2014 and October 2025 that investigated conjugated photodynamic therapy and chemotherapy of breast cancer. Both in-vitro and in-vivo studies were analyzed if they employed both chemotherapy and photodynamic therapy. Clinical trials evaluating PDT+chemotherapy were compared with studies investigating PDT combined with other conventional treatment modalities for breast cancer. The inclusion criteria encompassed all breast cancer subtypes, including metastatic or triple negative breast cancers. Various breast cancer cell lines and murine models are also included. The exclusion criteria were (i) primary cancers other than breast cancer, (ii) chemotherapy combined with treatment modalities other than PDT, and (iii) interstitial laser interventions. The data were categorized according to the main parameters of (1) CD and PS medications, (2) irradiation wavelength and dosage, (3) nanocarriers, and (4) types of combinational therapy of in vitro, in vivo, and clinical studies.

Results and Discussion

In vitro studies

In this section, studies investigating the combination of chemotherapy and PDT in breast cancer cell lines are reviewed to evaluate their synergistic therapeutic effects. Nanocarrier-based delivery systems for photosensitizers, including liposomes, extracellular vesicles (EVs), gold nanoparticles (GNPs), and lipid-polymer hybrid nanoparticles (LPHNPs), can enhance targeted drug delivery, improve PDT efficacy, and promote tumor shrinkage. Among these nanocarriers, liposomes are clinically approved due to their high biocompatibility; however, they suffer from stability issues. In contrast,

lipid-polymer hybrid nanoparticles (LPHNPs) offer the stability of polymer-based systems, although their clinical application remains limited. Metal nanocarriers can be manufactured in a wide range of sizes; however, their intrinsic cytotoxicity and potential non-biodegradability may restrict their clinical use.¹¹

An mPEG-PCL-based nanomedicine loaded with docetaxel (DTX) chemo drug and near-infrared (NIR) active agent of dye-IR820 has demonstrated remarkable cytotoxicity against 4T1 breast cancer cells. The formulation is further modified with the LyP-1 tumor-targeting peptide to facilitate binding to the p32 receptor.²⁴ The results indicate that simultaneous PDT/PTT/chemotherapy under 808-nm laser exposure exhibits substantial anticancer efficacy, including enhanced metastasis suppression and tumor-targeted delivery. In another study, a microneedle-based localized delivery system incorporating cisplatin (CDDP) and IR820 is proposed for localized chemotherapy and PDT, respectively. This approach delineates the enhanced therapeutic efficacy through the generation of superoxide anions and reactive oxygen species (ROS) which can mitigate malignant cell proliferation following NIR laser exposure. Furthermore, the controlled release platform reduces the toxicity of chemotherapy by significantly decreasing cisplatin blood levels.²⁵

In a separate report, a novel medication is synthesized from mertansine (MRT) /cabazitaxel (CBZ) CDs loaded onto TPC-CS photoactive nanoparticles. The tetraphenylchlorin (TPC) photosensitizer is conjugated with chitosan (CS), providing a high drug-loading capacity and prolonged retention through π - π stacking interactions.²⁶ Chemotherapy mediated by MRT or CBZ eradicates about 60% of the breast cancer cells under laser exposure. However, the notable induced phototoxicity of CD-loaded TPC-CS NPs is characterized with lower IC50 to demolish the entire malignant cells. The DIRA, as a biomimetic nanocarrier of CDs, has been engineered from red blood cell (RBC) membranes to support PDT through oxyhemoglobin (oxyHb) generation while incorporating ammonium bicarbonate (ABC) in favor of controlled drug release.²⁷

These DOX/ICG-loaded DIRAs function as an operative agent for combined chemo/PD-PT therapy. Higher treatment doses under laser exposure demonstrate enhanced cytotoxicity effects against breast cancer cells. The nanoemulsions (NEs) loaded by the chloroaluminum phthalocyanine (ClAlPc) photosensitizer and DOX chemo medication are examined over an in vitro model of murine breast. The resulting NEPC-DOX nano-carriers demonstrate strong synergistic cytotoxicity by modulating the expression of apoptosis-related genes.²⁸

Furthermore, novel multifunctional nanocomplexes composed of DOX and ALA dye have been developed for joint chemo/photodynamic therapies. These nanocomplexes possess the characteristics of surface charge reversal and pH-responsive drug release, enabling improved therapeutic performance.²⁹ The upgraded cellular uptake is achieved through the enhanced targeting capacity

of the anti-HER2 antibody of the nanocomplexes. Another promising strategy involves the hypoxia-responsive liposomal formulation Lip (IR780&TPZ). Encapsulated

liposomes with an IR780 photosensitizer and tirapazamine (TPZ) chemodrug benefit adjunct therapies. Encapsulation within liposomes brings about the elevated aqueous solubility and stability of IR780 while reducing its systemic toxicity. This formulation provides an implicit drug delivery method for tumor suppression with reduced side effects.³⁰ In another study, a multifunctional nanoparticle of Lip@PTX/CyA/Ce6 is developed by incorporating the paclitaxel (PTX) CD and Ce6 photosensitizer to revert multi-drug resistance (MDR) in breast cancer cells.³¹

The liposome-based nanoparticles of L@CY@DOX are utilized with encapsulated DOX and cyanine (CY) PS for simultaneous NIR imaging and effective combined chemo-PD treatment. These NPs with an average diameter of 160.9 ± 1.7 nm exhibit a considerable laser-responsive release profile and a high capacity for ROS generation. L@CY@DOX nanoparticles induce substantial mitochondrial apoptosis against malignant MCF7 cells based on the enhanced cellular accumulation and increased singlet oxygen production. Treatment with L@CY@DOX alone resulted in approximately 60% cell survival, whereas the same dosage under laser irradiation reduced cell viability to approximately 20%, emphasizing the synergistic effect of chemotherapy and PDT.³²

Moreover, triple-negative breast cancer (TNBC), as the most aggressive type of breast cancer, has been extensively targeted by various CDs, including paclitaxel, doxorubicin, cisplatin, fluorouracil, and methotrexate in combination with different chlorin–vitamin conjugates during synergistic chemo-PD therapy. Among the investigated formulations in this report, the complex of chlorin–lipoic acid conjugate (InCLA) and paclitaxel, even at nanomolar concentrations, represents the best

antagonistic efficacy under visible light stimulation, which is quantified by the lowest combination index (CI) of 0.25 based on the Chou–Talalay method.³³

Under the ex vivo tissue model, the efficacy of combined chemotherapy/PDT for the treatment of stage IIB and III (locally advanced and metastatic) breast cancer has been investigated.³⁴ In this study, different doses of rose bengal (RB) PS are administrated to postoperative tumor fragments (> 10 mm) and adjacent healthy tissues following neoadjuvant chemotherapy. MRI relaxation times alongside the clinical radiological images and histopathological examinations are utilized for evaluating the treatment response of the malignant cells to PDT. Upon activation by 532-nm laser irradiation, RB generated reactive oxygen species (ROS), thereby enhancing the therapeutic effect against chemoresistant cancer cells. Histopathological findings and morphological assessments of tissues treated with post-chemotherapy PDT indicate the characteristic features of cellular damage, including cytoplasm degradation, irregular nuclear morphology, and chromatin homogenization. Accordingly, PDT+chemotherapy

represents high advantages in the shrinkage and suppression of malignant tumors. Furthermore, higher concentrations of RB are associated with enhanced apoptotic activity, indicating a dose-dependent enhancement in the therapeutic efficacy of PDT.³⁵

In most of the reviewed in vitro studies, synthesized CD/PS medications are loaded onto nanocarriers to improve drug delivery. DOX is the most common chemodrug, while other medications, including TPZ, CBZ, DTX, PTX and MTX, are also investigated in combined PDT+chemotherapy approaches. The most frequently employed photosensitizers are ALA, ICG, CY, Ce6, IR820, etc., which are tabulated in Table 1. These compounds are irradiated by visible/NIR lasers at variable irradiances ranging from 0.01 to 10 W/cm².

The results demonstrate a synergetic therapeutic effect enabling controlled and targeted drug delivery, resulting in enhanced drug accumulation in the cancerous cells. The conjugated treatment is capable of reverting the MDR by transforming the expression of involved genes to anti-cancer medications. Besides, ROS generation during PDT helps to overcome MDR by damaging resistant cancer cells, suppressing drug efflux pumps, depleting antioxidant defenses, promoting apoptosis and other forms of cell death, and enhancing the effectiveness of chemotherapy.³⁶ Finally, these characteristics entitle the combined therapeutic approach of chemo+photodynamic therapies, a vigorous method to overcome the TNBC. In Figure 1, multiple synergic procedures of conjugated photodynamic and chemotherapy are depicted successively.

In vivo studies

Numerous in vivo studies have investigated the synergistic effects of combined chemotherapy and photodynamic therapy (PDT) in preclinical models. Most studies highlight the role of nanoparticles as carriers for the photo-stimulated photoresponsive therapeutics, enhancing intratumoral accumulation through targeted delivery mechanisms. In vivo fluorescence imaging is usually employed within 24 hours of post-intravenous administration of the PS and PS+CD to trace the agents' biodistribution and tumor localization.

The conjugated medication of Ganetespib (Gan) chemodrug and zinc phthalocyanine (ZnPc) PS is developed for the treatment of breast adenocarcinoma in a murine model.³⁷ Notably, ZnPc holds negligible therapeutic efficacy in the absence of laser activation. Upon irradiation with a 671 nm visible red laser at an intensity of 500 mW/cm², reactive oxygen species (ROS) are generated through the photodynamic process. The tumor-targeted therapy by Gan-ZnPc reveals discriminative cytotoxicity over tumors while minimizing damage to surrounding healthy tissues. The ex vivo fluorescence imaging of resected tumors (~100 mm³) addresses medication selectivity and its

remarkable anticancer efficacy. Furthermore, this combined chemo-PD therapy with Gan-ZnPc leads to substantial tumor regression while effectively inhibiting metastasis and angiogenesis.

Table 1. A Summary of in vitro studies of breast cancer therapy using combined PDT/chemotherapy

Refs	Np type	Chemo drug	Photosensitizer	Laser WL (nm)	Laser irradiance /fluence	Key advantages
24	mPEG-PCL	DTX	IR820	808	2.5 W/cm ²	Metastasis control and tumor targeting delivery
25	-----	CDDP	IR820	808	100 mW/cm ²	Controllable delivery using a microneedle
26	TPC-CS	CBZ	TPC	420	13 W/cm ²	High drug-loading capacity and strong retention
27	DIRA	DOX	ICG	808	2 W/cm ²	Novel biomimetic nanocarrier based on RBC with PDT reinforcement by oxyHb generation
28	NE	DOX	ClAlPc	660	1 J/cm ²	Altering the expression of the related genes to anticancer drugs
29	AHA	DOX	ALA	635	200 mW/cm ²	Surface charge reversal and pH-responsive nanocomplex
30	Lip	TPZ	IR780	808	1 W/cm ²	Efficient hypoxia-responsive drug delivery
31	Lip@CyA	PTX	Ce6	660	5 W/cm ²	Reversing multiple drug resistance (MDR)
32	L@CY@DOX	DOX	CY	660	15 mW/cm ²	Elevated accumulation of medication inside the tumor
33	-----	CDDP, 5FU Taxol, DOX, MTX	InCLA, CBTN, CPA, MePheo, CBX, CLA	Visible	16 mW/cm ²	InCLA- Taxol with high potent synergic efficacy for targeting TNBC
34,35	-----	ADM + CTX and PTX	RB	532	10 J/cm ²	Cytoplasm degradation in chemo-resistant malignant cells

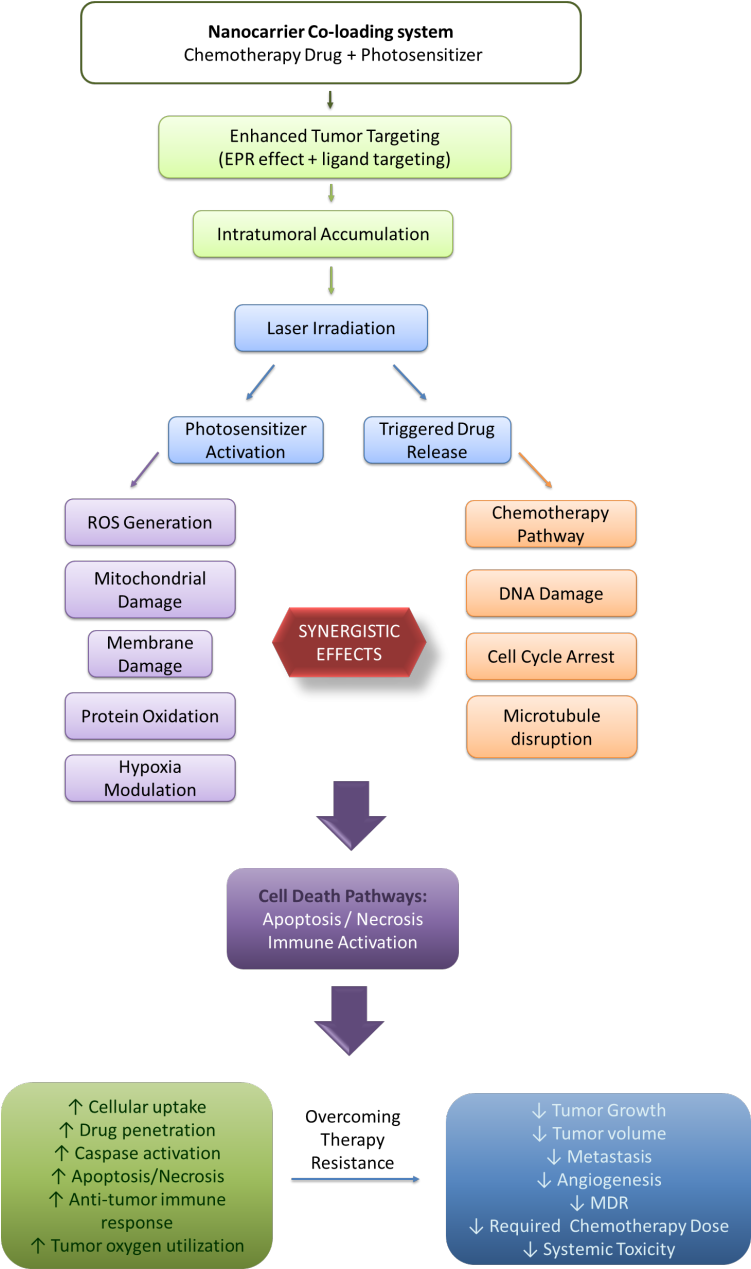


Figure 1. Summary of the major mechanisms responsible for the synergistic therapeutic efficacy of combined PDT and chemotherapy in breast cancer.

The NPs of FA-L@MD@CAT based on liposomal-encapsulated catalase (CAT), lyso-targeted

NIR photosensitizer (MBDP) and doxorubicin (DOX) are designed to defeat the hypoxia and reverse the immune-suppression of tumor microenvironment (TME). This multifunctional nanoplatform enhances the efficacy of combined chemo-PD therapy through the elevated tumor oxygenation, thereby promoting intratumoral drug accumulation and improving tumor therapeutic index. In this study, tumor-bearing mice with tumor volumes ranging from 90–200 mm³ in different groups are irradiated with a 640-nm laser at an intensity of 50 mW/cm² for 20 minutes at 24 h following intravenous administration of PBS, L@CAT, FA-L@MD@BSA or FA-L@MD@CAT. The in vivo data demonstrate remarkable tumor regression (~50%), coinciding with notable angiogenesis suppression as well as metastasis control.³⁸

In another article, chloroaluminum phthalocyanine-loaded nanoemulsions (NE-Pc) and doxorubicin are examined for combined PDT + chemotherapy of murine breast cancer under activation by visible laser exposure at 630 nm.³⁹ This combined therapy presents outstanding advantages in stepping down cancer cell proliferation, as indicated by decreased Ki67 expression, while simultaneously promoting substantial tumor volume shrinkage.

Moreover, this synergic therapy effectively decreases tumor vascular endothelial growth factor (VEGF) expression while increasing Caspase-2 and -3/8 intrinsic and extrinsic cell death pathway expressions, respectively. Notably, the treatment is validated as a promising targeted anticancer method through upregulating several pro-apoptotic genes (ABL1, CD70, CRADD, FASL, NME5) against down-regulating multiple cancer drug objected genes (CDK2, ERBB2, FIGF, IGF2, PARP and PGR).

The synthesized TPC-CS nanoparticles (NPs) with loaded CDs of mertansine (MRT) / cabazitaxel (CBZ) are examined on BALB/c mice bearing breast cancer tumors.²⁶ Although the biodistribution survey of harvested organs confirms the accumulation of the medication in the liver and lungs, histological analyses also reveal the raised apoptosis/necrosis within the treated tumors. In another study, the

targeted conjugate therapy consisting of paclitaxel (PTX) chemodrug encapsulated with indocyanine green (ICG) modified liposomes (ICG-Lipo-PTX) has been investigated in a murine breast cancer model.⁴⁰ The selectivity of the treatment is attributed to the

liposomal delivery platform, alongside combined PDT and PTT under ICG activation, followed by the PTX release through laser exposure at 810 nm. The results highlight the significant impression of ICG-Lipo-PTX in cancer treatment, accompanied by the reinforcement of systemic immune response. A schematic illustration of the cellular apoptosis pathways during chemotherapy +PDT is given in Figure 2.

Another study focuses on the treatment of triple negative breast cancer (TNBC) using a combination of immunomodulatory chemotherapy and photodynamic therapy. The therapeutic procedure is based on antibody drug conjugate (ADC) incorporating 5-aza-2'-deoxycytidine (5-ADC) chemodrug and verteporfin photoactive agent (by a 690-nm laser). The competence of the method has been evaluated using tumor volume measurements, histopathology profiling assessments, and the evaluation of antitumor immune responses and tumor necrosis. Furthermore, this combined approach offers a distinctive advantage in controlling metastatic progression up to 40%.⁴¹

Dual-responsive, shape transformable, and reversibly charged nanoparticles of PEG His@BPC are developed from berberrubine (BBR) chemodrug and chlorin e6 (Ce6) PS for enhanced treatment of breast cancer. Tumor shrinkage in a BALB/c mouse model is associated with elevated apoptosis under laser irradiation at 660 nm. The preferential accumulation of these nano medications at the tumor site enables the targeted PDT+ chemotherapy exhibiting no apparent toxicity around the liver or kidney.⁴²

In recent surveys, photodynamic gel-bombs (DCM@OPR) have been engineered by loading chlorin e6 PS and DOX CD into the MnO₂ NP crosslinked Ca²⁺-gel. This formulation facilitates laser-triggered explosive energy release and receptor-mediated transcytosis to facilitate deep penetration into malignant cells, thereby enhancing the therapeutic efficacy against breast tumors. The improved

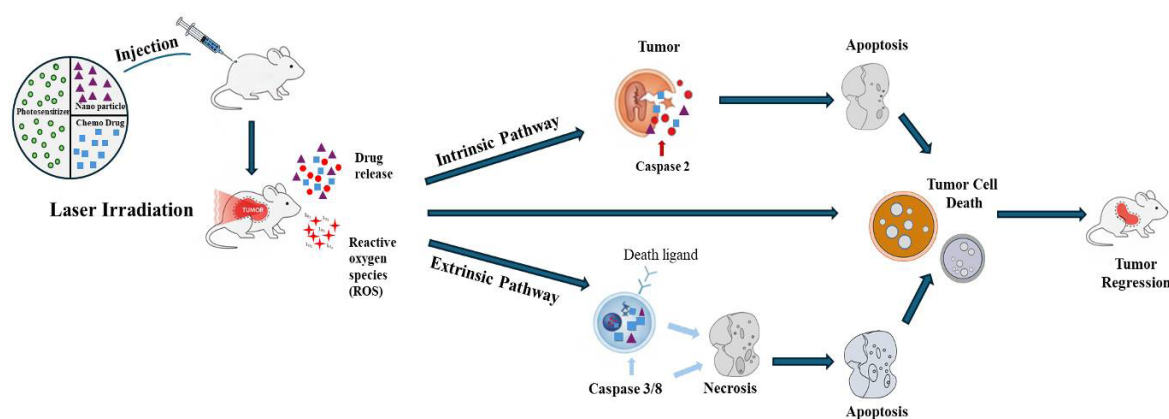


Figure 2. Schematic diagram of the cascaded procedures of intrinsic/extrinsic laser-induced drug release and ROS generation leading to malignant cell damage and necrosis using increasing intrinsic/extrinsic tumor death expressions. The resulting cellular apoptosis could demolish the whole tumor in the in vivo model

antitumor activity is attributed to the anti-proliferation capacity of gel-bomb nanofragments. In addition, the Gibbs free energy of these gel-bombs is also calculated for the verification of the treatment-induced prohibition of tumor growth.⁴³

The Ce6/DOX@NPs-cRGD nanoparticles (CDNR) comprise Ce6 and DOX encapsulated in cRGD-functionalized NPs with cyclic Arg-Gly-Asp-d-Phe-Cys (cRGD) peptides, enabling targeted delivery to $\alpha\beta 3$ integrin- and HER2-expressing breast cancer cells. In vivo experiments attest that the CDNR demonstrates a superior tumor-targeting capability by laser activation (670 nm, 1 W/cm²) against Ce6/DOX@NPs alone with approximately 65% of tumor volume reduction and 50% improvement in the survival rate.⁴⁴ As shown in Table 2, DOX and Ce6 are the most frequently used chemotherapeutic drug and photosensitizer, respectively, in combined in-vivo PDT-chemotherapy studies. The enhanced capability of conjugated chemo/photoactive treatments relies on CD/PS agents for the treatment of breast adenocarcinoma in the murine model. The privileges include efficient tumor suppression, angiogenesis and metastasis control alongside targeted therapy with lower CD dosages and reduced toxicity to healthy tissue. Similar to the in-vitro model, DOX and Ce6 are the most frequently used CD and PS, respectively, in combined in vivo photodynamic therapy and chemotherapy investigations. Encapsulation of these compounds within liposomal, metallic or other nanocarriers upgrades the efficient accumulation of the medications in the tumor cells to evolve the targeted impacts. This conjugated therapy enables localized, laser-induced cytotoxic effects on the malignant cells avoiding the probable side effects on healthy tissue. The synergetic treatment method is promising for upregulating pro-apoptotic genes, inhibiting malignant cell proliferation, and stimulating antitumor immune responses according to the ROS generation.

Clinical approach

Photosensitizers (PSs) used in PDT differ substantially in their photophysical properties, tumor selectivity, depth of light penetration, ROS generation efficiency,

and clinical applicability. As a result, they could be stimulated with different induced laser wavelengths and power settings. First-generation PSs, such as Photofrin, are clinically approved, while bearing the disadvantages of prolonged skin photosensitivity and low efficacy in singlet oxygen generation. Second-generation PSs, including oral aminolevulinic acid (ALA), Chlorins, or Verteporfin, benefit from higher ROS generation and deeper tissue penetration. However, the shortcomings of these photosensitizers consist of limited tumor specificity alongside their potential accumulation in healthy tissues.⁴⁵ Although a number of photosensitizers have received FDA approval, particularly for imaging and photo-diagnosis applications, they are not licensed for clinical practices. For intense, oral aminolevulinic acid (ALA) is not clinically recommended, whereas other photosensitizers like Chlorin e6 have been extensively investigated for PDT of breast cancer.⁴⁶

Many trials have focused on the advantages of PDT in the treatment of breast cancer; however, a limited number of studies have evaluated the therapeutic efficacy of combined PDT and chemotherapy in clinical trials. PDT was first used in 1966 for the treatment of breast cancer. Subsequent studies have since investigated the efficacy of this method against various types of malignant breast cells.⁴⁷ In 2011, ICG was exploited for the treatment of patients with stage III-IV breast cancer over phase II study expressing positive therapeutic responses for end stage cases with 75 % clinical benefits.¹¹

In a Phase I clinical trial (NCT02872064), the enrolled patients with cutaneous and subcutaneous metastases of breast cancer who had failed to respond to radiation therapy and surgery were treated with continuous low-irradiance photodynamic therapy (CLIPT) using a 630 nm laser at low irradiance and photofrin injection. The findings demonstrate that the method could be effective in controlling metastases of breast cancer following mastectomy.⁴⁸ Tumor necrosis was observed in most cases without causing considerable damage to the surrounding healthy tissues.

The advantages of conjugated PDT and radiotherapy (RT) for the treatment of breast cancer and chest wall

Table 2. List of in-vivo reports of breast cancer treatment using combined PDT+ chemotherapy

Refs	Np type	Chemodrug	Photosensitizer	Laser WL (nm)	Laser irradiance/ fluence/ power	Tumor shrinkage (%)	Metastases Control	Angiogenesis Suppression	Selectivity
26	TPC-CS	CBZ	TPC	420	13 W/cm ²	√	√	NA	√
37	-----	Ganetespib	zinc phthalocyanine	671	500 mW/cm ²	√	√	√	√
38	liposomal CAT	DOX	MBDP	650	50 mW/cm ²	√	√	√	√
39	nanoemulsions	DOX	chloroaluminum phthalocyanine	630	50 J/cm ²	√	√	NA	√
40	ICG-Lipo-PTX	PTX	ICG	810	100 mW/cm ²	√	NA	NA	√
41	-----	5-ADC	verteporfin	690	50 mW	√	√	√	√
42	PEG His@BPC	BBR	Ce6	650	100 mW/cm ²	√	NA	NA	√
43	MnO ₂	DOX	Ce6	660	30 mW/cm ²	√	NA	NA	√
44	CDNR & Ce6/DOX@NPs-cRGD	DOX	Ce6	670	1 W/cm ²	√	√	√	√

recurrence versus traditional RT have been investigated.⁴⁹ In this phase III study, 40 patients are equally randomized into two groups. In the first treatment group, photodynamic therapy (PDT) is administered using a 632.8 nm laser at a fluence of 288 J/cm², 48 h after 5-aminolevulinic acid (5-ALA) infusion. The conjugated PDT+RT treatment represents better antitumor efficacy, with a 50% complete response rate compared to 20% for RT alone. Besides, the conjugated treatment reduces the RT exposure time and provides a faster recovery rate.

The efficacy of combined treatment of PDT and chemotherapy has been examined in patients with unresectable hilar nonresectable cholangiocarcinoma (NCC) using Cisplatin/Oxaliplatin/Gemcitabine CDs alongside the Photofrin II photosensitizer. This clinical study involving 68 patients verifies the priority of chemo+PD for significant improvement of overall survival extension of 12 months versus monotherapy.⁵⁰ A similar survival benefit has been reported in patients with extrahepatic cholangiocarcinoma (EHCC) treated with combined PDT and chemotherapy compared to either individual method.⁵¹ Moreover, a considerable reduction in mortality risk has been observed in patients with stage III/stage IV non-small cell lung cancer under synergic PDT and chemoradiotherapy.⁵²

In 2025, several clinical observations confirmed the distinct capability of intra-arterial administration of chlorin Ce6 photosensitizer combined with low-dose cisplatin chemotherapy (~0.5 mg/kg) for the treatment of head and neck squamous cell carcinoma (HNSCC). The effectiveness of this conjugated tumor feeding, intra-arterial approach with limited systemic exposure and localized drug delivery is validated through histopathological analysis, confocal microscopy and spectral fluorescence spectroscopy.⁵³

The therapeutic potential of sonodynamic photodynamic therapy (SPDT) with/without the low-dose chemotherapy is evaluated as a novel systemic treatment strategy for advanced refractory breast carcinoma.⁵⁴ In this study, PDT is performed using chlorophyll derivatives, including SF1, SFa and UF sensitizers, which are activated by a red LED. Sonodynamic therapy (SDT) is completed by Ultrasono-155I bearing 153 ultrasonic transducers operating in continuous and pulsed modes with 380V power output and 1.00MHz frequency. Prescribed chemotherapy regimen of liposomal DOX (30mg/M² dosage) + Paclitaxel liposome (120mg/M² dosage) is examined.

The study demonstrates that combined sonodynamic-photodynamic therapy (SPDT) with low-dose chemotherapy acts as a more efficient alternative treatment with negligible side effects. The overall response rate of 75% is achieved among 12 participants, with complete response in 2 patients and partial response in 7 patients following

the first treatment round. Table 3 lists studies of combined PDT with chemotherapy and other alternative treatments.

Overall, combined PDT/chemotherapy enhances the treatment efficacy through multiple mechanisms of tumor suppression, metastasis inhibition and improved treatment response rate compared to conventional clinical approaches. This conjugated treatment strategy makes the low-dose chemotherapy feasible, reducing the side effects on healthy tissues. Furthermore, the synergic consequences are enhanced by incorporating other treatment modalities such as SD therapy.

Achieved outcomes include improved quality of life and extended survival rates associated with these synergic therapies. The combined therapies prevent metastasis to other organs efficiently by provoking apoptosis in cancerous cells. The NP-loaded CDs could improve the treatment output yield through enhanced drug delivery and targeted action to a great extent.

Despite the promising potential of PDT for breast cancer treatment, several limitations associated with PSs continue to hinder its widespread clinical translation. The clinical translation of PSs in PDT is hindered by poor tumor selectivity and off-target toxicity with complex and costly modification strategies for targeted delivery. Furthermore, conventional PSs exhibit aggregation-induced quenching with reduced ROS generation, hypoxia and long-term safety, limiting their therapeutic efficiency. Although advanced PSs can enhance ROS production, their complex design, potential long-term accumulation and reliance on oxygen reduce their effectiveness in hypoxic tumor tissues.¹¹

Conclusion

The scientific evidence compiled from these investigations establishes a consensus regarding the superior therapeutic efficacy of combined chemo-photodynamic treatment of breast cancer. This synergic approach effectively addresses two of the most formidable challenges of modern oncology: systemic toxicity caused by high-dose chemotherapy and the widespread development of multidrug resistance in cancerous cells. These advantages are quantitatively underpinned by in vitro studies demonstrating a statistically significant and substantial reduction in IC₅₀ values of key chemotherapeutic agents within resistant malignant cell lines. Besides, the conjugated therapy leads to a significant rise in the mortality rate of malignant cells by overloaded cytotoxicity.

The benefits of the combined therapy among in vivo studies are also confirmed through multiple indicators, including reduced tumor volume, suppressed malignant cell proliferation, and downregulated cancer-related genes/receptors. Moreover, conjugated CD + photosensitizer

Table 3. List of the clinical reports of breast cancer treatment based on combined PDT/chemotherapy/alternative treatments

Refs	Combined Treatment	PDT Photosensitizer	Laser /LED WL (nm)	Key advantages
47	PDT+Radiotherapy	5-aminolevulinic acid	632.8 nm	Raised complete response rate with negligible side effects
52	PDT+ Sonodynamic + chemotherapy	SF1, SFa and UF	Red	Efficient in upgrading the overall response rate

therapy maintains its superiority over each monotherapy in conducted clinical trials. This efficacy is validated through a higher survival rate, enhanced tumor necrosis by elevated uptake of medications by malignant cells, mitigated CD dosage, and fewer attributable side effects.

Precisely engineered nanocarriers of loaded CD + photosensitizer render a promising approach for the localized cancer therapy, considering their efficient drug delivery capabilities. Besides, encapsulating the medications inside the nano-shells inspires the controlled tumor treatment through stimulus-responsive drug release upon light exposure. Advanced mechanisms such as ROS-responsive self-destructive cascade reactions triggered by laser irradiation not only enhance drug release but also promote apoptotic activity, which is quantitatively evidenced by shifts in key protein levels.

In sum, these unparalleled quantitative achievements in malignant cell suppression, raised cellular accumulation through efficient drug delivery, localized targeting, and reversing MDR under photo-responsive procedures support the clinical translation of these combined chemo-PD therapy platforms. The synergistic combination of photodynamic therapy (PDT) and chemotherapy, either as a standalone treatment or in combination with other therapeutic modalities, such as photothermal therapy (PTT), radiotherapy (RT), and sonodynamic therapy (SDT), represents a significant advancement in improving the prognosis and quality of life of patients with aggressive and drug-resistant breast tumors. Nevertheless, the clinical translation of the PDT method still faces multiple challenges, such as PS selectivity, fluorescence quenching, and other factors that may compromise therapeutic efficacy and clinical applicability.

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Competing Interests

The authors declare no conflict of interest.

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