Journal of Photochemistry and Photobiology C: Photochemistry Reviews 23 (2015) 103–131

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology C: Photochemistry Reviews

journal homepage: www.elsevier.com/locate/jphotochemrev

Review

Enhancing photodynamic therapy of refractory solid cancers: Combining second-generation photosensitizers with multi-targeted liposomal delivery

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ARTICLE INFO

Article history:
Received 2 September 2014
Received in revised form 5 May 2015
Accepted 6 May 2015
Available online 11 May 2015

Keywords:
Cancer
Drug delivery
Metallated phthalocyanines
Photodynamic therapy
Photosensitizers
Reactive oxygen species
Singlet oxygen
Tumor targeting

ABSTRACT

Contemporary photodynamic therapy (PDT) for the last-line treatment of refractory cancers such as nasopharyngeal carcinomas, superficial recurrent urothelial carcinomas, and non-resectable extrahepatic cholangiocarcinomas yields poor clinical outcomes and may be associated with adverse events. This is mainly attributable to three factors: (1) the currently employed photosensitizers exhibit suboptimal spectral properties, (2) the route of administration is associated with unfavorable photosensitizer pharmacokinetics, and (3) the upregulation of survival pathways in tumor cells may impede cell death after PDT. Consequently, there is a strong medical need to improve PDT of these recalcitrant cancers. An increase in PDT efficacy and reduction in clinical side-effects may be achieved by encapsulating second-generation photosensitizers into liposomes that selectively target to pharmacologically important tumor locations, namely tumor cells, tumor endothelium, and tumor interstitial spaces. In addition to addressing the drawbacks of clinically approved photosensitizers, this review addresses the most relevant pharmacological aspects that dictate clinical outcome, including photosensitizer biodistribution and intracellular localization in relation to PDT efficacy, the mechanisms of PDT-induced cell death, and PDT-induced antitumor immune responses. Also, a rationale is provided for the use of second-generation

Abbreviations: $^1O_2$, singlet oxygen; 5-ALA, 5-aminolevulinic acid; ε, molar absorptivity; Φ_T, triplet state quantum yield; AlPC, chloroaluminum phthalocyanine; $AlPCS_4$, tetrasulfonated chloroaluminum phthalocyanine; APCs, antigen-presenting cells; ATG7, autophagy-related protein 7; BCL2, B-cell CLL/lymphoma 2; BECN1, beclin 1; BID, BH3-interacting domain death agonist; CD91, cluster of differentiation 91; CPO, 9-capronyloxytetrakis (methoxyethyl) porphycene; CTL, $CD8^+$ cytotoxic T-lymphocyte; DAMP, damage-associated molecular pattern; DC, dendritic cell; DC-chol, 3β-[*N*-(*N*′,*N*′-dimethylaminoethane)-carbamoyl] cholesterol; DOTAP, 1,2-dioleoyl-3-trimethylammonium-propane; DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; DPPG, 1,2-dipalmitoyl-*sn*-glycero-3-phosphoglycerol; DSPE-PEG, 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy(PEG)-2000]; ecto-CRT, surface-exposed calreticulin; EGFR, epidermal growth factor receptor; EPR effect, enhanced permeability and retention effect; ER, endoplasmic reticulum; ETLs, endothelial cell-targeting liposomes; Fab' fragment, antigen-binding fragment; HDL, high-density lipoprotein; HER2, human epidermal growth factor receptor 2; HMGB-1, high mobility group box-1; HpD, hematoporphyrin derivative; HPPH, 2-(1-hexyloxyethyl)-2-devinylpyropheophorbide-a; HSP, heat shock protein; HUVEC, human umbilical vein endothelial cell; ICD, immunogenic cell death; ITLs, interstitially-targeted liposomes; LD_{50}, lethal 50% dose; LDL, low-density lipoprotein; LDLR, LDL receptor; log *P*, octanol/water partition coefficient; MHC, major histocompatibility complex; MPT, mitochondrial permeability transition; MT-1-MMP, membrane type-1-matrix metalloproteinase; mTHPC, *m*-tetrahydroxyphenylchlorin; NBD, nitrobenzoxadiazole; NF-κB, kappa-light-chain-enhancer of activated B cells; NGR, asparagine–glycine–arginine; NLRP3, NLR family; NPe6, mono-L-aspartyl chlorin e6; $O_2^{\bullet-}$, superoxide anion; PAA, polyacrylamide; PAcM, poly(acryloyl morpholine); PC, phthalocyanine; PDT, photodynamic therapy; PEG, polyethylene glycol; POPC, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine; PpIX, protoporphyrin IX; PRR, pattern recognition receptor; PS, photosensitizer; PVP, poly(vinylpyrrolidone); RAGE, receptor for advanced glycation end products; RGD, arginine–glycine–aspartic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; T4CPP, meso-tetrakis[4-(carboxymethyleneoxy)phenyl]porphyrin; TAAs, tumor-associated antigens; t-BID, truncated-BID; TLR, toll-like receptor; TTLs, tumor cell-targeting liposomes; UPR, unfolded protein response; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; ZnPC, zinc phthalocyanine; $ZnPCS_4$, tetrasulfonated zinc phthalocyanine; ZnTPP, zinc tetraphenyl porphyrin.

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http://dx.doi.org/10.1016/j.jphotochemrev.2015.05.002
1389-5567/

photosensitizers such as diamagnetic phthalocyanines (*e.g.*, zinc or aluminum phthalocyanine), which exhibit superior photophysical and photochemical properties, in combination with a multi-targeted liposomal photosensitizer delivery system. The rationale for this PDT platform is corroborated by preliminary experimental data and proof-of-concept studies. Finally, a summary of the different nanoparticulate photosensitizer delivery systems is provided followed by a section on phototriggered release mechanisms in the context of liposomal photosensitizer delivery systems.

Contents

1. Introduction

Photodynamic therapy (PDT) is a minimally-to-noninvasive treatment modality for numerous types of solid cancers. PDT involves the systemic administration of a photosensitizer (PS), accumulation of the PS in the tumor, and irradiation of the tumor with light of a wavelength that is well absorbed by the PS. Resonantly irradiated PSs undergo intersystem crossing from the singlet state to the triplet state, from which either an electron is transferred (type I photochemical reaction) or energy is donated (type II photochemical reaction) to molecular oxygen [1]. Type I reactions result in the formation of superoxide anion ($O_2^{\bullet -}$) and, in biological systems, derivative reactive oxygen and nitrogen species (ROS and RNS, respectively) [2], whereas type II reactions yield singlet oxygen ($^1O_2$). ROS/RNS are capable of (per) oxidizing biomolecules and ultimately induce tumor cell death by causing shutdown of intratumoral vasculature, tumor cell death, and an anti-tumor immune response (Fig. 1) [3,4].

While some solid cancer types respond very well to PDT [5–14], there are cancer types that are relatively recalcitrant to PDT, including superficial recurrent urothelial carcinoma [15], nasopharyngeal carcinoma [16], and extrahepatic cholangiocarcinoma [17,18]. In addition to the therapeutic recalcitrance, systemic administration of the PS may lead to non-selective tissue damage and phototoxic reactions due to inadvertent accumulation of the PS in the skin. With respect to the latter, patients are instructed to stay inside and avoid direct exposure to sunlight until the PS has been completely cleared to prevent unbridled photochemical damage to the skin. Although PDT is still being used in specialized treatment centers, the significant burden on patients has led several treatment centers, including ours, to abandon PDT as a treatment option for terminal cancer patients due to ethical considerations [19].

Such decisions are unfortunate in light of the relatively good treatment outcomes achieved with PDT in many other types of cancer, as a result of which researchers are striving to further improve this modality while minimizing the drawbacks. The negative side-effects associated with PDT may be circumvented in several ways. Firstly, novel and more efficacious second-generation PSs with improved photophysical and photochemical properties have emerged, including chlorins and metal-coordinated phthalocyanines. These PSs are excited at longer wavelengths at which deeper light penetration into tissue and more homogeneous treatment of the tumor can be achieved. High-power laser systems have become available to accommodate PDT with these PSs. Secondly, the new generation of PSs, which are often lipophilic, can be incorporated into nanoparticulate drug delivery systems to ensure compatibility with plasma (required for intravenous administration) and to facilitate selective targeting. The targeting is expected to improve PS accumulation in the tumor [20,21], as a result of which lower PS plasma concentrations will be required for