

Sonodynamic Cancer Therapy: A Non-invasive and Repeatable Approach Using Low-intensity Ultrasound with a Sonosensitizer

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Abstract

The low-intensity ultrasound that is used in clinical diagnoses, such as abdomen echo inspection, is a non-invasive treatment, and penetrates deeper into the body than light. Recently, sonodynamic therapy (SDT), which uses low-intensity ultrasound together with a sonosensitizer, has been developed for cancer therapy in applying such properties of ultrasound. So far, most sonosensitizers that have been developed are sensitive to light as well as ultrasound, implying that the shortcomings of photosensitizers used during photodynamic therapy, such as skin sensitivity, still need to be overcome in SDT. Some exceptions were, however, reported in recent studies in which sensitizers were activated mainly by ultrasound but not by light. Furthermore, recent in vivo studies have demonstrated that SDT with a sonosensitizer has a great potential as a non-invasive and repeatable treatment for cancer therapy.

Low-intensity ultrasound sonodynamic therapy sonosensitizers review

Major treatments for malignant tumors are surgery, radiotherapy, chemotherapy and a combination of these. Although combination therapy is considered to be an option with potential additive benefits, the increasing side-effects often cause patients to elect to discontinue treatment, such as radical radiotherapy or chemotherapy, which are limited to a single course even if patients have recurrent disease or a second primary manifestation in the irradiated field. Novel therapeutic strategies, preferably consisting of non-invasive treatments, are therefore required.

The use of light is one of the options that could be considered for non-invasive treatments. Light treatment for therapeutic purposes has been performed for thousands of years but more recently, the use of light with certain chemicals in photodynamic therapy (PDT) has been developed to treat diseases, especially in oncology (1-4). It is known that PDT requires a sensitizing agent, light energy and oxygen to generate reactive oxygen species (ROS), such as singlet oxygen and free radicals, which mediate cellular toxicity (5-7). Thus far, many chemical products can act as photosensitizers and new agents are regularly discovered. Very few,

however, are carried through to clinical trials, and even fewer become clinical photosensitizers. Ideal photosensitizers should not be toxic chemicals and not create new toxic byproducts. Photofrin, which has the longest clinical history and patient track record, is a hematoporphyrin derivative. In clinical PDT, red light (50-500 J/cm²) is needed to activate photofrin (8). Once a sensitizer is activated by specific wavelengths of light from its ground state into an excited state, there are two types of reactions that occur during PDT: (i) the activated sensitizer can react directly with substrates or molecules, transforming a hydrogen atom to form radicals, and then the radicals need with oxygen produce oxygenated products, or (ii) the activated sensitizer can transfer the energy to oxygen resulting in singlet oxygen formation, and then this highly reactive oxygen species oxidizes surrounding substrates. In PDT, cancer cell death occurs directly by the efficient induction of apoptosis, as well as through a non-apoptotic pathway. Recent evidence indicates that autophagy, in addition to necrosis as a mode of non-apoptotic cell death, is induced by PDT in order to allow repair and survival of key photodamaged organelles and can be turned into a death signal when the initial recovery response fails (9, 10). These signaling cascades are triggered in cancer cells exposed to photodynamic stress and, depending on the subcellular localization of the damaging ROS or sensitizers, transduce these signals into a cell death response (11, 12). As mentioned above, PDT is a useful non-invasive treatment for cancer therapy; however, there are at least two notable shortcomings that need to be overcome: limited penetration of light into deep tumor tissue, which is required to activate the photosensitizer, and certain potentially serious side-effects, such as long-lasting skin sensitivity due to the retention of the photosensitizer in cutaneous tissues (13, 14).

When considering the other non-invasive therapy that overcomes the problems of PDT, low-intensity ultrasound together with a sonosensitizer, termed sonodynamic therapy (SDT), is a promising candidate because of the non-invasive and deeper penetrating properties of ultrasound. Recent in vivo studies have demonstrated that SDT with a sonosensitizer has great potential as a non-invasive and repeatable treatment for cancer patients, even when tumors are located too deep to be treated using regular PDT.

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[Ultrasound](#)

Ultrasound is a type of mechanical sound wave with periodic vibrations in a continuous medium at frequencies greater than 20 kHz over the range of human hearing (16-20 kHz). Changes in ultrasound, such as scattering, reflection and absorption, among others, which allow ultrasound to reach the object, are useful to explore the object's inside or interface. The actions changing an object by ultrasound are classified as either actions by acoustic cavitation or others. Acoustic cavitation involves the formation, growth and near-adiabatic collapse of gas bubbles in liquids by irradiating ultrasound (15). When gas bubbles in liquid violently collapse temperature and pressure reach values in excess of 10,000 K and 10,000 atm with shockwaves and microjets. Acoustic cavitation also generates light, an emission known as sonoluminescence.

Ultrasound mediates both thermal and non-thermal effects in biological tissues. Ultrasound can

penetrate into tissue better than light, and generally its bioeffects are intensity- and frequency-dependent. A higher intensity results in efficient heat production, and a lower frequency facilitates acoustic cavitation (15, 16). Because ultrasonic waves can be focused like optical and audio waves using an acoustic lens, a bowl-shaped transducer or electronic phased array, high-intensity focused ultrasound (HIFU) has been developed to mediate thermal effects (17, 18). Once the energy density at the focus point is high enough, tissue is damaged. During HIFU treatment, the temperatures become much greater than 80°C. In such a case, thermal toxicity or irreversible cell death from coagulative necrosis occurs immediately within one second. Recently, magnetic resonance imaging (MRI)- or ultrasound-guided HIFU has been developed not only for prostate cancer but also for liver cancer (19, 20). Non-thermal bioeffects, on the other hand, are generally associated with oscillating or cavitating bubbles, but also include non-cavitating effects, such as radiation pressure, radiation torque, and acoustic streaming.

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[Drug Delivery System and Gene Therapy with Ultrasound](#)

Due to the highly disorganized nature of tumor vasculature, high blood pressure in the tumor tissue and high blood viscosity, the administration of drugs alone does not work at the site of tumor mass. In order to improve anticancer therapy, various strategies have been attempted in the last two decades to deliver anticancer drugs to the site of interest and minimize the dose, such as liposomes, micelles, micro/nanoparticles, polymer-drug conjugates and implants (21-23). Recently, new strategies using low-intensity ultrasound have been established in order to introduce new methods of drug delivery and to develop useful carrier systems for anticancer agents (24-26). Ultrasound increases membrane permeability and intracellular drug uptake by cavitation on the cell membrane, called sonoporation, although the mechanism of sonoporation is still unclear. Furthermore, cavitating and/or non-cavitating effects help to release a drug from micelles and the increase in concentration at tumor site enhances intracellular uptake (27, 28). In the first studies investigating the efficacy of ultrasound for gene therapy, typical ultrasound frequencies employed in drug delivery studies are in the range of 20-90 kHz and the optimal power density (intensity) of ultrasound ranges from 1 to 5 W/cm², depending on the irradiation time, which is usually 30-60 s at continuous ultrasound irradiation. However, therapeutic ultrasound that uses frequencies of 1-3 MHz and intensities of 0.5-3 W/cm² with pulse-mode has been employed because of tissue damage with higher frequencies along with cavitation. Although experimental conditions with high power ultrasound, including pulsed HIFU exposure, led to higher efficacy in enhancing drug delivery, there is still considerable debate regarding the development of standard protocols for successful anticancer therapy. More recently, researchers developed ultrasound-mediated gene delivery by injecting gene and nano/microbubbles (bubble liposomes) into blood flow (29, 30). According to these reports, bubble liposomes quickly transduced plasmid DNA into the tissue of interest by cavitation, even with the existence of a blood stream. After significant successes of in vitro studies of ultrasound-mediated drug and gene delivery, a recent in vivo animal study indicated that low-frequency ultrasound significantly reduced tumor size in xenograft models (31-33). Alternatively, a combination of tumor-associated antigens and bubble liposomes was developed in dendritic cell

(DC)-based cancer immunotherapy with low-intensity ultrasound (34). The exogenous antigens, interestingly, were recognized as endogenous antigens when delivered to the cytosol using bubble liposomes in combination with ultrasound, resulting in presenting antigens to MHC class I, which is essential for activating tumor-specific cytotoxic T lymphocytes.

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Table I.

Sonosensitizers used in SDT in an in vivo animal model and SDT conditions.

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[Sonodynamic Therapy](#)

Exposure to ultrasound and subsequent cavitation collapse can have similar effects in producing free radicals by facilitating porphyrin derivatives, such as the effect of light on PDT (35, 36). Thereafter, SDT together with a sonosensitizer was developed for cancer therapy (37). Although the mechanisms for activating sensitizers by ultrasound irradiation from a steady state to an excited state are still unclear, it is thought that the process is likely to be identical to that when light is cast on PDT, as mentioned above. This hypothesis is doubtful for two sonosensitizers: 13,17-bis(1-carboxyethyl)-8-[2-(2,4-dichlorophenylhydrazono)ethylidene]-3-ethenyl-7-hydroxy-2,7,12,18-tetramethylchlorin, disodium salt [DCPH-P-Na(I)], a novel porphyrin derivative, and titanium dioxide (TiO₂), a photocatalyst. Both sensitizers showed different reactivity from those so far reported to light and ultrasound irradiation. The former had quite weak reactivity to visible light of approximately 6,000 lux for 10 min compared to ATX-70, a strong photosensitizer, which showed potent cytotoxicity (38). The latter required 60-fold longer periods of UV irradiation (5 mW/cm²) to obtain similar cytotoxicity on ultrasound exposure (1.0 W/cm²) (39). Furthermore, the cytotoxicity of TiO₂ induced by UV exposure was completely inhibited by a radical scavenger while that by ultrasound irradiation was only partly inhibited. Taking into consideration the fact that ATX-70 demonstrated less sonotoxicity than DCPH-P-Na(I) on a human gastric cancer cell line, MKN-45, in addition to the results mentioned above, a promising sonosensitizer candidate in SDT might be facilitated by different mechanisms observed on PDT, namely cavitation and collapsing energy, but not sonoluminescence. Skin hypersensitivity or 30 days of sunlight photosensitivity might be a small price to pay for non-invasive or painless treatment for patients who have been through surgery, radiotherapy and/or multiple chemotherapy agents, whereas SDT with a sonosensitizer without photosensitivity may be an ideal treatment in non-invasive and repeatable cancer therapy.

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[Sonosensitizer on SDT in an In Vivo Animal Model](#)

Except in cell cultures, there are very few recent studies of ultrasound-mediated antitumor effects in combination with a sonosensitizer performed on animal models, as summarized in

Table I. Knowledge of the mechanism of sonoporation in SDT is still very limited, and constitutes a major obstacle in determining the factors affecting acoustically triggered activation of sensitizers and in the development of standard protocols for successful anticancer therapy.

Porphyrin derivatives thus far used most often as a sonosensitizer in in vivo animal models are photofrin, protoporphyrin IX (PPIX), ATX-70 and DCPH-P-Na(I) (38, 40-42). Although the mechanisms by which porphyrin derivatives selectively accumulate in tumors are complex and not fully understood, it is presumably because of the high vascular permeability of the agents, as well as their affinity for proliferating endothelium and the lack of lymphatic drainage in tumors. Pharmacokinetic parameters of these derivatives were investigated except for DCPH-P-Na(I), and showed similar patterns in tumor, skin and muscle, supporting this hypothesis. Furthermore, the antitumor effect of DCPH-P-Na(I) in SDT indicated a higher efficacy for preventing tumor growth from 6 up to 24 h after intravenous administration (unpublished data).

SDT using 5-aminolevulinic acid (5-ALA) was also reported in this issue with low-intensity but focused ultrasound in deep-seated glioma model (43). 5-ALA-induced fluorescence has been used in malignant glioma in order to render more complete resection in surgical operations (44). Neoplastic cells synthesize abundant intracellular PPIX after administration of 5-ALA. Therefore, the administration of 5-ALA may work with mechanisms similar to that of PPIX in SDT. The other advantage of using 5-ALA in malignant glioma in SDT is that it can be orally administered to patients.

The potential of TiO₂ nanoparticle as a novel sonosensitizer was reported recently using C32 melanoma tumor cells in vivo (45). In the chemical industry and environmental treatment, TiO₂ is well known as a photocatalyst that has a strong oxidizing activity and produces oxidative radicals with irradiating UV light or ultrasound (46, 47). These properties are useful not only for photosensitizers in PDT, but also for sonosensitizers in SDT. The lack of selective accumulation of particles in a tumor mass resulting in insufficient selectivity and low efficiency is one of the shortcomings in a clinical setting.

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Theoretically, SDT using low-intensity ultrasound in combination with a sonosensitizer might be effective in all types of cancer without a need for choosing the target molecules, proteins and/or genes. Recent reports performed in both in vivo and in vitro studies support this hypothesis, and thus, SDT is a promising candidate for non-invasive and repeatable cancer therapy. Most sonosensitizers reported thus far, including a very recent one, mono-l-aspartyl chlorin e6 (NPe6), a chlorophyll-like substrate, are also known as photosensitizers, implying that skin sensitivity, a serious adverse effect of such sonosensitizers in PDT, still remains a problem that needs to be overcome in SDT (48). It is expected, however, that a growing amount of experimental data and number of sensitizers would lead to the extensive application of SDT in various cancer models in vivo in the near future.

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