

Rationale of Combined PDT and SDT Modalities for Treating Cancer Patients in Terminal Stage: The Proper Use of Photosensitizer

Integrative Cancer Therapies
9(4) 317–319
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DOI: 10.1177/1534735410376634
<http://ict.sagepub.com>


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We read with interest the recent article by Wang et al,¹ reporting the clinical application of SF1 (Sonoflora 1)—a sensitizer that can be activated by light and ultrasound. SF1 is an analog of chlorophyll in that its macrocycle backbone is porphyrin-based and the center of the porphyrin ring consists of a metal ion.² The chlorophyll derivative has light absorption peaks at 402 and 636 nm.³ A very unusual combination of this investigational agent and various prototype light sources and ultrasound devices was used in the treatment of three patients who suffered from late stages of breast cancer with systemic metastases to multiple organs. The combination of photosensitizer and light illumination is commonly known as photodynamic therapy (PDT) and the combination of drug or sonosensitizer and acoustic activation as sonodynamic therapy (SDT). In theory, the direct tumoricidal effects of these modalities are mediated by cytotoxic agents generated through photochemical or sonochemical reactions inside tumor tissue. The narrow gap between potential benefit and potential risk is determined by intrinsic cellular sensitivity and the *sensitizer ratio* between tumor and normal tissue.

The synergistic effects of sensitizer and low-power ultrasound have been examined in many in vitro studies and to a lesser extent in in vivo models.^{4,5} Although the sonosensitization-induced cytotoxicity might be attributed to the sonochemical reaction, such as sensitizer-mediated energy transfer and free radical generation, data suggest that the mechanism of sonosensitization is probably not governed by a universal mechanism, but may be influenced by multiple factors including the nature of the biological model, sensitizer distribution, ultrasound parameters and acoustic energy distribution.⁶ Nevertheless, to date, the correlation between ultrasound parameters and biological effects has not been fully established in preclinical investigation (in vitro or in vivo). There is no convincing data that shows that ultrasound used in this way is effective in the treatment of primary tumor and multiple metastases. Therefore, this article raises a few basic questions. First of all, without those critical safety and efficacy information, it is unjustifiable to

test the unproven prototypes in humans, particularly those in terminal stages for any purposes.

The authors state that acoustic activation was delivered after intravenous administration of the chlorophyll derivative in two different modes—local and whole body ultrasound activation. A handheld ultrasound transducer was used for two patients, which was associated with a side effect of pain. Another patient was placed in a water tub to receive whole body ultrasound treatment. It was expected that ultrasound could reach deep-seated tumor(s) and sensitizers that are beyond the reach of external light of 630 nm. Although no details were provided in terms of the number of transducers in the water tub, the geometric distribution of acoustic energy within the body, and its accessibility to the multiple tumor sites (e.g., breast, lung, bones, liver, neck, axillary lymph nodes, and abdominal lymph nodes), the authors indicated that high acoustic power (2 W/cm² at 1 MHz for 20 minutes) was used in both settings without providing justifications on the selection of those parameters. It is also questionable that sufficient acoustic energy will reach the deep-seated metastases in lung and bone tissues.

Second, single high-dose PDT and metronomic PDT (i.e., to deliver photosensitizer and/or light doses at low rates over an extended period) have distinct and complementary therapeutic goals. In contrast to the conventional PDT regimen of single dose drug administration (intravenous or oral), the authors used a repeated lingual delivery of the chlorophyll derivative (a total dose of 30 or 60 mg) for 2 to 3 consecutive days followed by light plus ultrasound treatment daily for 3 days starting at day 3 or day 4 after the onset

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of sensitizer administration. The same protocol was repeated once at 1- or 2-week intervals. Although no pharmacokinetics data were provided in the article, if more than 48 hours of accumulation time is required for tumor tissue as implied by the authors, it can be expected that the drug clearance time could be much longer. Although the repeated sensitizer delivery might improve the uptake in cancerous tissue, the skin and organs of the reticuloendothelial system including the liver (healthy and impaired) can take up and retain the sensitizer for a longer period. Even though PDT does not have significant cumulative toxicity and can be repeated in the same area, the drug spatial distribution and accumulative effect of repeat administration of the investigational agent must be studied in order to define or predict any PDT or SDT effect.

Indeed, PDT as a disease-site treatment modality has been used as an off-label alternative to treat chest wall recurrence of breast cancer.^{7,8} Distinct local responses can be identified and such responses are a reliable predictor of tumor regression. However, none of these responses were mentioned in the article.

Third, the modulation of light delivery in PDT has often been manipulated to further enhance the selectivity of PDT.^{9,10} Unlike conventional local or focal light delivery, in addition to the light illumination delivered by a handheld light emitting diode (LED; 630 nm) to the primary tumor site(s), the authors state that a light box type "light bed" is used for "whole body illumination" without providing any rationales and consequences. The attenuation coefficient of 630 nm light in human skin is estimated in the range of 1.6 to 1.7 mm.¹¹ Because of the limited tissue penetration, it is questionable that the superficial illumination will have any direct effect on deep-seated metastases. Clearly, if the sensitizer concentration reaches the therapeutic threshold level in tumor tissue, the repeated whole body illumination at 36 J/cm² (i.e., 20 mW/cm² for 30 minutes) opts to cause strong systemic cutaneous responses and possibly other adverse effects as well.¹² If none of these biological responses take place, it is unlikely that the PDT regimen used in this article would have any significant therapeutic benefit.

Fourth, regardless of whether those PDT and SDT protocols are beneficial, because of the fact that they were used either simultaneously with or immediately after other aggressive interventions, based on known scientific and clinical evidence, it is impossible to rule out the potential that the other interventions might be responsible for the effects observed in these cases.

Last, but not least, in addition to technical issues associated with PDT and SDT protocols described by the authors, the article also raises serious ethical issues on testing unproven and unconventional interventions in cancer patients in the terminal stage. Although PDT is often used for palliative treatment with the goal of debulking solid tumor(s) in selected patients, it is rarely used, as stated by the authors, in

intensive care conditions for terminally ill patients who are too weak to speak, move, feel, eat, and breathe. It is true that it is hard to say that PDT is a strongly "evidence-based" treatment because only a few PDT applications have been rigorously proven superior to conventional alternatives in randomized controlled clinical trials, but history demonstrates that the improper use of photosensitizer and PDT can give PDT a bad name that would be very difficult to clear.¹³

Cancer patient care at the end of life has changed markedly in the past years and a growing number of patients demand more than just evidence-based interventions. Indeed, clinical studies involving cancer patients who have failed standard treatment also present an especially challenging set of complexities. On the one hand, patients still hopeful for a miracle cure may not always appreciate the costs and risks associated with unproven interventions and physicians may unwittingly be ambiguous about likely therapeutic gain of such interventions.¹⁴ On the other hand, physician's own goals may play significant roles in putting patients through unproven treatment intentionally. This may well be the case of this and another similar article¹⁵ because the authors proceeded to the next patient even though there was no solid proof of clinical efficacy from SF1-mediated PDT and SDT in the previous patient.

Undoubtedly, it is premature to say that the combined PDT and SDT protocol used by the authors "is a promising new therapeutic combination for the treatment of breast cancer." Better designed preclinical studies and clinical trials are certainly needed to define the roles of PDT and/or SDT for the late stages of breast cancer with systemic metastasis.¹⁶

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