

Photodynamic Therapy: A Light in the Darkness?

□□ Commentary on Kabingu et al., p. 4460

Alexander Lin and Stephen M. Hahn

Photodynamic therapy (PDT) is used to treat localized premalignant or early malignant disease. This study reports the enhanced, systemic antitumor immune response from PDT, suggesting that it may have a potential role as a therapy to address both local and disseminated disease.

In this issue of *Clinical Cancer Research*, Kabingu and colleagues (1) present their results demonstrating the ability of photodynamic therapy (PDT), a local therapy, to elicit an enhanced, systemic antitumor immune response. This is the first time that a specific tumor-associated antigen immune response has been shown in patients after treatment with PDT. This finding has important clinical implications for the development of PDT and other novel therapeutic strategies as a means to stimulate a tumor-specific immune response that might lead to improvements in long-term control of both local and disseminated disease.

PDT is a U.S. Food and Drug Administration (FDA)-approved modality for definitive therapy of precancerous lesions such as actinic keratoses and Barrett's esophagus, early stage microinvasive endobronchial lung cancer, and for palliation of advanced esophageal or endobronchial malignancies. PDT is also being studied in clinical trials for locally recurrent prostate cancer and serosal spread of abdominal and thoracic cancers (2–4). PDT exerts its local effects via light-dependent cytotoxicity. The treated area is exposed to monochromatic light after local or systemic administration of a chemical photosensitizer. The wavelength matches the absorbance peaks of the photosensitizer used. The photosensitizer absorbs light energy, and then interacts with reactive oxidative species or directly with cellular substrates, resulting in cell death via apoptosis or necrosis. FDA-approved treatment regimens are generally well tolerated, as the shallow depth of light penetration through tissue minimizes damage to deeper structures.

Although PDT is a focal treatment given to address localized disease, there is growing evidence that it may also have systemic effects, by stimulating an anticancer immune response. This has been shown by Korbek and colleagues (5), who compared the efficacy of PDT in Balb/C (immunocompetent) versus scid (immunocompromised) mice. Their results showed that PDT yielded similar efficacy in the initial ablation of mammary sarcomas from both sets of mice; however, long-term cure was

limited only to the Balb/C mice. Interestingly, the long-term efficacy of PDT in scid mice improved if bone marrow transplantation from Balb/C donors was done prior to PDT. This stimulated immune response may also have benefits on systemic disease, as evidenced by improved tumor control in mice outside the local PDT field (6). To date, the immunologic effects of PDT has been poorly understood, and prior to the current report from Kabingu and colleagues (1), had not been clearly observed in human studies.

Kabingu and coworkers (1) conducted their work on patients with nodular or superficial basal cell carcinoma (BCC). They identified several HLA-A2 peptides that bound to Hip1, a tumor-associated antigen (Fig. 1). Patients treated with PDT showed enhanced lymphocyte recognition of Hip1. A majority of patients treated with PDT had a greater than two-fold increase in immune response, a finding that was not seen in those treated with surgical excision alone. They also found that the enhancement in antitumor immunity was greatest with lower light doses and less surface area treated.

A growing understanding of tumor-host interactions and cellular immunology have led to the development of immune-based therapies that can specifically target and reject cancer-specific cells. Kabingu and colleagues (1) have taken the important first step by showing that PDT stimulates an enhanced, tumor-specific response. This is an important bench to bedside observation. The authors have previously shown that PDT is more effective than ionizing or UV radiation at creating effective antitumor vaccines and have shown that PDT-based tumor vaccines can be effective without the coadministration of an adjuvant (7). Additional preclinical work has shown that PDT likely results in increased activity of antigen-presenting cells (8), that neutrophils play a critical role in regulation of immune response (9), and that there may be a light delivery dependence of the immune response (10). These preclinical findings contributed to the design and execution of the current study in patients with BCC and provided a unique platform to assess PDT-associated immune response.

Technical issues and normal tissue toxicities currently preclude the broader applicability of PDT for the treatment of invasive malignancies (4, 11, 12). The use of PDT in these settings has been associated with a narrow therapeutic index and recurrent disease is common. The results of Kabingu and colleagues suggest that there may be opportunities to improve the efficacy of PDT for invasive malignancies by taking advantage of the enhanced immune response after light delivery. Altering the method of light delivery and/or using

Authors' Affiliation: University of Pennsylvania, Department of Radiation Oncology, Philadelphia, Pennsylvania

Received 4/30/09; accepted 5/5/09; published OnlineFirst 6/9/09.

Requests for reprints: Alexander Lin, Department of Radiation Oncology, University of Pennsylvania, 3400 Spruce Street, 2 Donner Building, Philadelphia, PA 19104. Phone: 215-662-3198; Fax: 215-349-5445; E-mail: lina@xrt.upenn.edu.

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doi:10.1158/1078-0432.CCR-09-0964

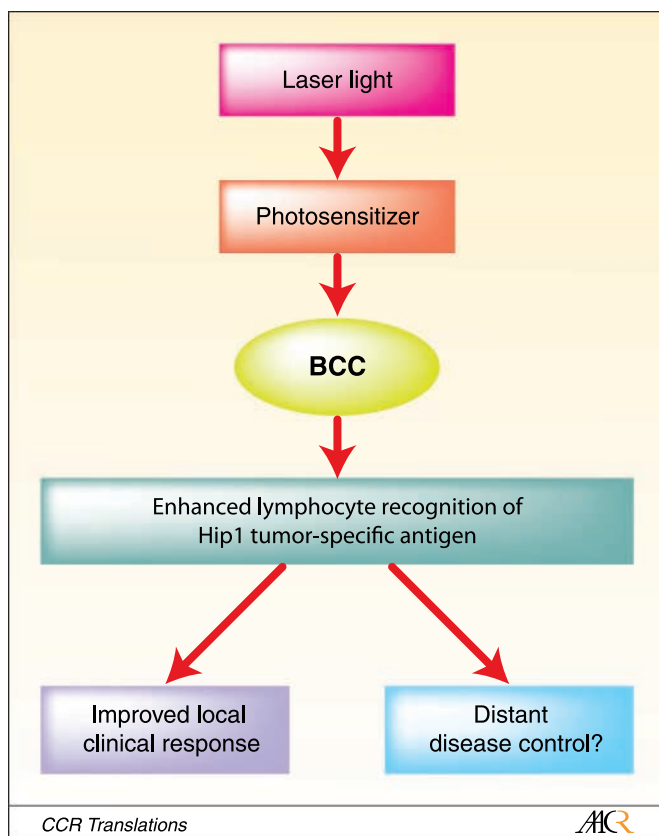


Fig. 1. PDT was delivered to superficial and nodular BCC by applying laser light directly to affected areas after local [5-aminolevulinic (ALA)] or systemic (Porfimer-sodium) administration of a chemical photosensitizer. Treatment with PDT initiated a significant tumor-specific immune response, resulting in improved local clinical responses, as well as observed responses of lesions outside of the treatment field.

regimens with fluence rates and fluences that have a more favorable effect on immune response may result in an improved therapeutic index for PDT. The rationale design and implementation of clinical studies using PDT in combination

with other immune-based therapies could also be considered. This is especially appealing given the author's previous work showing that PDT is one of the most effective methods for creating an antitumor vaccine (7).

The encouraging results of Kabingu are preliminary and based upon relatively small patient samples. Confirmation of these findings in other PDT trials is needed. It must also be determined whether the immune responses translate into improved local or systemic tumor control. Kabingu and colleagues (1) reported regression of lesions present at time of PDT but outside of the treatment field in two patients. They also allude to the fact that those with greater immune responses exhibited better clinical responses after treatment. However, findings such as these are limited, and are still largely anecdotal. To optimally use PDT-based cancer immunotherapy, we must further understand the basic mechanisms of the immune response and we must apply the current findings to other settings in well-designed clinical trials with correlative laboratory immunological endpoints. These studies would be most relevant in tumors for which current, standard therapies fail to adequately provide local control or prevent systemic dissemination.

The finding that a local therapy can stimulate a cancer-specific systemic response is certainly noteworthy. It lends optimism that new therapies are on the horizon for our patients who are diagnosed with cancers for which current therapies yield suboptimal results; however, as is often the case with such findings, additional questions and issues are brought to light, and will need to be addressed in moving forward. Despite these challenges and questions, studies such as this one done by Kabingu and colleagues (1) contribute significantly to our understanding of the potential role the host response may have on disease control. This will hopefully facilitate the development of treatments that will result in long-term disease control for our patients.

Disclosure of Potential Conflicts of Interest

S. Hahn is a consultant for Rasiris, Inc.

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