Lighting Up the Lives of Cancer Patients by Developing Drugs for Tumor Imaging and Photodynamic Therapy: A "See and Treat" Approach

by Ravendra K. Pandey, PhD

More than two decades ago, scientists discovered that cancer cells, pretreated with a photosensitive agent (drug), were destroyed when exposed to red light. Today, photodynamic therapy (PDT) has become a viable option for many cancer patients who are unable to have surgery or who cannot tolerate additional chemotherapy and/or radiation due to their associated side effects. PDT has been approved by the U.S. Food and Drug Administration (FDA), and is used worldwide for early- and late-stage lung cancer, obstructive esophageal cancer, high-grade dysplasia associated with Barrett's esophagus, age-related macular degeneration, and actinic keratoses.

PDT is widely practiced in both the community setting and in large hospitals. Due to the availability of diode lasers as the light source, this treatment is becoming more practical and economical.

Understanding Photodynamic Therapy

PDT uses photosensitizing agents and light to kill cancer cells. The photosensitizing agent can be injected into the bloodstream or applied to the skin. After a time interval to allow the drug to be absorbed by the cancer cells, a light source is applied to the treated area. The light causes the drug to react with oxygen, which then kills the cancer cells. PDT also may work by destroying the blood vessels that feed the cancer cells, by alerting the immune system to attack the cancer.

This novel treatment has several advantages over traditional cancer treatments of surgery, chemotherapy, radiation, and/or hormone therapy. Patients have fewer, if any, long-term side effects. Treatment with PDT is less invasive, can be precisely targeted, and can be repeated several times at the same site if necessary.

There are some limitations to PDT therapy, however. In general, these limitations stem from the fact that the light used to activate most photosensitizers can travel through tissue only to a depth of about 1 cm. Therefore, PDT is most often used to treat tumors on the skin, just beneath the skin, or on the lining of internal organs or cavities. Currently, PDT is most often used for local treatment and not for cancer that has metastasized, or to treat large tumors.

Clinical PDT was developed in the PDT Center at Roswell Park Cancer Institute with the discovery of Photofrin®, the first-generation, FDA-approved, porphyrin-based compound. Porphyrins are known to have two key properties that are essential to PDT. First, they migrate to and accumulate more in cancer cells than in normal tissue; and second, they are activated by tissue-penetrating red light generated by a laser, to create a cytotoxic event. It is the cytotoxic event resulting from the interaction of the drug, light, and oxygen that defines PDT. When the photosensitizer drug is activated in the body by the red light, it produces a molecule called "singlet oxygen." This highly reactive molecule oxidizes and kills the targeted cells while doing relatively little damage to surrounding tissue.

However, the first-generation photosensitizer, Photofrin, often caused inflammation at the treatment site and left patients sensitive to light for four to six weeks after treatment. As a result, the PDT group at Roswell Park initiated studies to further clarify how PDT works and used the information to design more effective photosensitizers that have greater selectivity and more desirable pharmacokinetics.

To develop effective photosensitizers with the required photophysical characteristics, the PDT Center focused on naturally occurring materials, such as chlorophyll-a, the molecule that makes plants green and is responsible in part for photosynthesis, and bacteriochlorophyll-a, a similar molecule found in bacteria. The result was a new photosensitizer—Photochlor, or HPPH—which is currently producing promising results in Phase II clinical trials.

Photochlor is considered a second-generation photosensitizer because of its improved properties over Photofrin®. These two photosensitizers have closely related molecular structures but significantly different photophysical properties. Clinical studies have shown that Photochlor stays in the tumor for a long time and clears faster from the rest of the system and does not show any significant skin phototoxicity, a main drawback associated with most of the porphyrin-based compounds, including Photofrin. Photochlor also offers the advantage of long wavelength absorption that increases light penetration and minimizes the number of laser fibers needed to deliver light within the tumor. These properties are important for treating large and deep-seated tumors.

Photochlor and other generations of photosensitizers with long wavelength absorption in the range of 700-800 nm are being developed at the PDT Center and show promising clinical and preclinical results, with improved efficacy over Photofrin,® and fewer side effects. Another important area of research in the PDT Center is aimed at identifying how PDT alters the adaptive immune response and how these changes contribute to the efficacy of PDT therapy. Recent results generated by scientists at the PDT Center clearly indicate a basis for PDT immune response in humans.

PDT: The Next Generation

Most deaths from cancer are caused by distant metastases—satellite tumors seeded by cancer cells that escape the original tumor site and take root and grow in distant organs. Chemotherapy, hormonal, and other therapies have been developed to try to prevent or kill these metastatic tumors. However, PDT may hold promise to more effectively

identify and treat metastatic disease. For example, Roswell Park investigators are analyzing the viability of this treatment by combining a variety of imaging technologies with PDT to more fully illuminate the precise location of tumors and to identify metastatic disease.

A photosensitizer for PDT that also functions as an imaging agent would create an entirely new paradigm for tumor diagnosis and therapy, because it would be both the contrast and therapeutic medium. Tumors could be continuously imaged without ambiguity as to their location. This paradigm would make the low toxicity and high efficacy of PDT applicable to virtually any location, from the skull base to the floor of the pelvis.

Roswell Park's translational research team of basic scientists and clinicians is using and evaluating image-guided placement of optical fibers followed by PDT in conjunction with diagnostic technologies such as PET, MRI, and fluorescence imaging. The information provided through this "one-two" punch of PDT combined with diagnostic imaging will allow surgeons to perform tumor removal more completely using this "see and treat" approach.

Photosensitizer-directed PET Imaging. PET has been used primarily to image and assay biochemical processes and cellular function. Used alone or with CT imaging, PET is a non-invasive procedure that reveals metabolic changes in the body that help physicians diagnose and treat certain diseases. In a recent study with certain radioactive analogs of chlorophyll-a-based compounds developed at the PDT Center, researchers were able to detect distant lesions from a breast tumor model known to metastasize to lung and bones. These results are exciting, and further comparative studies with the current PET imaging agents are in progress.

Photosensitizer-directed MRI. Conventional MRI relies on imaging advanced tumors with certain agents. The time course of tumor imaging with these agents depends on the concentration of the contrast media in tumors. As the contrast agent clears from the circulation, tumor image increases due to the rising tumor-to-background ratio. However, tumor image then rapidly declines, as the contrast agent leaches from the lesion. Slower clearance from the tumor would enable MRI scanning of larger tumors.

Scientists in Roswell Park's PDT Center have linked certain high tumor-avid porphyrin-based compounds to MRI contrast agents. These conjugates stay in the tumor for more than 24 hours and laboratory results suggest these novel structures can be used for tumor imaging and PDT. This approach is quite versatile, and shows an enormous potential for developing tumor-imaging and/or therapeutic agents.

Fluorescence Imaging and PDT. Photosensitizers generally fluoresce, and the fluorescence properties of these porphyrins *in vivo* have been exploited by several investigators to detect early-stage cancers in the lung, bladder, and other sites. In addition, the fluorescence can guide the activating light for treatment of early disease or for deep-seated tumors.

Optical tomography is a form of CT that creates a digital model of an object by reconstructing images made from light. Investigators are using optical tomographic techniques to visualize the fluorescent probes within tissue volumes. When using applications such as bronchoscopes, fluorescence imaging can allow precise assessment of the location and size of a tumor, and provide information on its invasiveness.

Studies suggest that tumor-avid porphyrin-based compounds can be used as "vehicles" to deliver the desired fluorescent agent(s) to the tumor. The development of a dual-function agent that combines fluorescence imaging and PDT has potential as a cost-effective approach to detect tumors and target PDT.

Nanotechnology for developing multifunctional agents. Nanotechnology has achieved the status of being a critical research endeavor of the early 21st century, as scientists harness and manipulate the unique properties of atomic, molecular, and macromolecular assemblies at the nanometer scale. The small size, surface tailorability, improved solubility, and the multifunctional nature of the nanoparticles open many new research avenues for biologists. Scientists and clinicians at Roswell Park are collaborating with colleagues at the University at Buffalo and University of Michigan to develop tumor-targeted nanoparticles that deliver a high payload of the photosensitizers and the desired imaging molecules to tumors. This research project is funded by the National Institutes of Health under the Platform Project mechanism. (For more on the promise of nanotechnology for cancer diagnosis and treatment, see *Oncology Issues* Sept./Oct. 2005 and Nov./Dec. 2005, archived at *www.accc-cancer.org.)*

While PDT has been around for more than 20 years, its potential as a novel diagnostic and therapeutic approach is just beginning to be explored. Although the challenges to discovering the full potential of PDT are complex, the benefits to current and future patients can be significant. The information provided by tumor-targeted multifunctional photosensitizers when combined with diagnostic imaging allows for additional localization of tumor and assessment of the effectiveness of the therapy, thus assisting the surgeon in performing tumor resection more completely via the "see and treat" approach.

Ravendra K. Pandey, PhD, Professor and Distinguished Member, is with the Photodynamic Therapy Center at Roswell Park Cancer Institute in Buffalo, N.Y.