The future of photodynamic therapy

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Before getting too far into this, I should tell you that in the past, my crystal ball has been distinctly cloudy. Therefore, I should refrain from predictions and try to assess where we are today and where current trends would indicate future directions.

One cannot discuss the future of PDT without including new photosensitizer development and light delivery systems, both of which will be covered in the JCIPA meetings. Therefore, some of this presentation will overlap talks by myself and others in other sessions. Recently, we carried out a computer search of papers relating to any aspect of PDT since 1972 and when we recorded 10,000, we stopped. As you can predict, the vast majority of them were in the last 5 years.

Important factors comprising the current status of PDT are in the areas of clinical research, pre-clinical research, light delivery systems and to some extent, mechanistic studies. I will briefly touch on each of these.

The future of this new treatment will depend upon convincing physicians that it can achieve effective clinical results not easily attained by existing treatments. Certainly, the results of the Japan PDT group in treatment of early stage cancers is an example of this uniqueness. Several papers dealing with these studies will be presented at this conference. It should be noted that Denis Cortese and his colleagues at the Mayo Clinic have initiated a comparative trial of PDT vs surgery in patients with early stage lung cancers [1]. This study is based upon the premise that preserving lung function by PDT will ultimately benefit these patients who are at high risk for developing additional lung cancers. Results from the Mayo Clinic, Tokyo Medical College and others have indicated the efficacy of PDT in such patients, some of whom are surviving nearly 10 years after treatment. Other new clinical protocols may indicate the unique advantage of PDT as an adjunct to surgery. In particular, the work of Abulafi and colleagues at the Royal London Hospital [2] indicates that applying PDT after resection of colo-rectal tumors, whether complete or not, can lead to increased survival compared to surgery alone, although larger numbers of patients will be required in this comparative trial to confirm these early results. (In 58 patients, the survival rate was 85.1% for PDT plus surgery vs 67% for surgery alone). Also, the work of Mueller in Toronto [3] and Kaye in Melbourne [4] in applying PDT following resection of malignant brain tumors also indicates a trend toward increased survival, although these are not comparative trials. These data have led to a multi-center Phase II trial in the U.S. and Canada for this disease. Equally exciting are the clinical data of Biel and co-workers in Minneapolis in applying PDT to early stage tumors of the head and neck [5]. Eleven patients with T_1 and T_2 tumors of the larynx and 8 patients with T_1 tumors of the tongue and floor of the mouth achieved a complete response where 4 patients with T_3 and T_4 cancers of the upper aerodigestive tract had partial responses. Also, in the adjuvant setting, are the trials initiated at the U.S. National Institutes of Health by DeLaney and Pass and associates [6]. These groups are investigating the feasibility of using PDT for removal of small tumors in the peritoneum, e.g. from ovarian cancers, and as adjunct to surgical resections of intrathoracic cancers, e.g., mesotheliomas. Both studies present challenges to light dosimetry both from the standpoint of area size (up to about 1000 cm² in the thoracic cavity and as much as 20,000 cm² in the peritoneum) and of geometry. In order to obviate the latter, the NIH group has used diluted intralipid as a scattering medium. In similar studies in the thoracic cavity at Roswell Park, by Takita, multiple bulb-type fibers (4-7) are placed strategically within the cavity without the use of scattering medium. To date,

these Phase I studies have defined acceptable doses of drug and light (1.5 to 2.5 mg/kg Photofrin and 3 Joules/cm² with boost to 10 J/cm² in critical mass for the peritoneum and up to 20-25 J/cm² following 2.0 mg/kg Photofrin in the thoracic cavity). In the Roswell Park study, it was found that patients undergoing pneumonectomy plus PDT for extensive mesothelioma did very poorly with excessive fluid loss and other complications while those undergoing only tumor debulking followed by PDT had more or less normal recovery. Phase II trials are now underway for both types of studies.

In terms of photosensitizer development, there are now five new materials in Phase I clinical trials in the U.S., Canada and Europe. Benzoporphyrin derivative, a chlorin-type photosensitizer having maximum red absorption at 690 nm, is being investigated by QLT (Vancouver, B.C.) in collaboration with Lederle Laboratories (Pearl River, NY). BPD is a short acting drug inducing skin photosensitivity for 3-5 days following injection (rather than 30-60 days for Photofrin). Lui and co-workers report a 74% complete plus partial response rate in 22 (64 lesions) patients with certain cancers [7,8]. Similarly, NPe6 (MACE) (red maximum, 664 nm) sponsored by Nippon Petroleum has produced a 79% complete plus partial response rate in 6 (19 lesions) patients with basal cell carcinoma and skin photosensitivity persisting for less than one week [9]. Meta-tetrahydroxyphenyl chlorin (mTHPC) with a red maximum at 650 nm has been examined by Ris and co-workers in Bern, Switzerland, for treatment of mesotheliomas and metastatic breast cancer [10,11]. This appears to be a very effective photosensitizer in that 0.3 mg/kg followed by 10 J/cm² of light 48-72 hours later, produced tumor necrosis up to 1.0 cm in depth. Unlike BPD and MACE, however, this is a long lasting photosensitizer which may result in long term skin photosensitivity. Interestingly, it appears that therapeutic ratio (selectivity) actually increases up to 9 days after injection. Tin etiopurpurin (SnET2) sponsored by PDT Pharmaceuticals of Santa Barbara, CA, which absorbs maximally in the red at 660 nm, has just been entered into Phase I clinical tests and no data has been reported to date. Delta-amino levulinic acid (ALA), sponsored by DUSA in the U.S., was proved by Kennedy and is quite unique in that it is a precursor to protoporphyrin and certain other porphyrins produced in-situ in the host. Thus, topical or systemic application of ALA produces the photosensitizers in ectodermal tissue (epidermis, nervous system, and mucous membranes) and apparently in tumors arising in this tissue. Topical application is being used to treat superficial skin cases. Kennedy (Ontario Cancer Center, Kingston, Ont.) reports a 94% complete response in 300 lesions [12]. He reports that failures did not respond well to a second treatment perhaps due to limited penetration of ALA and/or vehicle. Recently, Cairnduff, et al. found a recurrence rate of 50% in such products at 17 months post-treatment [13]. Systemic ALA-PDT is being investigated for head and neck cancers by Bown and colleagues at the National Medical Care Center, London, who reports biopsy proven necrosis following activation at 630 nm [14].

The future of PDT will certainly include diode laser systems. There is currently available a 670-690 nm diode laser capable of emitting 3 watts of power from a 420 μ m fiber (Spectra Diode Labs, San Jose, CA). These types of systems operative on 110 V, are electrically cooled, are small, portable and relatively inexpensive (approximately \$25,000 U.S.). This wave length range can be used with a number of the new photosensitizers discussed above. Systems emitting at 630 nm are not yet available but work on their development is underway. These easy to operate, inexpensive light sources may have a major impact on the acceptance of PDT by the medical community.

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