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Technology Review

# PHOTODYNAMIC THERAPY

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## INTRODUCTION

Photodynamic therapy (PDT) involves administration of a tumour-localizing photosensitising agent, followed by activation of the agent by light of a specific wavelength. This therapy results in a sequence of photochemical and photobiological processes that cause irreversible photodamage to tumour tissues [1] (level 1).

## 1. TECHNICAL FEATURES

The concept is relatively simple: Inject into a patient a light-sensitive drug that concentrates primarily in tumour cells, and 2 or 3 days later activate the drug with a light source (usually some kind of laser) directed at the tumour. The drug reacts with the oxygen in the tissue and produces singlet oxygen, which is cytotoxic to tumour cells. For PDT to work, the cancer must be accessible either directly (including in an operative bed) or endoscopically [1-2(level 9)].

Most of the light used is produced by lasers and is in the red part of the spectrum where tissue penetration is greater. More attention should be paid to dosimetry, or the amount, rate, and distribution of the light in tissues.

Photodynamic therapy produces a superficial effect. When a photosensitiser and oxygen are distributed uniformly over targeted tissue (which cannot be definitely determined), the volume of tissue destruction during PDT depends on the penetration depth of the light. For most combinations of photosensitisers, this penetration depth ranges from several millimetres to one centimetre [3] (level 9). The small penetration depth will restrict PDT application. PDT can be applied effectively in the treatment of superficial diseases, such as carcinoma in-situ and mucous dysplasia. In the same manner, one can treat microscopic residual tumours after resection. It seems that PDT with external tumour irradiation for cases of large locally spread tumours will be inefficient.

## 2. OBJECTIVE

This review is to determine the safety and effectiveness of photodynamic therapy for oncological indication.

## 3. METHODOLOGY

An electronic search using the following databases was carried out: PUBMED, EBSCO, PROQUEST, MEDLINE and Google. The following keywords were used: photodynamic therapy, photodynamic therapy for cancer and photodynamic therapy for metastases. Cross references were also carried out on the articles retrieved.

## 4. RESULT AND DISCUSSION

### 4.1 Safety

If side effects are taken into account, the superficial effect of PDT is an advantage over radiotherapy. When extensive surfaces (such as pleura or peritoneum) are irradiated, PDT becomes more preferable due to a smaller damage of healthy underlying tissues. PDT is indicated in both early (measuring < 8 mm in diameter) and advanced stage lung cancers. In patients with advanced disease and important exophytic tumours, the aim is palliation; in those with early central disease, treatment is done with curative intent [4-5] (level 7).

Photodynamic therapy (PDT) is a relatively new treatment modality for various types of cancer, including cancer of the head and neck. The advent of the second-generation photosensitisers such as meta-tetra (hydroxyphenyl) chlorine (mTHPC) which are more effective and less phototoxic to the skin than their forerunners, now makes this treatment a feasible alternative to surgery or radiotherapy in specific cases [6(level 9)-7(level 4)]. Patients with pre-malignant conditions in the oesophagus such as high-grade dysplasia or superficial cancers appearing in Barrett's oesophagus are candidates for oesophagectomy [8] (level 7). To avoid the morbidity and possible mortality associated with oesophagectomy, Wang used PDT on these patients. In many patients, the Barrett's and dysplasia improve considerably or disappear [8]. One problem in treating the oesophagus with PDT is pain, which can be severe and last for days. Although mTHPC is less phototoxic to the skin than the first generation of photosensitisers, patients still have to stay indoors for 1 week after injection and must avoid direct sunlight during the second week. For 3 months after injection of mTHPC, patients should be careful about inadvertent exposure of the skin or eyes to strong light whereby neglecting the postoperative sunlight exposure restrictions, can cause development of second degree burning wounds on the hands, neck, and abdomen.

PDT as a treatment for non-invasive bladder cancers has a bad reputation because of reports of toxic effects such as bladder contraction, bladder irritation, and other problems, occasionally permanent, after the treatment. Because of severe and long-lasting side effects, Nseyo et al. suggested multiple treatments at lower doses to reduce the incidence and severity of symptoms following PDT for superficial bladder cancer [9] (level 7).

## 4.2 Effectiveness

Superficial cytotoxic effects of PDT have some disadvantages. In the case of many massive, invasive, or deep tumours, superficial irradiation with light will be insufficient to produce an effect within the entire tumour. In this case, the application of PDT as a monotherapy will be inefficient. Because of this, PDT should rely either on the interstitial light delivery or the combination with surgical treatment [10] (level 1).

Another pathology which cannot be treated effectively with PDT is the treatment of metastases in regional lymphatic nodes. It is known that solid malignant tumours are accompanied by micrometastases in regional lymphatic nodes. The excision and/or radiotherapy of regional lymphatic nodes became routine techniques for many clinical entities of cancer, especially when tumours are located in the head and neck. The limited penetration depth of optical radiation during PDT may impede the application of this technique in the treatment of residual lesions of lymphatic nodes. This problem can be resolved by combining PDT with other therapeutic methods. It is also feasible to make use of new photosensitisers, which produce biological effects at a greater depth [11] (level 9).

It is difficult to assess therapeutic efficiency and side effects without definite quantitative estimation of the administered treatment. Among the reasons for using radiotherapy as a therapeutic technique was the feasibility of accurate dosing of radiation load on tissues and its correlation to both tumour responses and side effects. For PDT, this problem seems to be more intricate because this treatment involves light and photosensitiser dosimetry. Furthermore, the biological effect of photosensitiser and light doses is governed by many parameters (such as photosensitiser delivery, tissue geometry, photosensitiser inactivation, tissue oxygenation, and optical heterogeneity) [12-13] (level 9)

Because of limited migration of $O_2$ from the site of its formation [3], sites of initial cell and tissue damage of PDT are closely related to the localisation of the sensitisers [15] (level 9). Sensitisers that are not taken up by cells are extremely inefficient even though some of them gave high photochemical yield of $O_2$. The probability of cell inactivation per quatum of absorbed light is widely different among PDT sensitisers. Generally, this probability is lower for hydrophilic than for lipophilic sensitisers, indicating membrane structures are vulnerable. Uptake and retention of i.v. administered photosensitiser by tumour tissue is one of several fundamental determinants of the clinical effectiveness of PDT. It is important therefore that the residual tumour tissue that needs to be treated is well vascularised. Also, the cytotoxicity of PDT is dependent on oxygen as a substrate to create free radicals important in cell death. This requirement for oxygen is yet another reason that residual tumour tissues must be vascularised. Korbelik and Krosl have also shown that both photosensitiser accumulation and tumour cell death decreases with the distance of the tumour cells from the vascular supply [16] (level 9).

The first PDT application, which was approved by the FDA in the United States, was the palliative treatment of obstructive oesophagus cancer [17(level 1)-18(level 8)]. Randomised clinical trials confirmed that PDT had a palliative effect on obstructive oesophagus and bronchial tree cancers [19-20] (level 4). However, it is difficult to believe that PDT will produce serious changes in oncology. The superficial effect of cytotoxic reactions makes it impossible to apply PDT in the treatment of large obtruding tumours. As a result, PDT can mainly produce temporary and palliative effects. Furthermore, PDT has no obvious advantages over superficial radiotherapy or brachytherapy. Intraperitoneal treatment using PDT has been somewhat problematic. Intraperitoneal spread of cancers is a common clinical problem, with limited treatment options leading to morbidity and death. Intraperitoneal photodynamic therapy (IP-PDT) combines maximal surgical debulking of gross tumour with intraoperative light delivery to the peritoneum after preoperative i.v. injection of photosensitiser to treat residual disease. An issue of concern in IP-PDT is the potential lack of photosensitiser uptake by residual small tumour nodules (STNs) < 5 mm in maximum diameter and by microscopic residual disease caused by incomplete development of a vascular supply. A study examined the existence of vasculature and Photofrin (PF) uptake in STNs in 12 patients in a Phase II clinical trial for IP-PDT [5]

For years, Merrill Biel, M.D., has been treating several types of head and neck cancers with PDT. Treatment of superficial oral,

oral/pharyngeal, or nasal cavity tumours and cancer of the larynx has yielded a cure rate of 88% to 90% [2, 7, and 21(level 4)] Modern PDT is an effective treatment modality that should be considered as a possible alternative to surgery or radiotherapy in specific cases of head and neck cancer. None of the patients treated in this series experienced permanent impairment of these functions, which highlights the main advantage of PDT: the absence of the long-term loss of function often seen in radiotherapy and surgery. Photodynamic treatment kills malignant cells but spares the basic cellular architecture. This permits rapid healing after treatment during which the killed cells are replaced by new, normal cells, thereby avoiding the ulceration and fibrosis that commonly occur after other forms of tissue removal [6]

## 5. CONCLUSION

A serious PDT drawback was the limited penetration depth of laser radiation. Clinical photosensitisers have maxima of photodynamic action at 620 to 690 nm. In this range, optical radiation penetrates biological tissues poorly (at a depth of several millimetres). Maximum penetration lies in the far-red and near-infrared ranges from 750 to 1,500 nm. Many commercial lasers operate in these ranges. Hence, photosensitisers that would effectively generate singlet oxygen in these ranges are needed.

There seems to be a near consensus in all literature reviewed that the field of application of PDT is likely to expand and undergo many technological development, especially, with respect to the photosensitizing agents used, which may lead to its increased use in the years to come. Photodynamic therapy is not expected to replace surgery, radiotherapy or chemotherapy; rather, it is meant to complement them. Still, we will need stronger scientific evidence of the advantages of PDT over other treatments and to examine its impact on the Malaysian health-care system before its use can be justified in these new applications.

## 6. RECOMMENDATION

It is recommended that for the treatment of lung and bladder cancers and superficial oesophageal cancers, PDT should be used only for clinical research purposes and as yet, should not be authorized for public coverage. For the palliative treatment of advanced oesophageal

cancer PDT should be considered a possible option when recognized treatments are contraindicated and should undergo further clinical research. For the treatment of Barrett's oesophagus, PDT should be fully assessed before it is introduced into current practice. Modern PDT should be considered as a possible alternative to surgery or radiotherapy in specific cases of head and neck cancers such as treatment of superficial oral, oral/pharyngeal, or nasal cavity tumours and cancer of the larynx. This should undergo further clinical research.

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