Photodynamic therapy begins to shine

Photodynamic therapy (PDT) has been slow to catch on, says Thomas Dougherty (Roswell Park Cancer Institute, Buffalo, NY, USA). But now, PDT is being applied to a surprising variety of conditions. Cancers, precancers, non-cancerous dysplasias, inflammatory conditions, diseases of excess capillary proliferation, and restenosis after angioplasty are all being actively investigated. There are 61 US groups alone studying PDT, says Dougherty, who explains that although "injecting the photosensitiser is easy, we now have to apply the proper dose of light, and every tissue and organ is different".

In PDT, patients are given a drug (photosensitiser) that generates highly reactive "singlet" oxygen on absorption of light energy. High doses of singlet oxygen kill cells, while low doses somehow modify cell behaviour. The tissue selectivity of PDT depends on where the light is directed, how deep it penetrates, and where the photosensitiser concentrates—often in neoplastic and other abnormal tissues for reasons that may include increased metabolism, increased permeability, and decreased lymphatic drainage.

The antecedent of PDT, explains Dougherty, was the use of fluorescent porphyrins to detect cancer, a method that worked because these molecules collected in the abnormal tissue. "In the 1960s, Richard Lipson, the originator of PDT, realised that these same compounds could also act as photosensitisers and so could be used to kill tumour cells."

Most photosensitisers under development for PDT are based on porphyrin. So far, the only drug to be approved is Photofrin (QLT Phototherapeutics, Vancouver, Canada), a derivative of haematoporphyrin, but several other porphyrin-like compounds are in trials, as is 5-aminolaevulinic acid which is converted by cells to protoporphyrin IX, one of the sensitisers in porphyria.

PDT is ideal for treatment of skin cancers, for which, says Paul Baas (Netherlands Cancer Institute, Amsterdam), PDT gives better cosmetic results than surgery. However, PDT is not limited to treatment of easy-to-illuminate skin lesions. For example, PDT for early-stage lung cancer has recently been approved in the USA and elsewhere. "Endoscopy", says Dougherty, "allows both detection and PDT of high-grade dysplasia and microinvasive disease of the bronchial tree, surgical treatment for which used to mean removal of part or all of the lung. PDT avoids major surgery and causes less collateral damage than radiation or chemotherapy".

PDT is also approved in the USA for palliation of obstructive oesophageal cancer, and is now being tested against early oesophageal cancer. "In the past, the treatment was oesophagectomy, which has high mortality and morbidity. Now, Photofrin is in a phase III trial for this cancer", says Dougherty.

PDT is also proposed as an adjuvant to surgery whenever local recurrence is likely or resection of all visible tumour is impossible. Here, says Baas, PDT can be used to "sterilise the surgical field". Baas himself has had encouraging results with PDT in a small number of patients with malignant mesothelioma.

Although PDT can directly kill tumour cells, researchers believe that thrombosis of tumour capillaries is also crucial for eradication of tumours. Indeed, says Harvey Lui (University of British Columbia, Vancouver, Canada), "there is a debate as to whether PDT is primarily vascular-specific rather than directly cytotoxic for tumour cells". Dougherty concurs. "PDT needs to act both on the tumour and on the vessels. One or the other does not usually work." Tumour capillaries may allow more drug into tumours than into normal tissues, and "the endothelium in the tumour also retains more drug than normal endothelium", adds Baas. The drug-concentrating effect of abnormal capillaries is also exploited in treating age-related macular degeneration and diabetic retinopathy, where low-dose PDT can selectively eliminate excessive blood-vessel proliferation.

Immunomodulation may also be involved in tumour killing. After PDT, tumours contain many polymorphonuclear cells; but is this a "clean-up" response to cell death or are activated natural killer cells necessary to kill all the tumour cells damaged by PDT? Wim Sluiter (Erasmus University, Rotterdam, Netherlands) is studying PDT in rats and says that both an inflammatory response and PDT are needed for tumour killing. "When insertion of the light fibre causes an inflammatory response, polymorphonuclear cells are fully activated, but you cannot get rid of the tumour without PDT-induced injury to the tumour. Conversely, if there are no polymorphonuclear cells present, PDT has no effect."

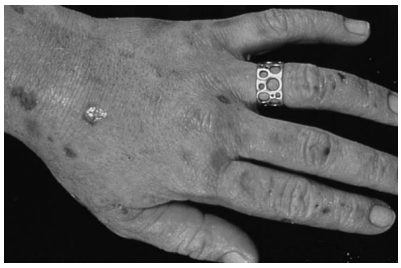
The fact that low-dose PDT can also be used to treat psoriasis and alopecia areata, both of which involve T-cell attack on tissue, is further evidence for PDT affecting the immune system. "We used to think PDT was all phototoxicity, but now it is clear it has immunomodulatory effects", says Lui. Activated T cells may preferentially take up sensitisers because they have a high metabolism and the immune response could then be modulated either through cell killing or by a change in T-cell behaviour.

PDT's uses do not stop here. Low-dose PDT is being used to induce reversion of dysplastic Barrett's oesophagus to normal oesophagus. And in Boston (MA, USA), Glenn LaMuraglia has prevented restenosis of rat carotid arteries after balloon injury by use of high-dose PDT.

PDT has a great future, Lui concludes. "It combines the best of radiotherapy and chemotherapy. It has low systemic toxicity and the treatment is repeatable. Photosensitisers in the dark may be as benign as antibiotics." The only limit now to PDT's development may be the imaginations of the researchers working on it.

Paul M Rowe

Photodynamic therapy—induced selective porphyria?



National Medical Slide Bank

In porphyria cutanea tarda and some other porphyrias, overproduction of porphyrins causes generalised cutaneous photosensitivity. The challenge in PDT is to temporarily induce maximal photosensitivity in the tumour or other lesion, while minimising the degree and duration of generalised photosensitivity.