

Photodynamic therapy – new light on cancer treatment

*Janet E Brown,
Stanley B Brown and
David I Vernon talk about
the latest developments in
the fight against cancer*

Around one-third of the population of Western Europe will develop cancer in their lifetime and the disease continues to present a huge cost in human suffering as well as in economic terms. Cancer can be defined as an uncontrolled proliferation of cells that usually invade adjacent local tissues and often spread, via lymphatic and blood vessels, to distant parts of the body giving rise to metastases. Although it is often thought of as a single entity, different types of cancer vary enormously in their behaviour and their progression. Cancer therefore encompasses a whole spectrum of disease from solid tumours such as in breast and lung to non-solid such as leukaemias.

Therapeutic improvements are continually being made (for example in treatment of the leukaemias) but there has been no substantial improvements in survival in some of the major cancers and the need to understand the scientific basis of the disease and develop new treatments therefore remains unabated. It is in this context that the newly developing treatment known as photodynamic therapy (PDT) appears to offer some potential.

Photodynamic therapy

PDT uses a combination of a photosensitising drug and light in the presence of molecular oxygen to obtain a therapeutic effect. If any one of the three components, photosensitiser, light, molecular oxygen, is absent, there is no

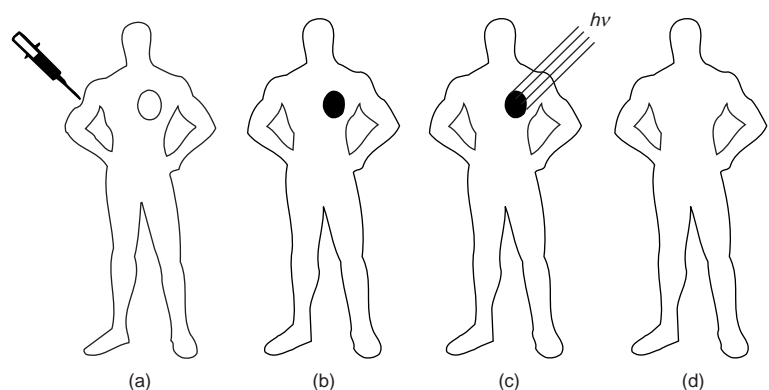
biological effect. PDT is currently being developed, not only for cancer but also for benign diseases such as macular degeneration and cardiovascular disease. In principle, the application of PDT to a patient is very simple (Figure 1) however, in practice the dosimetry is critical both in terms of the drug and the light, as well as the time between drug and light administration. Most PDT research has been aimed at working out which drug is best, what drug dose is best, what light dose is best and how the light might best be delivered for any given clinical indication.

Like all cancer treatments, the primary aim of PDT is to destroy tumours without causing unacceptable damage to normal tissue. In the case of PDT, the targeting of the therapy to tumours is assisted by a number of factors that are unique to this particular approach. These factors include:

- Photosensitiser variation. Although only one sensitiser (Photofrin) has currently been approved for general use by licensing authorities in various countries, literally hundreds of other

sensitisers have been assessed for PDT and a number of these are currently undergoing human trials.

- Localisation of photosensitisers in tumours. Some sensitisers have the ability to concentrate in tumours relative to the surrounding healthy tissue and therefore offer a beneficial therapeutic ratio for treatment.
- Activated oxygen. PDT is known to work through the production of activated oxygen known as singlet oxygen, which is so reactive that it cannot escape from the cell in which it was produced. PDT is therefore a local technique at the cellular level and does not produce a cytotoxic agent that may diffuse widely from its point of origin.
- Lasers and fibre optics. It is probably developments in lasers and fibre optics more than any other factors that have led to PDT becoming a viable clinical tool in recent years. By using fibre optics coupled with the various techniques of endoscopy it is possible to deliver light with precision to most parts of the body.



- (a) The photosensitising drug is administered intravenously to a tumour-bearing patient
- (b) After an optimum time (different for each drug) the sensitiser becomes localised preferentially in the tumour
- (c) At this stage the tumour area is irradiated with light of the appropriate wavelength for a pre-determined time
- (d) After several weeks the tumour disappears

Figure 1 Clinical application of PDT

- The healing process following PDT. One of the major features of PDT is the excellent healing of normal tissue around tumour beds, should this be damaged during the PDT process. This is particularly impressive in the healing of skin lesions.

Photosensitisers

By definition, a PDT photosensitiser must be able to absorb light and then to pass on this absorbed energy to molecular oxygen so as to cause biological damage. The wavelength and intensity of light required to carry out PDT is determined by the absorption properties of the photosensitiser. Most sensitisers have broad absorption spectra in the visible region and therefore permit a choice of irradiation wavelength for PDT. For example, the absorption spectrum of Photofrin shows a large absorption band around 400 nm (the Soret band) with progressively smaller bands out towards the red region of the spectrum.

It might therefore be thought that it would be most effective to use light around 400 nm for PDT. Surprisingly, this proves not to be the case because the penetration of light into tissue is strongly wavelength dependent, with red light penetrating much more effectively than blue or violet light. For this reason, it has been found to be most effective to carry out PDT with Photofrin at 630 nm. Of course, if it is specifically desired that light penetration and the resulting PDT effect should be restricted (as for example in treatment of carcinoma *in situ* of the bladder) then the wavelength may be chosen appropriately and green light has sometimes been used for this purpose.

The first photosensitiser to be used widely in clinical work was known as

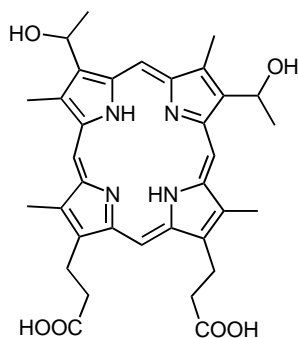


Figure 2 Structure of haematoporphyrin IX

Singlet oxygen

Normal ground state atmospheric molecular oxygen exists in a triplet state (electron spins unpaired). It is relatively unreactive and generally needs high temperatures or a catalyst, for example an enzyme, in order to react. When a sensitiser in its normal singlet ground state (electron spins paired) absorbs light it may be converted to an excited singlet state, which may then cross to an excited triplet state. This then may react with normal triplet oxygen to produce singlet oxygen, when the sensitiser returns to its ground state singlet form. This singlet oxygen is highly reactive, particularly towards the carbon-carbon double bonds found in biological membranes.

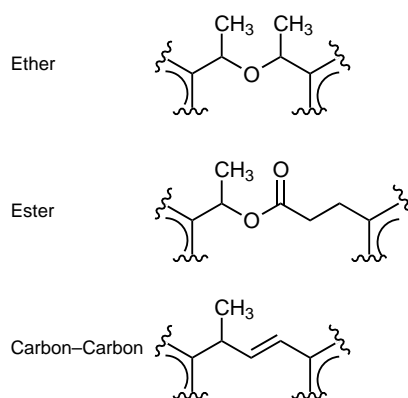


Figure 3 Structural features of the oligomers in HPD

haematoporphyrin derivative (HPD). Haematoporphyrin itself (Figure 2) is a powerful photosensitiser but not an effective PDT agent because it is not retained by tumours. However HPD, which is a mixture of porphyrin monomers and oligomers (Figure 3) is retained in tumours and also produces a good PDT effect (Figure 3). It was shown in a series of studies that it is the oligomers that are responsible for PDT activity. Photofrin is material prepared from HPD by removing most of the non-active-monomeric components. In spite of the fact that it is a very complex mixture, Photofrin has now been used to treat many thousands of patients by PDT and is the only drug so far approved by the FDA and other drug licensing authorities in Europe, Japan and Canada.

Because of the perceived imperfections with Photofrin such as the fact that it is a complex mixture, that it has a relatively low absorption at the treatment wavelength and also because it has a very long lifetime in the body which

causes prolonged skin photosensitivity, there has been a major effort over the past decade to develop new and improved sensitisers.

What properties would be required in an ideal sensitiser? The answer is that it depends what we want to use the sensitiser for. Improved absorption in the red region of the spectrum (650–800 nm), purity and ease of production of the sensitiser and rapid clearance from the body to avoid prolonged skin photosensitivity are often quoted. Of course, it is a pre-requisite that the sensitiser must be efficient at producing activated oxygen. Many candidate compounds have now been tested *in vivo* (Figure 4) and several of these are now at various stages in clinical trials.

ALA and protoporphyrin IX

In recent years, there has been considerable interest in the use of 5-aminolaevulinic acid (ALA) in photodynamic therapy. ALA itself is not a photosensitiser. It is a small, five carbon compound that is the first dedicated intermediate in the pathway of biosynthesis of porphyrins which leads to haem and chlorophyll. It is therefore a compound that occurs naturally in almost all cells, but normally it does not accumulate.

When ALA is given exogenously to cells in culture, to animals or to patients, it enters the porphyrin biosynthetic pathway, which becomes temporarily overloaded. For reasons that we do not yet fully understand, this temporary overload leads to the transient build-up of protoporphyrin IX (PpIX) (Figure 4) the immediate pre-cursor of haem. Although

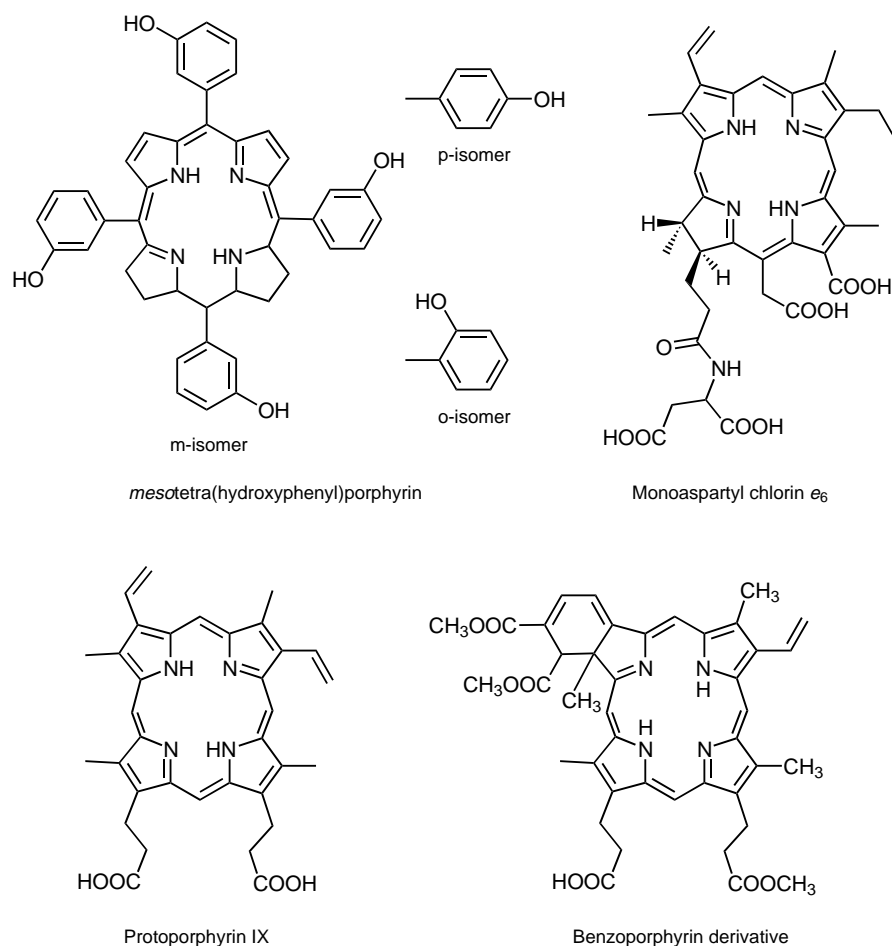


Figure 4 Structures of some second generation photosensitisers

haem itself is neither a photosensitiser nor fluorescent, PpIX is a powerful photosensitiser. Maximum build up of PpIX usually occurs about 3–4 hours after administration of the ALA, but the amount of PpIX then declines to zero over the next 24 hours as it is metabolised either on to haem or by other routes. If light at 635 nm is delivered to tissue containing the ALA-induced PpIX, then a powerful PDT effect may occur. This is the principle of ALA-PDT which is being increasingly used in dermatology and other clinical applications (see below).

The approach may also be used diagnostically since the PpIX formed is highly fluorescent. Again, for reasons that are not properly understood, tumours and other proliferating tissue usually accumulate more ALA-induced PpIX than the surrounding tissues.

Although ALA-PDT has proved very successful clinically for certain superficial applications, problems have arisen in treating deeper tumours such as thicker skin tumours where ALA applied topically

may not penetrate sufficiently deeply. Attempts to solve this problem are currently being made by the use of esters of ALA, rather than ALA itself. The principle here is that ALA esters are more lipophilic than the parent molecule and are therefore able to penetrate more deeply into tissues and are also taken up more efficiently by cells. Once inside the cell, the ALA ester is rapidly hydrolysed by cellular esterases to ALA free acid, which can then enter the metabolic pathway as before. Preliminary studies using these materials both for treatment and diagnosis have been very promising.

Light delivery

Both laser and non-laser light sources are in use for clinical PDT. For most photosensitising drugs, the absorption bands of interest are broad and monochromatic light is therefore not required. The coherence of the light produced by lasers is also of no advantage for PDT. The primary advan-

tage of a laser in PDT lies in its ability to produce a narrow beam of light that may be directed into an optical fibre of 200 microns or more. However, for applications where fibre optic delivery is not required, non-laser light sources that produce broad beams of light may be most appropriate.

Until recently, the only options available for laser light delivery were machines such as the Argon-dye laser and the copper-dye laser. These lasers are large and not easily transportable and are also expensive. Quite recently, a new generation of lasers, known as diode lasers, have revolutionised the PDT scene. These lasers are about briefcase size and are very stable and reliable. They have an output comparable to the much larger lasers but are much less expensive, costing around £25 000. They are therefore much more practical to use, especially since they may be moved from hospital to hospital very easily. They do suffer from the disadvantage that they are not tunable and may only be used at a fixed wavelength. However, for treatment with a particular drug for a given indication they are extremely convenient.

Non-laser light sources are also finding increasing use in PDT, especially for dermatological applications and other types of treatment where the use of narrow fibres is not required as, for example, in treatment of the cervix. They are generally cheaper even than diode lasers, costing around £10 000.

Clinical applications of PDT

PDT has now been applied in a wide variety of clinical situations in treatment of both cancer and benign disease. Development has been relatively slow, partly because of the large number of parameters which have to be specified for PDT (drug dose, light dose, light dose rate, drug-light time interval, light fractionation, light source, light delivery system, etc). Each particular application has its own optimum combination of these parameters and much of the development work has been aimed at determining these optimum parameters. The main areas of clinical work are outlined below.

Dermatology

In the dermatological field, since the lesions are almost always visible and accessible, there has been much interest in development of topical preparations of PDT drugs. So far, there has been little success, with the notable exception of ALA and its derivatives. These may be formulated into creams and the topical ALA approach has been used to treat non-melanoma skin cancers, primarily basal cell carcinoma (BCC) and Bowen's disease as well as benign conditions such as acne and psoriasis.

The treatment has proved particularly effective for Bowen's disease, which can often occur on wide areas and in elderly patients with fragile skin. The ALA cream is simply spread over the lesion and left for 3–4 hours before application of an appropriate light dose for perhaps 20 minutes. During the application of the light, most patients feel some discomfort or pain that can be controlled by local anaesthetic. In more than 90% of patients, this simple treatment leads to complete cure. A particular feature of PDT treatment of the skin with ALA is the remarkably good healing which occurs and a Phase III study of treatment of Bowen's disease with PDT versus cryotherapy (a current treatment option) showed considerable benefit for PDT-treated patients in this context.

Bowen's disease is very superficial but BCCs can be either superficial or can result in thicker lesions. For the superficial BCCs, ALA-PDT has again proved to be an effective treatment but for thicker lesions, substantial recurrence has occurred following the first treatment. Several centres are actively seeking ways of improving the BCC cure rate, either by more effective treatment with ALA initially or by the use of ALA esters. Since the treatment for these extremely common diseases by ALA-PDT is very simple and potentially inexpensive, it is likely that PDT will find a place in their routine treatment, provided the remaining problems may be overcome.

PDT in the bladder

PDT using Photofrin has been used to treat bladder cancer, including both focal disease and carcinoma *in situ*. The latter involves a very superficial occurrence of cancer in the bladder wall but the cancer

may cover a relatively large area. Carcinoma *in situ* appears to be an ideal situation for treatment by PDT since it is possible using endoscopy and light diffusion techniques to irradiate large areas of the bladder wall uniformly. This potential remains but initial treatments with Photofrin have been somewhat disappointing, due to difficulties in fine tuning light and drug dosimetry, problems which have sometimes led to damage to the bladder wall and consequent bladder shrinkage. More recently, work has been carried out using local administration of ALA or ALA esters in the bladder and this is potentially very promising since deep penetration and damage to the bladder wall is less likely.

PDT in the brain

PDT using systemic Photofrin has been used in the treatment of glioma by several groups. Following initial surgical resection, the mean survival time for patients with this condition is typically only a few months and there is evidence that PDT can extend this survival time. Again the full potential has not yet been realised and there is a need for more extensive clinical trials.

Very recently, treatment of tumours of the pituitary has begun using systemic Photofrin in the Centre in Leeds. The usual procedure for treatment is surgical resection followed by radiotherapy, but this can involve some morbidity and the radiotherapy cannot be repeated. We are investigating the possibility of using PDT following resection in place of radiotherapy. With around 16 patients treated so far the treatment looks promising and is well-tolerated without any serious side effects.

Gynaecological uses of PDT

There have been two main approaches to the use of PDT in the gynaecological field, namely the treatment of menorrhagia (unacceptably heavy or prolonged menstrual periods) and the treatment of

cervical intraepithelial neoplasia (CIN). In both cases topical ALA has been used as the source of photosensitiser.

Menorrhagia is a widespread problem and often ultimately requires hysterectomy. Many gynaecologists are looking for a less radical way to treat this condition. In principle, this can be achieved by ablation of the endometrium, the proliferative layer within the uterus. Endometrial ablation using ALA-PDT has been developed by the Centre in Leeds and is now being taken up by other groups in Europe and USA. Again, in principle, the approach is very simple. ALA, in the form of a gel or a capsule, is introduced into the uterus and some 3 or 4 hours later light is delivered through a hysteroscope. Biochemical studies have shown that there is a very high ratio of PpIX formed in the endometrium compared to the myometrium (the underlying muscle layer of the uterus), demonstrating a good potential for successful treatment.

Of the 25 patients treated so far in the Leeds study, almost half have seen sufficient improvement such that hysterectomy has so far been avoided. However, the treatment parameters require further optimisation and more extensive and rigorous clinical trials are required.

CIN is a precancerous condition of the cervix, which is diagnosed by smear testing. A number of groups are investigating the use of ALA cream for its treatment. Although it is too early to comment on success rates, preliminary work has demonstrated that the technique is feasible and has good potential for success.

PDT in the lung and oesophagus

Many studies have now been carried out of PDT in the lung and this is one of the indications for which Photofrin has been approved. In advanced and inoperable lung cancer PDT has proved to be a valuable palliative approach that potentially offers both an extension of life and an improvement in quality of life.

'Photodynamic therapy is a significant new approach to treatment of cancer and other diseases'

PDT has also proved to be successful in the treatment (cure) of early lung cancers, particularly in Japan where mass screening is carried out. There is a strong feeling that PDT will find a routine use in this field, although currently in the western world relatively few early lung tumours are detected and in the great majority of cases, tumours are advanced and inoperable at the point of diagnosis.

In the oesophagus, PDT has been used both to treat advanced tumours with palliative intent and to treat Barretts oesophagus, which is a pre-cancerous condition of the oesophageal epithelium.

Ophthalmological uses of PDT

A potentially major application of PDT in a non-cancer field is its use in treatment of age-related macular degeneration. This condition, caused by proliferation of neovasculature in the retina, is the major cause of blindness in the over 50s in the western world. Currently there is virtually no treatment to halt the progression of the disease. Using a photosensitiser (benzoporphyrin derivative, Figure 4)

which enters neovasculature very rapidly following administration and is subsequently quickly moved from the circulation, Phase II trials have shown that PDT can be a very effective technique for treating this condition. A Phase III trial is now well under way (PDT versus light alone) and it is likely that PDT for macular degeneration will become an approved treatment within the next year or two.

Other clinical treatments

Other areas where PDT has been used clinically include prostate, colon, head and neck and pancreas. It has also been used to treat vascular disease (restenosis) and is now being extended to treatment of bacterial infections.


Photodynamic therapy is a significant new approach to treatment of cancer and other diseases. It has been shown to have a high potential in many areas but there is a great need for more extensive and more rigorous clinical trials. With the approval of the first PDT drug, Photofrin, and the development by several large

pharmaceutical companies of second generation sensitisers, it may confidently be expected that PDT will play an increasing role in the range of therapies available to treat cancer and other diseases.

Acknowledgments

We thank Yorkshire Cancer Research for financial support.

Janet Brown is at the Christie Hospital NHS Trust, Manchester, UK; Stanley Brown and David Vernon are at the Centre for Photobiology and Photodynamic Therapy, School of Biochemistry and Molecular Biology, University of Leeds, UK.

<p>In black</p>	<p>In white</p>	<p>In cyberspace</p> 
-----------------	-----------------	--

<http://www.sdc.org.uk>