Photodynamic therapy for photochemists

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Photodynamic therapy (PDT) is an evolving technique for localized control of diseased tissue with light after prior administration of a photosensitizing agent and in the presence of oxygen. The biological effect is quite different from surgery, radiotherapy and chemotherapy. With no temperature change during treatment, connective tissues like collagen are largely unaffected, so maintaining the mechanical integrity of hollow organs. PDT is of particular value for pre-cancer and early cancers of the skin (not melanomas) and mouth as the cosmetic and functional results are so good. Another key indication is for small areas of cancer that are unsuitable for or have persisted or recurred after conventional management. It can be applied in areas already exposed to the maximum safe dose of radiotherapy. Outside cancer, in ophthalmology, it is established for age-related macular degeneration, and has considerable potential in arterial disease for preventing restenosis after balloon angioplasty and in the treatment of infectious diseases, where the responsible organisms are accessible to both the photosensitizer and light. New developments on the horizon include techniques for increasing the selectivity for cancers, such as coupling photosensitizers to antibodies, and for stimulating immunological responses, but many further pre-clinical and clinical studies are needed to establish PDT’s role in routine clinical practice.

1. Introduction

At the recent Royal Society meeting on Photoactivatable metallo complexes, some exciting and dramatic advances in scientific research on these compounds were presented, although much of the current work remains in the realms of pure science. One of the most promising practical applications of these compounds is in photodynamic therapy (PDT), an evolving technique that is being
explored for a range of indications in medicine, particularly for the treatment of cancer and pre-cancerous conditions [1,2]. PDT involves the administration of a photoactivatable compound (a photosensitizer), which is subsequently activated by light of a wavelength matched to an absorption peak of the administered compound. In most cases, the light raises the photosensitizer to an excited state, which then interacts with oxygen, leading to the formation of reactive oxygen species (ROS) such as singlet oxygen, resulting in cytotoxicity via oxidative stress mechanisms. This produces direct cell kill and/or microvascular shutdown.

As oxidative stress is a key component of the mechanism of action, PDT protocols can be derived for most tumour cell types (if adequate photosensitizer, light and oxygen can be present simultaneously in the target tissue). Furthermore, there is little evidence for the development of resistance. PDT is a therapy that can be used before or after other therapies such as surgery, chemotherapy or radiotherapy. It can also be used as a standalone treatment in appropriate patients.

PDT is a new way to destroy diseased tissue where it arises using minimally invasive techniques. In appropriate circumstances, it can offer patients more choice and provide benefits that are complementary to those achievable with conventional management [3]. Particularly attractive aspects are the preservation of appearance and function following treatment of lesions of organs such as the skin and mouth, with minimal loss of tissue related to the treatment. This contrasts with the inevitable loss of tissue associated with surgical excision and the chronic consequences of radiotherapy and chemotherapy.

In the 1970s and 1980s, the main attraction of PDT was thought to be the selective uptake of photosensitizers in cancers compared with adjacent normal tissue, although it is now recognized that far more selectivity comes from careful targeting of the activating light [4]. The real attraction of PDT is the nature of the biological effect, which is quite different from the effects produced by surgery, radiotherapy, chemotherapy or even just heat, and the nature of the healing of PDT treated areas as in many tissues, healing is more by regeneration of normal tissue than by scarring [5].

The purpose of this paper is to outline what PDT is, to explain why it produces different biological effects from other therapeutic options, to describe how it may fit into the range of treatment options available for the treatment of cancer and other diseases and to discuss the requirements for developing new photoactivatable compounds to be used as photosensitizers.

2. The biological effects of photodynamic therapy

Compared with many other treatments, PDT is relatively gentle and forgiving to living tissue. Most tissues have many component parts, but these can be divided broadly into living, functional cells and an underlying scaffold of components like collagen and elastin that are produced by living cells and provide mechanical strength and integrity to an organ, but are not actually living cells. As there is no increase in tissue temperature during PDT, there is little effect on these non-living connective tissues; as a consequence, the mechanical integrity of hollow organs can be maintained, even if the living cells in all layers of the wall of organs like the gastrointestinal tract or major arteries have been killed [6,7]. In organs like the skin and mouth, this maintenance of the underlying connective tissue encourages healing by regrowth of normal cells on the preserved scaffold, so reducing the risk of scarring. In the case of superficial cancers and pre-cancers of the skin and mouth, the healing can be so good that it is difficult to realize that there was ever a problem, but if the disease process itself had already destroyed some of the connective tissue prior to treatment, then some scarring is inevitable. Although PDT does not normally destroy collagen, new collagen may be laid down when treated areas heal; this has been documented in muscle and in arteries [7].

By contrast, local destruction of tissue with heat destroys the connective tissue, which can put the mechanical integrity of hollow organs at risk [6].
3. How is photodynamic therapy different and how does it complement conventional treatments for cancer?

The nature of cancers is to spread from their site of origin. This may involve

— direct infiltration within the organ of origin;

— spread via the lymphatic system, when the anatomical location of nodes that any particular cancer may go to are reasonably predictable, although it is often difficult to determine how far along the lymphatic chain a cancer has passed; and

— spread via the blood, when cancers can go to any part of the body.

Conventional management is by the following.

— **Surgery.** If the extent of disease can be confidently defined within the organ of origin and its immediately adjacent lymph nodes, then it can be removed surgically; this is often the best option, but it may involve removal of a significant amount of normal tissue to maximize the prospects of removing parts of the cancer that have infiltrated the surrounding normal tissue, as for example, in the breast. To minimize the extent of resection, other treatments such as radiotherapy and chemotherapy may be used to try to eradicate these few infiltrating nests of cancer cells. This is a possible future role for PDT. PDT may also have a role to treat small areas of cancer that have not been detected at the time of surgery or which are in areas that, for technical or functional reasons, cannot be resected, for example, a lung cancer that is predominantly in one lung, which can be removed, but which has extended a short distance into the second lung.

— **Radiotherapy.** Radiotherapy is also a local treatment, but can treat relatively large volumes of tissue without unacceptable effects on the normal tissues in the treated volume, as long as the dosimetry is carefully controlled. For radiosensitive tumours, it is very effective and can be curative, but there is a limit to the amount of ionizing radiation that normal tissues can tolerate. If the safe dose is exceeded, there may be serious and irreversible damage, particularly to sensitive areas like the spinal cord and gastrointestinal tract. PDT does not have this problem of cumulative toxicity and can be used (repeatedly, if necessary) in areas that have already received the maximum safe dose of ionizing radiation, so has considerable potential for treating small areas of persistent or recurrent cancer after conventional radiotherapy. It is difficult for PDT to treat the large volumes of tissue that can be covered by radiotherapy.

— **Chemotherapy.** Chemotherapy is a systemic treatment. The drugs are given by mouth or injection, so go everywhere in the body. For some cancers, such as testicular cancer, leukaemia and lymphomas (lymph node cancers), it can be curative, but unfortunately for many of the most common cancers, current drugs are rarely curative, although can increase the chances of cure when used in combination with surgery and radiotherapy. In the current state of the art, PDT is a local treatment and is rarely complementary to chemotherapy.

4. Photosensitizers

The chemistry of photosensitizing agents is one of the most challenging and exciting aspects of PDT. This paper will not attempt to go into this in any detail, but will limit itself to outlining the properties required for clinical use. The desirable basic requirements are the following.

— It must be activatable by red or near infrared light to a form that can stimulate the production of ROS from oxygen in the tissue. In a few situations where the target lesion
is very thin and on the tissue surface exposed to the light, a shorter wavelength of visible light may be acceptable.

— It should have no unacceptable toxicity.

— It should be chemically stable both for storage and after administration. Exceptions to this are 5-aminolaevulinic acid (ALA) and its derivatives methyl- and hexyl-aminolaevulinic acid (Metvix and Hexvix). ALA is a naturally occurring substance in the chemical chain for the synthesis of haem, which is metabolized in vivo to protoporphyrin 9 (the last step before haem), which is a naturally occurring photosensitizer. By exogenous administration of ALA, the tissue level of protoporphyrin 9 can be raised to levels high enough for a PDT effect as the rate-limiting step in the natural synthesis of haem is the production of ALA.

— It should be a single compound of known structure.

— For ease of administration, it should be soluble in aqueous solution. If not, it should be formulated in a way that makes it possible to administer it by mouth or by intravenous injection.

— After administration, it should be retained longer or at a higher concentration in cancers than in the normal tissue in which the cancer arose.

Few photosensitizers can meet all these criteria. The agents currently licensed for clinical use in the UK are the following.

Porfimer sodium (Photofrin). This is not a single chemical entity; it is a mixture of oligomers formed by ether and ester linkages of up to eight porphyrin units. However, it was the first photosensitizer to be approved anywhere for clinical use outside the context of clinical trials (Canada 1993). Its main use is for tumours of the lungs and gastrointestinal tract, but it has been used in clinical studies of cancers of a range of other organs. It is effective, but has the problem that patients may remain sensitive to bright sunlight for some weeks after administration.

mTHPC (meso-tetrahydroxyphenyl chlorin, Temoporfin, Foscarn). This is a powerful photosensitizer, approved for treatment of advanced head and neck cancers and under study for a range of other cancers. It also has the problem of prolonged skin photosensitivity.

ALA. The only formal approval for ALA in the UK (as Gliolan) is for fluorescence-guided resection of gliomas (discussed below), but it has been used widely for treating skin lesions and is approved for this indication in USA (as Levulan). It is also effective for treating dysplasia (pre-cancer) in the oesophagus and for preventing restenosis in arteries after balloon angioplasty.

Methyl aminolevulinate (as hydrochloride) (Metvix). This is an ester of ALA and is approved for topical use (applied as a cream) in dermatology for treating actinic keratosis (AK), Bowen’s disease and basal cell carcinomas (BCCs; also known as rodent ulcers).

Hexaminolevulinate (as hydrochloride) (Hexvix). This is another ester of ALA and is approved for endoscopic fluorescence detection (PD: photodiagnosis) of pre-cancers and early cancer of the bladder.

Verteporfin (Visudyne) is licensed in the UK for age-related macular degeneration (AMD), but is also being used for ongoing clinical trials in oncology.

Various chlorin e6 containing photosensitizers are approved in Russia (Radachlorin, Fotoditazin and Photolon) and Japan (Laserphyrin).

Methylene blue is licensed in the EU, Canada and USA for topical use in PDT treatment of periodontitis (gum inflammation).

None of these substances contain metals, although extensive laboratory and clinical studies have been undertaken with photosensitizers that do contain metals.

Aluminium sulfonated phthalocyanine is approved for clinical use in Russia (as Photosense; [8]) and has undergone extensive laboratory study in the UK and other countries [9]. Research has also been undertaken using silicon and zinc phthalocyanines and naphthalocyanines.

Palladium bacteriopheophorbide (Tookad soluble; [10]) is currently used in a multi-centre randomized controlled trial in 10 European countries for the treatment of prostate cancer.
5. Future development of photosensitizers

(a) Selective uptake in cancers

The key early claim made for PDT was that photosensitizing drugs were taken up selectively by cancers compared with the adjacent normal tissue in which the cancer arose. Although this is true to some extent and the peak concentration of photosensitizer in tumours is often later after drug administration than the peak in adjacent normal tissue, the degree of selectivity is seldom great enough to achieve selective necrosis (destruction) of cancers [9], although the effect can be used to identify early cancers and pre-cancers by fluorescence of photosensitizers (PD; [11]). Most selectivity comes from controlling where light is delivered and to some extent, by the timing of the delivery of light in relation to the drug administration. Inevitably, there is some effect on normal tissue where it meets cancer, but this is acceptable if the treated area heals safely without significant loss of structure or function [4].

Current research is looking for ways to improve selectivity of uptake of photosensitizers compared with uptake in the adjacent normal tissue. In cancers of common organs like the lungs and the gastrointestinal tract, with current photosensitizers, it is difficult to get a tumour to normal drug concentration ratio of more than 2–3 : 1. In the brain, the ratio is much higher, but normal brain is exquisitely sensitive to PDT, making it difficult to exploit the concentration ratio without damaging normal brain, which cannot regenerate in the way so many extracranial tissues can heal after PDT. Many new tricks are being tried to overcome this problem of selectivity. These include binding photosensitizers to antibodies [12] and formulating photosensitizers in nanoparticles of a size that enhances their retention in malignant tissue [13]. Delayed lymphatic drainage from cancers is thought to be one of the reasons that photosensitizers are retained in cancers.

(b) Light delivery

The best wavelength range of light used to activate photosensitizers in vivo is determined by the optical properties of living tissue. For most tissues, the optimum range to maximize tissue penetration is from about 600 to 1000 nm, in the visible and near infrared part of the spectrum. In the visible range, the main chromophores are haemoglobin and melanin, with melanin remaining important up to about 1000 nm in organs that contain significant amounts. Beyond this value, water absorption increases rapidly. There is an enormous variation in the penetration depth of light between tissues like liver, with strong absorption, and tissues like bone, with much lower absorption, related to their haemoglobin and melanin content.

Even in organs with good transmission, the penetration depth (fluence rate dropping to \(1/e\) of that at the surface) is rarely more than a few millimetres, and it is difficult to produce PDT effects at a depth of more than three to four penetration depths, which typically means 10–15 mm. This is not a problem if PDT is to be used to treat thin lesions on the surface of hollow organs, as, for example, pre-cancers and early cancers in the airways and oesophagus, but is much more of a challenge for treating tumours in the centre of solid organs like the prostate or pancreas. The practical solution to the latter problem is to insert thin needles into the target lesion under image guidance and to pass thin diffusing laser fibres (typical core diameter 0.3–0.5 mm, with a diffusing length of 1–5 cm, depending on the size of the target lesion) through the needles. The needles can then be partly withdrawn to expose the fibres, so light from each fibre is emitted in a cylindrical distribution. To cover a defined area, the needles must be inserted in a grid pattern so no point in the target lesion is more than 5–7 mm from a fibre. This requires inserting needles at 1 cm intervals (figure 1).

These considerations make it difficult to treat large volumes of tissue with PDT, although up to 12–15 fibres have been used in studies on the treatment of prostate cancer [15].

PDT has the major attraction that there are almost no effects of photosensitizers in the absence of light (some may cause self-limiting changes to liver function if used at a high dose), so
Figure 1. PDT for cancer of the pancreas. Needles are inserted through the abdominal wall skin directly into the tumour under ultrasound guidance. Laser fibres can then be passed through the needles and the needles partially withdrawn over the fibres so light can be delivered directly into the tumour. Reproduced with permission [14].

there are essentially no significant effects on internal organs unless light of an appropriate wavelength is applied. However, caution is required to prevent unwanted effects from ambient light, particularly on the skin and eyes. The duration of skin and eye photosensitivity depends on the particular photosensitizer used and can vary from a few hours with palladium bacteriopheophorbide (Tookad soluble) to up to two to three months with porfimer sodium (Photofrin), although moderate indoor lighting is usually safe within a few days of drug administration. The danger comes from prolonged exposure to direct sunlight. Like sunburn, the effect is not apparent immediately and is only apparent some hours later, so care must be taken to warn patients of the risks, which are directly related to the total light dose to which they are exposed. Patients should wear dark glasses and cover all areas of exposed skin if exposed to bright lights, until the drug level in the body has fallen to safe levels. Systemic skin and eye photosensitivity does not occur with topical administration of photosensitizers.

Treated areas can be painful during illumination and during the healing period. This may require the administration of strong analgesics, particularly for treatment of sensitive areas such as the mouth, skin and genitalia.

The only extra item of equipment required to deliver PDT is the light source. For dermatology, this is usually a light-emitting diode (LED) array or filtered lamps, although most internal applications require lasers. All major hospitals have suitable endoscopy units and scanners for image-guided procedures. For most applications other than topical PDT to the skin, it is necessary to give the drug intravenously (the main exception is ALA, which can be given by mouth). It is also usually necessary to use a laser as the light source, as this is the best way of producing light at just one wavelength (matched to an absorption peak of the drug) and the most practical way to deliver light internally via flexible fibres, although some LED devices are now being developed for internal use. For lesions in solid organs, laser fibres are inserted through needles positioned percutaneously under image guidance (ultrasound, computerized tomography or magnetic resonance imaging).

Light dosimetry is relatively straightforward for skin and superficial lesions in hollow organs, although it is becoming more complex as image-guided treatments are developed. This will be comparable to radiotherapy planning and will require help from medical physicists [16].

It is important to carry out a risk assessment to determine what safety precautions should be taken when using a laser. It may be necessary to wear protective goggles if the laser beam is exposed in the treatment room (figure 2). For applications where the light is only delivered
Figure 2. (a) Two small cancers on the lip. (b) Delivery of light for PDT to cancers and a rim of immediately surrounding normal tissue, two days after administration of Photofrin. (c) Four days after PDT showing destruction of cancers and immediately surrounding tissue. (d) Final result, one month after PDT. The treated area, including the cancers and adjacent normal tissue, has healed by regeneration of normal tissue. The small scar is because a small amount of tissue was removed to confirm the diagnosis of cancer before treatment. Reproduced with permission [4].

deep within the body, for example, by inserting the laser fibre through an endoscope or through a needle positioned under image guidance, the precautions required are much less stringent.

6. Review of clinical indications

Most interest in PDT has focused on oncology (the treatment of cancers and pre-cancers), although one of the earliest strong indications was for AMD. Oncology and non-oncology indications will be considered separately.

(a) Photodynamic therapy in oncology

(i) Skin cancer and pre-cancer

PDT has been well established in dermatology for many years, and this speciality provides by far the most widely used indications [17]. More than 100 specialist dermatology centres (National Health Service and private) offer this service in the UK. It is one of a range of well-established treatments for superficial non-melanoma skin cancers and pre-cancers, particularly AK, Bowen’s disease and BCC. Conventional treatments such as surgical excision, cryotherapy and radiotherapy often work as well in terms of controlling the disease process, and PDT is not often the cheapest option. However, it is of special value for lesions in cosmetically and functionally sensitive areas like the head and neck region. The excellent quality of healing after PDT minimizes the risk of scarring on such key areas as the face. It is also the treatment of choice for lesions in areas where skin directly overlies bone, such as on the shins, as in these
areas, preservation of the collagen in the skin makes healing considerably faster and safer than treatments that damage or remove all layers of the skin (figure 3).

PDT is a promising approach to treating pre-malignant and malignant changes in the increasing number of patients who are on immunosuppressant drugs after organ transplantation [19]. PDT is not suitable for treating malignant melanoma because of the nature of the disease and the way it spreads.

In dermatology, PDT is one of a range of alternative treatments for the conditions mentioned above, and is usually used on its own. For indications in oncology outside dermatology, PDT is often one of a combination of treatments offered to individual patients. One of the most promising applications is for treating small volumes of persistent or recurrent cancer in patients who have already received as much surgery, radiotherapy or chemotherapy as can be tolerated. These individuals often have no other options for active intervention and are just faced with supportive and palliative care until their disease catches up with them. Another suitable group are those with early and localized tumours but who are not fit for conventional treatment owing to their poor general condition, such as poor lung or heart function.

Although PDT has been around for some years, much current evidence of efficacy comes from observational rather than controlled studies. For this reason, PDT is only offered in a small number of specialist centres and in many cases, further studies are required to establish the value of PDT compared with conventional treatments in terms of efficacy, recovery time, complications, patient acceptability and cost. In this way, the use of PDT in clinical practice can be evaluated, prospective audits undertaken and well-designed clinical trials undertaken to build the required quality of evidence to indicate which treatments should be made more widely available. However, this is not as simple as it may sound. Identifying suitable patients to include in randomized studies can be difficult and for individuals with advanced cancers whose only option for active treatment is PDT, few patients are likely to be willing to be randomized between PDT and ‘best supportive care’, which is only palliative. A possible way around this ethical dilemma is to set up national registries to compare the results of patients treated in centres with PDT and those without access to PDT.

Despite these comments, for small numbers of carefully selected patients, the observational evidence for the value of PDT is strong. The current situation for PDT for a range of cancer and pre-cancers is outlined here.

(ii) Head and neck

Advanced cancers of the lips, tongue, wall of mouth and pharynx are extremely unpleasant. Heroic surgery may be technically feasible, but at the price of serious loss of function of speech, mastication and swallowing together with the likely cosmetic deformities. High-dose radiotherapy may dry up saliva production and destroy bone. PDT may be able to provide...
palliation of the worst symptoms, such as bleeding, pain and airway obstruction without further loss of function, and if the volume of the active tumour is small, it may be able to stabilize the disease progression. For patients in whom all conventional options have failed, PDT is an approved indication using the photosensitizer mTHPC (Foscan) [20].

Pre-cancers and early cancers of the mouth can often be simply excised by surgery, but in areas difficult to access, where scarring may cause functional problems or where new cancers develop in areas adjacent to a previous excision, PDT and radiotherapy are alternative options (figure 2). This is an area where a clinical trial is required [21,22].

(iii) Lung cancer

Most lung cancers are only detected when the disease is too far advanced for there to be any prospect of cure. For bulky cancers that are bleeding or causing mechanical obstruction of a major airway, palliative endoscopic re-canalization using PDT is an approved treatment, although most centres prefer alternative endoscopic procedures such as coring out the tumour with a high-power thermal laser or inserting an expanding metal stent to hold the airway open.

However, the situation with early cancers is much more promising. For early disease that has not spread beyond the bronchial wall, in patients who are not fit for surgery or chemoradiation, PDT is an approved treatment [23]. This can be for primary disease, but is especially attractive for small volume, localized, persistent or recurrent disease when conventional treatments have not been completely successful. Patients who have had one lung cancer treated successfully have a high risk of developing further cancers. If these are detected at an early enough stage, they are most suitable for PDT, as this can be applied without further loss of functional lung that would be associated with further surgery or radiotherapy.

Currently, only a very small proportion of lung cancers are detected at an early enough stage for PDT to be an appropriate management option, but as screening, either by testing of sputum samples or by some form of imaging, becomes more common, more cases suitable for PDT are likely to be found.

(iv) Oesophageal dysplasia (pre-cancer) and cancer

Barrett’s oesophagus (a condition due to long standing, excessive reflux of stomach contents) is a common condition, but 10–15% of these patients develop dysplasia or cancer. If detected early enough, this can be treated endoscopically with either PDT (figure 4) or radiofrequency ablation (RFA; [24]). The two techniques are equally effective, although RFA is used more frequently as it is simpler.

For cancers that have spread to deeper layers of the oesophageal wall but no further, PDT (but not RFA) may still be possible, particularly in patients who are not fit for conventional treatment with surgery or chemoradiation, but this is an indication that should be tested in clinical trials [25].

For very advanced cancers that are causing problems with swallowing, PDT can be used for palliation, but other endoscopic techniques like thermal laser re-canalization and stent insertion are simpler, cheaper and just as effective.

(v) Bile duct cancer

The main problem with bile duct cancers is that they cause jaundice by obstructing the flow of bile. The first line of treatment is usually to insert a stent across the obstructed segment. The value of PDT as a way of slowing the growth of the cancer to prolong survival is controversial. Several trials from around the world suggest a significant increase in survival [26], but one major trial in the UK comparing treatment with stenting with and without adjuvant PDT showed that the patients receiving PDT had shorter survival times (full results not yet published). There are weaknesses in all these trials, particularly in the use of additional chemotherapy, which in the UK trial, was not the same in both treatment arms, but this is not the only factor. This controversy can only be resolved in future trials, but for the present, PDT is not used for this indication in the UK.
Figure 4. PDT to treat pre-cancerous changes in Barrett’s oesophagus (the dark red, smooth areas). (a) View before therapy. (b) View one day after PDT showing destruction of the oesophageal mucosa (the innermost layer of the wall of the oesophagus, where the disease arises). (c) View one month after PDT showing regeneration of the normal lining of the oesophagus. (d) Shows the balloon used to deliver light to the oesophagus. This is inserted over a guide wire positioned endoscopically. The wire is then removed and replaced by a diffuser laser fibre, which can be seen as a thin red line in the centre of the balloon. Photographs courtesy of Dr L. Lovat.

Figure 5. Blue light view of surgery to resect a large glioma (malignant brain tumour) in a patient who has been sensitized with Foscan. The blue areas are normal brain and the red areas are fluorescence from Foscan in the tumour area. As it is often difficult to define tumour margins in white light, this technique enables more precise tumour excision. Photograph courtesy of Prof. H. Kostron.

(vi) Brain

The selectivity of uptake of photosensitizers in gliomas (malignant brain tumours) has attracted considerable interest over the last 20 years, but the evidence that adding PDT after surgical resection of these tumours can significantly improve survival is borderline [27]. Nevertheless, administering the photosensitizing agent ALA prior to such surgery makes it much easier to identify the tumour margins as there is much stronger fluorescence in the tumour (figure 5). This makes tumour resection more complete, but unfortunately has not been shown to increase the overall survival time [28].
(vii) Pancreas

Pancreatic cancer is one of the most rapidly progressive cancers, with the average survival time being no more than about six months after diagnosis. Preliminary clinical studies have shown that these tumours may respond to PDT [14], but the main problem is that once they have spread beyond the pancreas itself, there is little that a local treatment like PDT can offer. The technique for treatment is shown in figure 1.

(viii) Prostate

Prostate cancers are much more indolent than pancreatic cancers. Far more men die with the disease than of it. The standard treatment is radical surgery or radical radiotherapy, but both carry a significant risk of incontinence and impotence, so simpler, safer treatments are being sought, one of the most promising of which is PDT (others are high-intensity focused ultrasound and cryotherapy; [29]). Many patients hardly progress over many years, and older men are often managed by active surveillance. This means that the activity of the disease is closely monitored, but no treatment is given unless the disease shows signs of progression. By far the biggest randomized, clinical trial of PDT in oncology currently underway is comparing PDT with active surveillance for low-grade prostate cancer. More than 300 patients have already been recruited.

(ix) Bladder

In the 1980s, PDT was thought to have the potential to be an attractive option for pre-cancer and early cancer of the bladder, but a lack of understanding of the biology led to serious complications as illumination of the entire lining of the bladder using the photosensitizer Photofrin caused irreversible bladder contraction [30]. It should now be possible to overcome this problem using a less-penetrating photosensitizer such as Hexvix, which does not lead to sensitization of the muscle layer in the bladder. However, a recent study showed that PDT for non-muscle invasive bladder cancer was no better than conventional treatment [31]. This is an indication that may be worthy of further research. PDT may be a useful adjuvant to endoscopic resection [32]. The main value of Hexvix in the bladder is to detect areas of pre-cancer by fluorescence.

(x) Bone

It has been known for many years that normal bone is relatively resistant to PDT [33]. This makes PDT an attractive option for cancers either arising in bone or spreading to bone from other organs, such as the breast and prostate. Little has yet been done to explore this option.

(xi) Breast

The breast is another organ in which imaging may be able to locate cancers precisely and in which, for cosmetic reasons, all surgeons are keen to minimize the amount of tissue that they need to remove. PDT might have a role as an adjunct to surgery, although this possibility has yet to be explored.

(xii) Pre-malignant conditions of the genitalia and pelvic regions

These include intraepithelial neoplasia (pre-cancerous changes that may progress to invasive cancer) of the vulva, vagina, cervix of the uterus, penis and peri-anal region and are often related to infection with human papilloma virus or human immunodeficiency virus. These are sensitive areas and the lesions can be sore and uncomfortable, although some are symptom free. All have the potential to develop into invasive cancers, although apart from the cervix, they are relatively rare. Surgical excision can be mutilating and a technique like PDT, which has the potential to destroy the disease process with healing by regeneration of normal tissue rather than with significant scarring, is a most attractive option. Pilot clinical studies of PDT have been undertaken for all these conditions, with promising results, but full clinical trials are now needed to establish for which ones PDT might become the treatment of choice [34,35].
In theory, pre-cancers or early cancers of any solid or hollow organ may be suitable for PDT, but for this to become a realistic option, studies must be done to establish how the normal organ in which these lesions arise will respond to PDT and that the treatment will not lead to any unacceptable changes in structure or function at any time during healing.

(xiii) Photodiagnosis

In addition to PDT, autofluorescence and fluorescence of photosensitizing drugs (PD) are established techniques for defining the extent of cancers and pre-cancers. PD is an approved technique for guiding glioma resection during open surgery (as discussed under brain tumours) and also for guiding endoscopic resection of dysplastic (pre-cancerous) areas in the bladder [11,34].

7. Non-oncology uses of photodynamic therapy

(a) Ophthalmology

In ophthalmology, PDT has now been used on about two million eyes since its US Food and Drug Administration approval in 2000 for the treatment of wet AMD. The treatment has been shown to block progression of the disease for at least five years. More recently, anti-vascular endothelial growth factor treatments have been shown to increase visual acuity in certain classes of AMD patients by about two lines. The equivalence of these two treatments is under intensive investigation as their costs are quite different. Combining the two treatments is also looking particularly promising [36].

(b) Localized infections

With the increasing incidence of bacterial resistance to antibiotics, new methods are being sought to control infections. Many micro-organisms respond to PDT under conditions that produce little effect on mammalian tissues. For clinical use, the key requirement is that the organisms should be accessible to both the photosensitizer and light. PDT using methylene blue as the photosensitizer is already an approved treatment for gum infections (periodontitis) and used widely, particularly in Canada. Studies are currently underway for skin infections, including infected ulcers and acne. Studies are planned for using PDT to sterilize indwelling items such as urinary catheters and the tissue bed if infected joint protheses have to be removed.

The whole field of PDT for localized infections is attracting a great deal of interest, particularly for organisms like methicillin-resistant *Staphylococcus aureus* [37].

(c) Arterial disease

Pre-clinical studies have shown that PDT can reduce stenosis due to proliferation of arterial smooth muscle cells after balloon angioplasty without reducing the mechanical strength of the artery or increasing the incidence of thrombosis [7]. Pilot studies of adjuvant PDT after repeat angioplasty for recurrent femoral artery stenosis have shown a low incidence of subsequent re-stenosis. This could be an alternative to drug eluting stents, especially at sites of arterial narrowing suitable for balloon angioplasty but unsuitable for stenting [38].

(d) Menorrhagia

Many techniques have been proposed for local ablation of the lining of the uterus (the endometrium) as an alternative to hysterectomy for menorrhagia (heavy periods) in women who have completed their families. Pre-clinical studies of intra-uterine infusion of a photosensitizer...
followed by intra-uterine light delivery have demonstrated endometrial ablation with little effect on myometrium. This is a simple technique that may be worthy of clinical study and is likely to have a low risk of complications.

(e) Lymphangiomas

The size of congenital vascular malformations like angiomas and neurofibromas can be reduced by PDT. This is of particular value in the head and neck region for reasons of preservation of appearance or if the lesion is compressing vital structures. Normal nerves are relatively immune to PDT, which is of great functional importance when treating malformations in the tongue close to the hypoglossal nerve (which controls tongue movements), or in the cheek, where facial nerve function is important for control of facial expression. The repeatability of PDT is particularly important in these conditions as recurrence rates are high, whether treated with conventional therapy or PDT [39].

8. Future developments

Outside dermatology and ophthalmology, the role of PDT in routine clinical practice is still quite limited, although the potential is considerable. However, there are more exciting developments on the horizon, but these are still at early stages of development.

(a) Photochemical internalization

This is a technique that uses PDT to break down intracellular membranes. When some macromolecules are taken up into cells by endocytosis, they are contained in organelles such as lysosomes and rendered inert. However, if the membranes of these intracellular organelles are broken down by photochemical internalization (PCI), the macromolecules can become biologically active. This mechanism has been shown to overcome the resistance of some breast cancer cells to chemotherapy agents such as doxorubicin [40] and may be a way of undertaking gene transfer [41]. Preliminary clinical trials are already underway on the PCI of bleomycin using the photosensitizer TPCS2a (Amphinex, a chlorin derivative), on advanced head and neck cancers.

(b) Immunological effects

As used [42,43] at present, PDT is a local treatment, but there is increasing evidence that it can stimulate immunological responses. The power of these depends on the treatment conditions. A gentle treatment is thought to release some immune stimulant from the breakdown of cells dying in response to PDT. This could be a powerful approach if it can be appropriately harnessed, but is still at an early stage of development [44].

(c) Bioluminescence

When a photosensitizer is given systemically, it goes everywhere in the body, but light must be directed to where it is required. Thus, PDT with external light sources can only treat defined areas, making it essential to know exactly where every area of diseased tissue is located. If light could be generated internally on, for example, cancer cells, there would be the potential for treating small areas of cancer without knowing exactly where they were. Light can be generated chemically, as in fireflies. They carry the enzyme luciferase, which can produce light from the substrate luciferin. There is no luciferase in mammalian cells, so the challenge is to selectively label the target cancer cells with luciferase. Experimentally, it has been demonstrated that cells in culture can be transfected with luciferase and can be killed by the addition of a photosensitizer and luciferin [45]. The amount of light generated chemically is very small compared with that
available from a laser and it will be a major task to make this work in vivo. It requires getting luciferase and a photosensitizer selectively to the target cancer cells. This might be possible by coupling them to highly specific antibodies, but it will be many years before this approach could be considered for clinical trials.

9. Conclusions

For PDT clinicians, the short-term challenge is to undertake the clinical trials required to convince the somewhat sceptical and conservative medical profession that PDT has a significant role to play in the management of a range of cancers and other conditions. These trials will take lots of time and money, but can be done with the currently available photosensitizers, light delivery systems and imaging technology. Apart from dermatology, the use of PDT in the UK (and indeed globally), at present is on a small scale.

However, there is a great deal of scope for developing new photosensitizers, particularly those containing metals, and using these in combination with the new techniques outlined above to achieve increasingly selective, safe and effective treatments for a range of cancers and other diseases, to complement the existing, well-established therapeutic options.

There is an international association that brings together clinicians and scientists with a wide range of skills and interests in PDT. This is the International Photodynamic Association (http://www.sites.pcmd.ac.uk/ipa/).

References


