It is more than 25 years since photodynamic therapy (PDT) was proposed as a useful tool in oncology, but the approach is only now being used more widely in the clinic. The understanding of the biology of PDT has advanced, and efficient, convenient, and inexpensive systems of light delivery are now available. Results from well-controlled, randomised phase III trials are also becoming available, especially for treatment of non-melanoma skin cancer and Barrett’s oesophagus, and improved photosensitising drugs are in development. PDT has several potential advantages over surgery and radiotherapy: it is comparatively non-invasive, it can be targeted accurately, repeated doses can be given without the total-dose limitations associated with radiotherapy, and the healing process results in little or no scarring. PDT can usually be done in an outpatient or day-case setting, is convenient for the patient, and has no side-effects. Two photosensitising drugs, porfirmer sodium and temoporfin, have now been approved for systemic administration, and aminolevulinic acid and methyl aminolevulinate have been approved for topical use. Here, we review current use of PDT in oncology and look at its future potential as more selective photosensitising drugs become available.

Photodynamic therapy (PDT) uses the combination of a photosensitising drug and light (figure 1) to cause selective damage to the target tissue. An adequate concentration of molecular oxygen is also needed for tissue damage. If any one of these components is absent, there is no effect, and the overall effectiveness therefore requires careful planning of both drug and light dosimetry. The drugs are generally given systemically, but because the targeting process is mainly achieved through precise application of the light—usually from a laser source—the effect is local rather than systemic. The local nature of the effect of PDT should be recognised from the outset because it contributes to both the limitations and the opportunities for PDT as a successful treatment in cancer.

A limitation of PDT is that it cannot cure advanced disseminated disease because irradiation of the whole body with appropriate doses is not possible (at least with current technologies). Nevertheless, for advanced disease, PDT can improve quality of life and lengthen survival. For early or localised disease, PDT can be a selective and curative therapy with many potential advantages over available alternatives. A single treatment can eradicate disease and can have an excellent cosmetic result (figure 2). Although the clinical potential of PDT has been recognised for more than 25 years, it is only now starting to be used in the clinic.

PDT harnesses the energy of light to damage or destroy target tissue (see panel). A sensitiser absorbs energy directly from a light source, which it then transfers to molecular oxygen to create an activated form of oxygen called singlet oxygen. It is this singlet oxygen that is the true cytotoxic agent and that reacts rapidly with cellular components to cause the damage that ultimately leads to cell death and tumour destruction. During this process, the sensitiser is regenerated so that it acts catalytically, and many cycles of singlet-oxygen production can occur for each molecule of sensitiser.
PDT uses several different mechanisms to destroy tumours. A photosensitiser can target tumour cells directly, inducing necrosis or apoptosis. Alternatively, by the targeting of tumour vasculature (or indeed of healthy surrounding vasculature), the tumour can be starved of oxygen-carrying blood. Thus, together with inflammatory and immune responses, damage to the tumour can be maximised by use of PDT.

**Practical considerations**

At a predetermined time after administration of the drug (called the drug-to-light interval), light is directed into the tumour and surrounding healthy tissue. The tumour is destroyed rapidly, and any damage to healthy tissue heals over the following 6–8 weeks.

The targeting and selectivity of PDT is aided by several factors, the first of which is the delivery of light. By use of modern fibre-optic systems and various types of endoscopy, light can be targeted accurately to almost any part of the body. Singlet oxygen generated by the activated photosensitiser has a very short life, and is deactivated before it can escape from the cell in which it was produced, further assisting targeting.

Some photosensitising drugs can reach higher concentrations in tumour tissue than in surrounding healthy tissue. Although the exact mechanisms that drive this process are not understood fully, the abnormal physiology of tumours (e.g., poor lymphatic drainage, leaky vasculature, decreased pH, increased number of receptors for low-density lipoprotein, and abnormal stromal composition) might contribute to the selectivity of photosensitisers. Furthermore, the healing of healthy tissue after PDT is very efficient, usually without scarring (figure 2). Even if healthy tissue is damaged at the time of treatment, the cosmetic result after 2–3 months is usually excellent—i.e., the effect of healing is itself a type of selectivity.

In the past 10 years, substantial advances have been made in the understanding of the behaviour of light in human tissues and in the development of equipment for light delivery for PDT. Light of adequate dose can now be delivered precisely to most tumour sites (both internal and external), and PDT is now rarely rejected because of difficulties in delivery of light. Generally, a laser source is needed for internal treatment by use of endoscopy or for interstitial treatment because lasers are the most efficient way of channelling light into one or more optical fibre. For cutaneous or subcutaneous lesions, a non-laser source is usually effective. The power of the source is important because it will determine treatment times. However, achievement of sufficient power is rarely difficult with modern laser or non-laser sources, which have typical treatment times of 5–20 min.

One of the main advances has been the availability of diode lasers, which are small, portable, very reliable, and inexpensive (about £20 000 or less) compared with earlier lasers for PDT. Diode lasers are ideal for routine use as clinical tools and need little technical expertise for use. However, because their wavelength is fixed and must be specified for use with a particular photosensitiser, diode lasers are less useful for research in which different photosensitising drugs are being assessed. Many non-laser light sources have also been developed, especially for treatment of skin lesions. These non-laser sources can be either various types of filtered lamps or, more recently, light-emitting diodes. In all cases, the light field produced needs to be uniform so that the dose delivered can be calculated precisely. As with most fixed-cost medical equipment, the real cost of lasers for PDT depends on the intensity of their use. A PDT laser that treats only one patient a week is expensive, whereas the same laser that treats 20–30 patients a week gives a low cost per treatment.

**Photosensitisers**

**Systemic sensitisers**

Early preparations of photosensitisers for PDT were based on a complex mixture of porphyrins called haematoporphyrin derivative. Porfimer sodium was the first drug...
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to receive approval for PDT and is based on haematoporphyrin derivative, with some of the non-active components removed. Although porfimer sodium is a complex mixture, it is now used widely and remains the most common photosensitiser for treatment of non-dermatological tumours. The drug has been approved for use in advanced and early-stage lung cancers, superficial gastric cancer, oesophageal adenocarcinoma, cervical cancer, and bladder cancer (and has been used on a trial basis for many other indications). The advantages of porfimer sodium are that it: destroys tumours effectively, is non-toxic in the absence of light, and can be easily formulated in a water-soluble preparation for intravenous administration. As the first drug product to be approved, porfimer sodium has also highlighted the fundamental safety and advantages of PDT as a treatment option for cancer: the drug has been used in thousands of patients for more than 20 years. No long-term safety issues have emerged, and it seems that PDT can be used repeatedly without limit (ie, there are no lifetime dose limitations, as there can be with radiotherapy).

Despite the continuing effectiveness of porfimer sodium, it has several disadvantages that could potentially be overcome in subsequent candidate compounds. The drug induces protracted skin photosensitivity, and the initial selectivity between tumour tissue and healthy tissue can be low. Although reasonable selectivity is seen after 2–3 months, this selectivity might be mainly the result of selective healing of healthy tissue, rather than selective initial damage by porfimer sodium. Furthermore, the time between administration of porfimer sodium and light is typically 48–72 h, during which the patient must be protected from light.

Much chemical and biological research has been done over the past 20 years to identify new photosensitisers with improved properties over porfimer sodium. However, most of this work has been aimed at development of photosensitising drugs that are pure chemically and that absorb more strongly at longer wavelengths, rather than photosensitisers directly into the lesion has been unsuccessful. In both cases, delivery of photosensitisers into sensitive subcellular sites, through binding to serum proteins, seems necessary for effective PDT.

With the exception of porfimer sodium, the only other PDT drug currently approved for systemic use in cancer treatment is temoporfin (table 1). A mixture of aluminium-sulphonated phthalocyanine has been used widely in Russia, but not in any other country. Temoporfin is effective for the palliative treatment of head and neck cancer and was approved in Europe for this indication in 2001. It is a very active photosensitiser and thus requires a much lower dose of both the drug and light than does porfimer sodium. Furthermore, temoporfin is a pure compound with a very strong absorption at 652 nm. However, like porfimer sodium, the drug is also associated with a pronounced and lengthy generalised skin photosensitivity and can show little initial selectivity, with the selective benefits arising later from selective healing of healthy tissue. Temoporfin also needs to be administered up to 96 h before light is applied.

Verteporfin (benzoporphyrin derivative) has been developed for the treatment of macular degeneration (table 1). Although not indicated for cancer, this drug is one of the most useful ophthalmology drugs ever developed and thus might have lessons for the development of PDT drugs for cancer. Verteporfin is cleared rapidly and does not induce a generalised skin photosensitivity that lasts longer than 24 h. Moreover, treatment with this drug is convenient for patient and clinician: 10 min intravenous infusion, followed 15 min later by 83 s of laser light (690 nm) at 600 mW/cm².

Sensitisers for topical application

None of the systematically administered sensitisers shown in table 1 have been developed for topical application to treat skin lesions, despite many attempts. Furthermore, achievement of effective PDT through the injection of photosensitisers directly into the lesion has been unsuccessful. In both cases, delivery of photosensitisers into sensitive subcellular sites, through binding to serum proteins, seems necessary for effective PDT.

All nucleated cells in the body contain the biochemical apparatus needed to make haem for cytochromes and other haemoproteins (figure 3). The immediate precursor of haem (which is not a photosensitiser), is protoporphyrin IX, which is a powerful photosensitiser. The concentration of porphyrin that will support PDT can

<table>
<thead>
<tr>
<th>Class</th>
<th>Approved drugs for photodynamic therapy</th>
<th>Typical maximum absorption (nm)</th>
<th>Typical absorption coefficient*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porphyrins</td>
<td>Porfimer sodium</td>
<td>630</td>
<td>10 000</td>
</tr>
<tr>
<td></td>
<td>Protoporphyrin IX (eg, from methyl aminolevulinate and aminolevulinic acid)</td>
<td>633</td>
<td>10 000</td>
</tr>
<tr>
<td>Chlorins</td>
<td>Verteporfin (benzoporphyrin derivative)</td>
<td>690</td>
<td>35 000</td>
</tr>
<tr>
<td></td>
<td>Temoporfin (meta-tetrahydroxyphenylchlorin)</td>
<td>652</td>
<td>30 000</td>
</tr>
<tr>
<td>Bacteriochlorins</td>
<td>None yet approved</td>
<td>740</td>
<td>32 000</td>
</tr>
<tr>
<td>Phthalocyanines</td>
<td>Sulphonated aluminium phthalocyanine mixture (approved in Russia)</td>
<td>680</td>
<td>110 000</td>
</tr>
<tr>
<td>Phenothiazinium compounds</td>
<td>None yet approved</td>
<td>670</td>
<td>60 000</td>
</tr>
<tr>
<td>Texaphyrins</td>
<td>None yet approved</td>
<td>734</td>
<td>42 000</td>
</tr>
</tbody>
</table>

*Absorption of light cm⁻¹ mol⁻¹ L⁻¹.

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be achieved by topical application of either aminolevulinic acid or methyl aminolevulinate to the site of a skin cancer or precancerous lesion. This finding has led to approval of aminolevulinic acid in the USA, and of methyl aminolevulinate in Europe.

**PDT in clinical practice**

Thousands of patients have been given PDT over the past 20 years but most trials have involved only a few patients, commonly have provided anecdotal data, and have not been sufficiently convincing to persuade medical practitioners and health-service providers of the benefits of PDT as standard treatment. This situation has partly been caused by difficulties in establishing the optimum treatment conditions for an approach that requires the setting of several variables (ie, drug and light dose, and drug-to-light interval), as well as difficulties in skin photosensitivity and low selectivity. However, greatly improved understanding of the tissue and cellular factors that control PDT and increased experience in the clinic has led to much larger, better-controlled clinical trials and the approval of four PDT drugs for cancer (table 2).

Hopper presented a comprehensive account of clinical trials on PDT up to 2000; several of which have contributed to the approval of the drugs outlined in table 2. Table 3 shows the scope of these trials. Here, we discuss subsequent and continuing clinical trials, and assesses the future of PDT in clinical practice.

### Table 2. Approved photodynamic-therapy drugs for oncological indications

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Generic name</th>
<th>Date and country of approval</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematoporphyrin derivative, polyhaematoporphyrin</td>
<td>Porfimer sodium</td>
<td>First approved in 1995; now approved in more than 40 countries</td>
<td>Advanced and early lung cancer, superficial gastric cancer, esophageal adenocarcinoma, cervical cancer, and bladder cancer</td>
</tr>
<tr>
<td>Methyl-tetrahydroxyphenyl chlorin</td>
<td>Temoporfin</td>
<td>Approved in 2001 in European Union, Norway, and Iceland</td>
<td>Palliative head and neck cancer</td>
</tr>
<tr>
<td>5-aminolevulinic acid</td>
<td>Aminolevulinic acid</td>
<td>Approved in 1999 in USA</td>
<td>Actinic keratoses</td>
</tr>
<tr>
<td>Methyl 5-aminolevulinate</td>
<td>Methyl aminolevulinate</td>
<td>Approved in 2001 in Europe</td>
<td>Actinic keratoses, superficial basal-cell carcinoma, and basal-cell carcinoma</td>
</tr>
</tbody>
</table>

**Treatment of skin cancer**

The very high incidence of skin cancer and the striking rates of increase in white populations (up to 5% per year) place an increasing burden on both patients and health services. PDT already plays a substantial part in treatment of non-melanoma skin cancer and will expand with new trials and with approval of aminolevulinic acid for treatment of actinic keratinosis in the USA, and of methyl aminolevulinate for actinic keratinosis and basal-cell carcinoma in Europe. Use of PDT for melanoma has not yet been pursued substantially in any study partly because of the difficulty in achieving good penetration of light through pigmented lesions, and partly because of ethical considerations about the aggressive nature of the disease.

Non-melanoma skin cancer is very common and includes both superficial and nodular basal-cell carcinoma, superficial squamous-cell carcinoma, squamous-cell carcinoma, and Bowen’s disease (squamous-cell carcinoma in situ). Actinic (solar) keratoses are potentially precancerous lesions that can progress to squamous-cell carcinoma. Non-melanoma skin cancer is not usually life-threatening because it rarely metastasises and is treated readily. However, the treatment options have been associated with morbidity effects (eg, scarring), and the drugs can be expensive (especially in view of the demands on the time of dermatologists and plastic surgeons). PDT has the potential to substantially decrease morbidity effects and improve health economics.

Intravenous administration of porfimer sodium or temoporfin is effective in treatment of cutaneous lesions. However, systemic administration of these drugs is unlikely to be justified for large-scale treatment of local disease (with the corresponding long periods of photosensitivity).

By contrast, use of PDT with topical applications of either aminolevulinic acid or methyl aminolevulinate is simple and convenient, without substantial systemic toxic effects. A cream or solution that contains either drug is applied to the lesion and secured under a dressing. Aminolevulinic acid is licensed in the USA for application as a solution for 14–18 h, but in Europe (where the drug is unlicensed but widely used) it is usually applied as a cream for 3–4 h. Methyl aminolevulinate is applied as a cream for 3–4 h, during which photosensitivity is generated. The licence given by the US Food and Drug Administration for use of aminolevulinic acid requires use of blue light. However, red light is generally used in Europe to improve penetration.
Photodynamic therapy

Table 3. Summary of photodynamic therapy clinical trials up to 2000

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Photosensitisers</th>
<th>Trials</th>
<th>Patients (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premalignant tumours (eg, Barrett’s oesophagus, oral cavity, bladder)</td>
<td>Porfimer sodium, aminolevulinic acid, temoporfin, haematoporphyrin derivative</td>
<td>8</td>
<td>5–100</td>
</tr>
<tr>
<td>Cutaneous malignant tumours (eg, non-melanoma skin cancer, chest-wall recurrence of breast cancer)</td>
<td>Porfimer sodium, aminolevulinic acid, temoporfin</td>
<td>9</td>
<td>16–151</td>
</tr>
<tr>
<td>Tumours of the head, neck, and oral cavity</td>
<td>Porfimer sodium, temoporfin</td>
<td>7</td>
<td>14–108</td>
</tr>
<tr>
<td>Lung, gastrointestinal, and other tumours</td>
<td>Porfimer sodium, temoporfin</td>
<td>13</td>
<td>21–218</td>
</tr>
<tr>
<td>Tumours managed with intraoperative and adjunctive treatments (eg, pituitary)</td>
<td>Porfimer sodium, temoporfin</td>
<td>4</td>
<td>5–54</td>
</tr>
<tr>
<td>Interstitial application (eg, pancreatic)</td>
<td>Porfimer sodium, temoporfin</td>
<td>2</td>
<td>9–26</td>
</tr>
</tbody>
</table>

penetration. Methyl aminolevulinate is always used with red light. The site of the lesion is usually irradiated for 5–20 min. During the initial period of irradiation, the patient might feel some discomfort or pain at the site. This discomfort does not usually need intervention, but local anaesthetic can be given if required.

Clinical use of aminolevulinic acid in non-melanoma skin cancer has been reviewed in the guidelines produced by the British Photodermatology Group in 2002. At present, this unlicensed drug is available in Europe, but it is not known how long this situation will be sustained.

The registration of aminolevulinic acid in the USA was based on two randomised, placebo-controlled investigator-blinded phase III trials that had identical designs (table 4). Patients with multiple actinic keratoses of the face and scalp were randomly assigned either 20% aminolevulinic acid in hydroalcoholic topical solution or vehicle (hydroalcoholic topical solution) only, followed by irradiation with blue light (417 nm, 10 mW/cm² to a total fluence of 10 J/cm²). In one of the trials (n=241), 72% of patients in the treatment group had a complete response, compared with 20% of those assigned placebo. The overall recurrence rate was 5.0% for the treatment group and 27.9% for placebo. In the other trial (n=243), a complete response in the treatment group was seen in 128 of 166 patients (77%) at week 8 and in 133 of 149 patients (89%) at week 12. In the group assigned vehicle only, ten of 55 patients (18%) responded at week 8, and seven of 52 patients (13%) by week 12 (p<0.001 for both groups). These data thus confirmed that PDT with aminolevulinic acid is a safe and effective treatment for actinic keratitis.

The development and approval of methyl aminolevulinate has led to a licensed product for topical PDT for superficial and nodular basal-cell carcinomas, as well as for actinic keratoses. Results from trials involving more than 2500 patients in 14 countries have shown that this drug is safe and effective, with excellent cosmetic results. After administration of methyl aminolevulinate, porphyrin accumulates more in skin tumours than in healthy skin (figure 4). PDT with methyl aminolevulinate has been compared with cryotherapy for superficial basal-cell carcinoma, and with excision surgery for nodular basal-cell carcinoma, and with and . In one study, 60 patients were randomly assigned to PDT with methyl aminolevulinate and 58 patients to two freeze-thaw cycles of cryotherapy. Complete-response rates at 3 months were similar for both groups (97% for PDT versus 95% for cryotherapy), but the rate of recurrence at 12 months was less for the PDT group (8%) than for the cryotherapy group (16%). However, the cosmetic outcome was more favourable for the group assigned methyl aminolevulinate.

PDT with methyl aminolevulinate has also been compared with cryotherapy in two randomised controlled studies involving about 400 patients with actinic keratoses. The results showed that one application of methyl aminolevulinate was equally as effective as cryotherapy, and that two applications were more effective than cryotherapy. In all cases, cosmetic outcome and satisfaction were more favourable in the groups assigned methyl aminolevulinate than in those assigned cryotherapy.

Gorlin’s syndrome is a rare disease in which patients are prone to develop several lesions of basal-cell carcinoma. Although the number of patients is small, PDT with aminolevulinic acid has been used to treat patients with this disease, and leads to excellent healing and lack of scarring. Thus, topical PDT by use of licensed drugs seems set to have a major role in future routine treatment of non-melanoma skin cancer.

Localised disease and precancerous lesions

With the exception of skin cancer, PDT has so far not been used widely for early or localised cancer, or for premalignant disease. This finding is surprising, since PDT is a local technique and could potentially be curative. This situation could change along with improvements in the availability of screening techniques to enable early detection of disease, and the probable development of improved PDT drugs that do not have long-term skin photosensitivity or long drug-to-light intervals. Table 5 shows clinical trials involving more than ten patients done since 2000 on PDT for treatment of localised disease.

Barrett’s oesophagus

This disease, widely regarded as a precursor of adenocarcinoma of the oesophagus, is increasing in incidence and is one of the most promising targets for use of PDT in early disease. Trials of PDT with systemic (oral) aminolevulinic acid have shown encouraging results, with regeneration of healthy epithelium. Most trials have been small and non-randomised; however, in a prospective double-blinded study by Ackroyd and co-workers 36 patients with dysplastic Barrett’s oesophagus who were
receiving acid suppression with omeprazole were randomly assigned either PDT with 30 mg/kg oral aminolevulinic acid plus laser endoscopy, or placebo plus laser endoscopy. In the group assigned aminolevulinic acid, 16 of 18 patients responded, with a median decrease in the area of Barrett’s mucosa of 30% (range 0–60%). In the group assigned placebo, a 10% decrease in area was seen in only two of 18 patients. No dysplasia was seen in the treated area of any patient in the PDT group, but persistent low-grade dysplasia was seen in 12 patients (p<0·001) in the placebo group. These findings showed that PDT with aminolevulinic acid could be delivered safely and effectively for low-grade dysplastic Barrett’s oesophagus. However, there is some concern that after PDT with aminolevulinic acid, submucosal islands of Barrett’s epithelium can remain, with the long-term possibility that they might act as foci for future disease.52

Treatment of Barrett’s oesophagus with more powerful systemic sensitisers than aminolevulinic acid is less likely to result in formation of residual islands, as shown in a large, phase III randomised trial with porfimer sodium.40 The study included 208 patients with high-grade dysplastic Barrett’s oesophagus who were randomly assigned PDT plus omeprazole (n=138) or omeprazole only (n=70).40 Patients were assessed every 3 months by a four-quadrant biopsy

Table 4. Selected dermatological trials of photodynamic therapy, 2000–February, 2004

<table>
<thead>
<tr>
<th>Photosensitisers and comparators</th>
<th>Treatment</th>
<th>Trial type</th>
<th>n</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Actinic keratoses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminolevulinic acid</td>
<td>Aminolevulinic acid (20%) in alcohol solution followed by 10 J/cm² blue light</td>
<td>Randomised controlled phase III trial</td>
<td>241</td>
<td>22</td>
</tr>
<tr>
<td>Aminolevulinic acid</td>
<td>Aminolevulinic acid (20%) in alcohol solution followed by 10 J/cm² blue light</td>
<td>Randomised controlled phase III trial</td>
<td>243</td>
<td>23</td>
</tr>
<tr>
<td>Methyl aminolevulinate vs cryotherapy</td>
<td>Topical methyl aminolevulinate cream (160 mg/g) for 3 h followed by 75 J/cm² red light</td>
<td>Multicentre randomised trial</td>
<td>193</td>
<td>24</td>
</tr>
<tr>
<td>Methyl aminolevulinate vs cryotherapy</td>
<td>Topical methyl aminolevulinate cream (160 mg/g) for 3 h followed by 75 J/cm² red light, One session</td>
<td>Multicentre randomised trial</td>
<td>204</td>
<td>25</td>
</tr>
<tr>
<td>Aminolevulinic acid vs fluouracil</td>
<td>Aminolevulinic acid (20%) in alcohol solution for 1 h followed by 10 J/cm² blue light, or dye laser</td>
<td>Randomised clinical trial</td>
<td>36</td>
<td>26</td>
</tr>
<tr>
<td>Methyl aminolevulinate vs placebo photodynamic therapy</td>
<td>Topical methyl aminolevulinate cream (160 mg/kg) for 3 h followed by 75 J/cm² non-coherent red light</td>
<td>Multicentre double-blind randomised study</td>
<td>80</td>
<td>27</td>
</tr>
<tr>
<td>Aminolevulinic acid</td>
<td>Topical aminolevulinic acid (20%) in alcohol solution for 14–18 h followed by 10 J/cm² blue light</td>
<td>Multicentre randomised controlled trial</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td><strong>Actinic keratoses and basal-cell carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminolevulinic acid</td>
<td>Aminolevulinic acid (20% in cream base) applied for 4–6 h followed by 105 J/cm² non-coherent red light</td>
<td>Phase I/II trial</td>
<td>88</td>
<td>29</td>
</tr>
<tr>
<td><strong>Basal-cell carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminolevulinic acid vs cryotherapy</td>
<td>Photodynamic therapy (20% water-in-oil, cream, 6 h application) vs cryotherapy over 12 months (red-light laser)</td>
<td>Single-centre randomised clinical trial</td>
<td>88</td>
<td>30</td>
</tr>
<tr>
<td>Methyl aminolevulinate</td>
<td>Topical 160 mg/kg methyl aminolevulinate for 3 h followed by 75 J/cm² red light, Two treatments, 1 week apart</td>
<td>Open uncontrolled prospective multicentre trial</td>
<td>94</td>
<td>31</td>
</tr>
<tr>
<td><strong>Basal-cell carcinoma and Bowen’s disease</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Aminolevulinic acid</td>
<td>Topical aminolevulinic acid in cream base (20%) applied for 8 h followed by 10–20 J/cm² blue light</td>
<td>Non-controlled phase II trial</td>
<td>38</td>
<td>32</td>
</tr>
<tr>
<td><strong>Bowen’s disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminolevulinic acid vs fluouracil</td>
<td>Topical aminolevulinic acid in cream base (20%) for 4 h followed 100 J/cm² 630±15 nm light</td>
<td>Multicentre randomised trial</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>Aminolevulinic acid. Red vs green light</td>
<td>Topical aminolevulinic acid in cream base (20%) for 4 h (630 ± 15 nm and 540 ± 15 nm)</td>
<td>Randomised clinical trial</td>
<td>16</td>
<td>34</td>
</tr>
<tr>
<td><strong>Nodular basal-cell carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyl aminolevulinate vs excision surgery</td>
<td>Topical 160 mg/kg methyl aminolevulinate for 3 h followed by 75 J/cm² red light, Two treatments, 1 week apart</td>
<td>Multicentre randomised trial</td>
<td>101</td>
<td>35</td>
</tr>
</tbody>
</table>
sample taken at 2-cm intervals for surveillance of disease progression. A maximum of three courses of PDT were given at least 90 days apart. At a minimum follow-up of 24 months, 76·8% of patients in the PDT group showed ablation of all areas of high-grade dysplasia, compared with 38·6% of patients in the control group (p<0·001). At a mean follow-up of 24·2 months, 13·0% of patients in the PDT group had progressed to develop cancer, compared with 28·0% in the control group (p=0·006). The rate of stricture was substantial (37·1%), but all except 2·0% of strictures resolved after dilation. At present, although surgery is the standard procedure for high-grade dysplasia and early malignant disease, this randomised study on a substantial number of patients clearly highlights the potential of PDT for treatment of this disease.

Because of the increasing incidence of adenocarcinoma of the oesophagus and deaths from the disease, there is pressure to improve screening procedures and hence a need for a simple routine treatment. PDT might be well-placed to fill this role, although new systemic drugs that do not have the disadvantages of porfimer sodium or temoporfin, will probably be needed.

Bladder cancer
Porfimer sodium has been approved for treatment of carcinoma in situ of the bladder, but does not seem to be used widely. This restricted use could be because of reported difficulties in damage to healthy tissues, which leads to shrinkage of the bladder and, in some cases, the need for cystectomy. However, preliminary data have shown PDT’s potential, with intravesically applied aminolevulinic acid, to treat the whole bladder. Furthermore, such treatment might be a simple procedure, with no substantial side-effects.

In theory, bladder carcinoma in situ should be well-suited to treatment with PDT and is another indication that could be investigated further when better sensitising agents become available.

Early non-small-cell lung cancer
Porfimer sodium has also been approved for treatment of microinvasive, non-small cell lung cancer in the USA, Japan, and Europe. Although early disease is often not identified (up to 80% of lung cancer is already sufficiently advanced as to be inoperable at time of diagnosis), detection of disease should improve in the future, at least in patients at high risk, when PDT will become an important treatment option.

Intraepithelial neoplasias
PDT should also be very well suited to elimination of intraepithelial neoplasias, such as those of the cervix and the vulva. Difficulties in light delivery have already been resolved, but results so far with aminolevulinic acid have been disappointing. Systemic sensitisers will probably be more effective, provided that drugs with greater selectivity and less photosensitivity can be developed.

Pituitary tumours
An interesting example of the benefits of PDT in localised disease is the ablation of pituitary tumours. In a phase I/II trial, use of a transphenoidal approach for light delivery with systemic porfimer sodium effectively prevented a second recurrence in 12 patients who had recurrence of disease after initial resection and radiotherapy.

Glioblastoma
Several studies have used PDT in an adjuvant setting in treatment of glioblastoma after surgical resection. Improvements in both quality of life and survival were reported, but the trial sizes were small. Early work has used porfimer sodium, but temoporfin has also been used. The potential benefit of use of PDT in an adjuvant setting for this disease is the possibility of attaining adequate concentrations of photosensitiser in the tumour, without the accumulation of substantial concentrations in healthy brain tissue because of the blood–brain barrier. This setting is another application where early trials have shown promise, but where larger well-controlled randomised trials are needed.

Other early diseases
There are many other early diseases and precancerous disorders in which PDT has great potential, provided that sensitisers can be developed that have little or no skin photosensitivity, are more selective for neoplastic tissue, and...
have a short drug-to-light interval to facilitate a single treatment in the outpatient or day-patient clinic.

**Advanced cancer**

PTD has been used for various indications in which a cure is not feasible, but where survival can be lengthened and quality of life improved. These indications are the main non-dermatological disorders for which licensed drugs are approved. In advanced disease, the intrinsic advantages of PDT are minimum invasiveness and that it does not restrict the use of other subsequent treatments, including retreatment with PDT. However, the imposition on a patient of a sustained skin photosensitivity should be weighed against the advantages PDT treatment has on quality of life. Table 6 shows the details of trials on use of PDT for advanced cancer.

**Lung cancer**

Porfimer sodium is licensed for the reduction of obstruction and palliation of symptoms for patients with completely or partially obstructing endobronchial non-small-cell lung cancer. Palliation is necessary because patients can die from obstruction of the airway before they succumb to the metastasising tumour.7 By maintainance of the airway, quality of life and survival can be improved. Trials in our group8 and elsewhere,9 with many patients (table 6), have shown clearly the benefits of PDT in terms of quality of life and survival. Compared with alternatives, PDT is easy to use, which is particularly beneficial for treatment of smaller bronchi.10 However, there are also factors that have limited the use of PDT for advanced lung cancer. The debulking of tumour and subsequent relief of dyspnoea takes longer after PDT than after laser treatment with neodymium yttrium-aluminium-garnet (NdYAG), making PDT less suitable for patients with acute respiratory distress.11 Another disadvantage of PDT with porfimer sodium could be the apparent high cost (in excess of £1500 per treatment for a patient who weighs 75 kg), although alternative treatment methods might approach or exceed this amount when calculated properly. Despite these limitations, a review and meta-analysis80 of all relevant clinical trials concluded that bronchoscopic PDT was beneficial in the treatment of selected patients with advanced lung cancer. Almost all the 636 patients treated had relief of symptoms, including improved ventilatory function and relief of dyspnoea, with few adverse events.

**Carcinoma of the oesophagus**

Porfimer sodium is also licensed for palliation of patients with completely obstructing oesophageal cancer, or for patients with partial obstruction of the oesophagus who cannot be treated satisfactorily with NdYAG laser therapy.11 Although palliative control of obstruction is often necessary, survival can be short, and whether use of drugs that cause lengthened skin photosensitivity (such as porfimer sodium and temoporfin) is justified is debatable. This disorder is thus another indication in which improved drugs with little or no skin photosensitivity could have a role.

**Head and neck cancer**

Temoporfin was licensed in the European Union, Norway, and Iceland in 2001 as a local treatment for patients with...
advanced head and neck cancer who did not respond to previous therapies, and who were unsuitable for radiotherapy or chemotherapy. PDT is an attractive option for treatment of cancers of the head and neck because of the good cosmesis achieved and the accurate localisation of therapy, limiting damage to organs in the head.61

Other applications
Several other indications in advanced cancer, such as non-resectable cholangiocarcinoma, have been investigated in PDT trials, although approval for the drugs used has not yet been obtained.62 Data from a prospective randomised controlled trial on non-resectable cholangiocarcinoma showed that PDT used in conjunction with plastic stents improved quality of life and survival, with a low rate of adverse side-effects. Patients assigned PDT with porfimer sodium had decreased serum concentrations of bilirubin, increased scores in physical function, and decreased symptoms. The beneficial effects of PDT on the first 39 patients enrolled in the trial were so great that it was

Table 6. Selected trials on photodynamic therapy for advanced cancer, 2000–February, 2004

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Photosensitiser</th>
<th>Treatment</th>
<th>Trial</th>
<th>Patients</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Temoporfin</td>
<td>Temoporfin (0.15 mg/kg) 96 h before treatment. Light dose 20–140 J/cm² (652 nm)</td>
<td>Phase II trial</td>
<td>25</td>
<td>61</td>
</tr>
<tr>
<td>Non-resectable</td>
<td>Porfimer sodium</td>
<td>Patients randomly assigned stenting and porfimer sodium (2.0 mg/kg) or stenting alone. 48 h drug-to-light interval. Light dose 180 J/cm² (630 nm)</td>
<td>Randomised prospective study</td>
<td>39</td>
<td>62</td>
</tr>
<tr>
<td>cholangiocarcina-</td>
<td>Temoporfin</td>
<td>Generally, 0.1 mg/kg temoporfin 6 days before surgery. Light dose 10 J/cm² (652 nm)</td>
<td>Phase I trial</td>
<td>26</td>
<td>63</td>
</tr>
<tr>
<td>Lung</td>
<td>Haematoporphyrin</td>
<td>Oral aminolevulinic acid (60 mg/kg), with 6–8 h drug-to-light interval (18 patients). Intravenous haematoporphyrin derivative (2 mg/kg), with 48 h drug-to-light interval (24 patients). Laser-light dose 100 J/cm² (630 nm) for both groups</td>
<td>Non-randomised study</td>
<td>40</td>
<td>64</td>
</tr>
<tr>
<td>or bronchus</td>
<td>Haematoporphyrin</td>
<td>Oral aminolevulinic acid (60 mg/kg), with 6–8 h drug-to-light interval (21 patients). Intravenous haematoporphyrin derivative (2 mg/kg), with 48 h drug-to-light interval (24 patients). Laser-light dose 100 J/cm² (630 nm) for both groups</td>
<td>Prospective phase I/I trial to determine effect of hyperbaric oxygen</td>
<td>30</td>
<td>65</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Temoporfin</td>
<td>Temoporfin 96 h before light interval, followed by irradiation with 652 nm laser light (20 J/cm²)</td>
<td>Prospective phase I/I trial to determine effect of hyperbaric oxygen</td>
<td>25</td>
<td>66</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Temoporfin</td>
<td>Temoporfin 96 h before light interval, followed by irradiation with 652 nm laser light (20 J/cm²). Mean follow-up of 37 months</td>
<td>Prospective phase I/I trial</td>
<td>25</td>
<td>68</td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td>Porfimer sodium</td>
<td>2.5 mg/kg, with 48 h drug-to-light interval. Intraperitoneal tumours resected and analysed for presence of porfimer sodium</td>
<td>Phase II trial</td>
<td>12</td>
<td>69</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Aminolevulinic acid</td>
<td>60 mg/kg oral aminolevulinic acid 6–8 h before illumination (22 patients); 2 mg/kg intravenous haematoporphyrin derivative 48 h before illumination (27 patients). Light dose 300 J/cm² of 630 nm laser light</td>
<td>Non-randomised study</td>
<td>49</td>
<td>74</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Porfimer sodium</td>
<td>1.5–2.0 mg/kg 48 h drug-to-light interval before 630 nm laser light (300–400 J/cm²)</td>
<td>Non-randomised study</td>
<td>77</td>
<td>75</td>
</tr>
<tr>
<td>Hilar bile-duct</td>
<td>Porfimer sodium</td>
<td>2.0 mg/kg 1–4 days before treatment with light (630 nm, 242 J/cm²)</td>
<td>Phase II trial</td>
<td>23</td>
<td>76</td>
</tr>
</tbody>
</table>

advanced head and neck cancer who did not respond to previous therapies, and who were unsuitable for radiotherapy or chemotherapy. PDT is an attractive option for treatment of cancers of the head and neck because of the good cosmesis achieved and the accurate localisation of therapy, limiting damage to organs in the head.61

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deemed unethical to continue with the randomisation procedure. Use of PDT with temoporfin in pancreatic cancer is under development by Bown and colleagues to provide an alternative treatment for this aggressive disease, which is commonly unresponsive to chemotherapy or radiotherapy. Other indications in which PDT is being assessed include mesothelioma, and intraperitoneal tumours.

Why is PDT not a mainstream therapy in oncology, and what is its future?

It is more than 25 years since PDT was first used in oncology. Since then, thousands of patients have been treated. The approach has progressed slowly but surely, and four drugs have now been licensed for general use. In some specialties of medicine (eg, dermatological oncology and ophthalmology), PDT is used widely; however, in other specialties its use remains marginal. Why has PDT not achieved a more sustained entry to the therapeutic scene in oncology, and will it become mainstream in future?

There are many answers to the first question, including the difficulty in the establishment of the optimum variables for a treatment that has several components, clinician and hospital resistance to a new approach, the capital cost of setting up a PDT centre, and the previous lack of inexpensive and convenient light sources. However, the main answer must be that the existing combinations of drugs and light sources in the applications in which they have been used have not established clear advantages over alternatives in large controlled comparative randomised clinical trials. This situation is probably because the drugs have been effective in establishing the viability and feasibility of PDT, but have not been optimum in terms of effectiveness. The development of PDT could be compared with that of radiotherapy, which has been used for more than 50 years but is only now approaching optimum use. The competitive situation for PDT is even more acute because of the very existence of radiotherapy.

The effectiveness of PDT with verteporfin for treatment of macular degeneration (which does not lead to lengthened skin photosensitivity, is selective, and has a very short drug-to-light interval) points the way to similar success in oncology. To date, most sensitiser development for cancer treatment seems to have been driven chemically, rather than biologically or clinically, with a focus on improved optical properties: focus is needed on solving the problems of early selectivity, and inconveniently long drug-to-light intervals. Modification of the photosensitising moiety through its chemical or convenient light sources are now available. However, improved drugs that are more selective and that can be used conveniently and without sustained skin photosensitivity are needed. If such drugs can be developed, then the advantages of PDT in terms of minimum invasion in the body, patient and practitioner convenience, and health economics will ensure a substantial future role for this type of treatment in oncology.

Conflict of interest

SBB is a consultant and minority shareholder in Photopharmica Ltd, a company formed under the auspices of the University of Leeds, UK, which is involved in development of new-generation photosensitisers, for which SBB is named on several patent applications. These drugs are in the early stage of preclinical development in oncology and are not mentioned in the manuscript.

Acknowledgments

We thank Colin Hopper, Hugh Barr, and Colin Morton for advice and information about recent clinical trials. We thank Even Angell-Peterson for permission to use figure 4 and Yorkshire Cancer Research, UK, for financial support.

References


Search strategy and selection criteria

Published data up to 2000 were reviewed in a previous article in The Lancet Oncology. More recent publications were identified by extensive searching of PubMed, Web of Science, and our own reference base. Search terms included combinations of: “Photofrin”, “photodynamic therapy”, “PDT”, “5-aminolaevulinic acid”, “ALA”, “methyl 5-aminolaevulinate”, “MAL”, “Foscan”, “porphyrin sodium”, “temporoprin”, and “Metvix”. Selection of material focused on clinical applications that use recently licensed drugs. Trials included in tables 4–6 were published between 2000 and February, 2004, and included more than ten patients.
Photodynamic therapy


