Photodynamic therapy in gastroenterology.

S G Bown and C E Millson

Gut 1997 41: 5-7
doi: 10.1136/gut.41.1.5

Leading article

Photodynamic therapy in gastroenterology

Photodynamic therapy (PDT) is a technique for producing local necrosis of tissue with low power light (most conveniently from a laser) after prior administration of a photosensitising drug.[1] It is a photochemical rather than a thermal effect and the presence of oxygen is essential as the cytotoxic intermediary is the reactive species, singlet oxygen.[2] Although the principles of PDT are straightforward, a full understanding requires knowledge of physics, chemistry and photobiology, and applying it to best effect requires close collaboration between scientists and clinicians. PDT has attracted a lot of interest as many photosensitising agents are taken up with some degree of selectivity by malignant tumours, which raised the possibility of ablating cancers without damaging the surrounding normal tissue. Unfortunately, it is now clear that in general terms, this was over optimistic, but PDT is proving valuable for other reasons, mainly related to the nature of the tissue damage produced and the subsequent excellent healing.[3]

Early clinical reports on PDT for advanced cancers of the oesophagus, stomach and colon using the photosensitiser haematoporphyrin derivative were anecdotal. A few millimetres were removed from the surface of advanced tumours at the price of two to three months skin photosensitivity to sunlight, with a functional result that could probably have been achieved with lower morbidity using other techniques like the Nd:YAG laser or a stent.[4 5] One paper reported increased effects on oesophageal cancer with a higher laser power, but the effects described were almost certainly thermal and not PDT, and would probably have been seen even if the patients had not been photosensitised prior to laser treatment.[6] Initial clinical enthusiasm waned while the scientists tried to understand more about the biological effects involved.

PDT experiments on normal colon and colon cancers growing in the colon (rather than the non-physiological situation of tumours transplanted subcutaneously) were first reported only about 10 years ago. There was little selectivity of either uptake of sensitisers[7] or PDT necrosis[8] between cancers and adjacent normal colon. However, full thickness necrosis in normal and tumour areas healed remarkably well with less scarring than comparable thermal lesions and no reduction in the mechanical strength of the organ at any stage of healing, due to preservation of collagen.[9] These results suggested that PDT would be most appropriate for treating small cancers in patients unsuitable for surgery. As the treatment is local, the likelihood of cure depends on tumour penetration and local, nodal spread, best assessed with endoscopic ultrasound. Furthermore, although muscle healing looks good on conventional histology, it is not perfect,[10] so strictures should be anticipated if treatment is circumferential. These principles have been borne out in a series of reports of the treatment of early tumours of the oesophagus, stomach and colon.[11–15] The best series with long term follow up for early oesophageal cancer is from Sibille *et al* in France.[11] They treated 123 patients between 1983 and 1991 with T1 and T2 adeno- and squamous carcinomas who were unfit for surgery. The complete response rate at six months was 87%. The overall five year survival was 25%, but the five year disease specific survival was 75%, confirming the efficacy of PDT in appropriately selected patients. The photosensitiser used was haematoporphyrin derivative, and as might have been expected, oesophageal stenosis was seen in 43 (35%) patients, but all responded to dilation. Japanese groups realised the potential for treating early gastric cancers at a very early stage.[12] Barr *et al* quantified the effects in small colonic tumours with endoscopic ultrasound.[13]

Recently, there has been renewed interest in PDT for palliation of advanced oesophageal cancers, perhaps partly as a way of getting some application of PDT approved by the Food and Drugs Administration (FDA) in the USA.[16 17] The most comprehensive report is a phase III, randomised, multicentre study comparing PDT using Photofrin to Nd:YAG laser therapy in 236 patients with advanced malignant dysphagia from Lightdale *et al*.[16] The response rates, median survival times (PDT: 123 days; Nd:YAG: 140 days), time to palliation failure (PDT: 34 days; Nd:YAG: 42 days) and dysphagia scores were similar for both groups, although the authors admit that their response rates in the Nd:YAG laser group (48% at one week and 29% at one month) are way below the figures of 65–80% in most other studies. They reported fewer treatment endoscopies with PDT, but including the debridement endoscopies required after each PDT treatment, the total number of procedures was similar for both. Overall, the incidence of severe complications was the same in both groups. The only complication seen more frequently in the Nd:YAG laser group was perforation, which occurred in 7%, half of which were associated with dilation. Again, they comment that this is higher than the perforation rate of 0–5% reported by others using the Nd:YAG laser. Of the patients undergoing PDT, 19% had sunburn and all had cutaneous photosensitivity for one to two months. Follow up data were not available for 22% of patients at one week and 39% at one month. These results do not paint a convincing picture of the superiority of PDT in this situation! Nevertheless, the FDA has now approved PDT with Photofrin for the palliation of advanced oesophageal cancer if no alternative treatment is available. It is understandable that they have chosen this "last ditch" situation as the first for approval, but in our experience, there are very few patients whose dysphagia cannot be relieved just as effectively and safely by other means without making them photosensitive for much of their remaining life. On purely scientific grounds, the approval of the Japanese authorities for PDT with Photofrin for the treatment of early oesophageal cancers is more logical. PDT has not yet been approved for any application in the United Kingdom, although it has been approved for early and advanced oesophageal cancers in

Leading articles express the views of the author and not those of the editor and editorial board.

The Netherlands and for advanced oesophageal cancers in France.

Although Photofrin is the only photosensitiser yet to receive regulatory approval in any country, it is unlikely to be used widely because of the associated long period of skin photosensitivity. Several second generation drugs are now entering clinical trials, including mTHPC (meso tetrahydroxyphenyl chlorin), Sn Et2 (tin etiopurpurin), BPDMA (benzo-porphyrin derivative mono acid), and AlSPc (aluminium disulphonated phthalocyanine).[18] However, one of the most interesting is ALA (5-aminolaevulinic acid) which is converted in vivo into the photoactive derivative, protoporphyrin IX (PPIX, the last intermediary before haem).[19] In contrast to other photosensitisers, many of which localise predominantly in the microvasculature of the submucosa of hollow organs like the gastrointestinal tract, PPIX builds up to much higher levels in the mucosa than in the submucosa or muscle. It has been shown experimentally that this can be exploited to achieve selective mucosal necrosis and leave the underlying muscle undamaged,[20] as is required to treat areas of mucosal disease. Clinically, this is only of value if necrosed dysplastic mucosa heals with regeneration of normal mucosa, but this has now been described in the treatment of severe dysplasia in Barrett's oesophagus with PDT using ALA. No strictures were seen (in contrast to the results with Photofrin[11]), although there has been concern that superficial healing could mask underlying severely dysplastic epithelium and further long term evaluation is needed.[21] On current knowledge, it is unlikely that PDT with ALA will be effective for disease that has spread deeper than the mucosa, although this might be possible by giving it intravenously to increase the dose that can be tolerated and by fractionating the light.[22] The other major advantage of ALA is that skin photosensitivity only lasts for one to two days.[21]

Thus PDT with ALA is quite different to PDT with the other currently available photosensitisers. This can be called selective PDT but it must be stressed that the selectivity is between the mucosa and the underlying submucosa and muscle and *not* between normal and neoplastic mucosa. Normal and abnormal mucosa are necrosed equally effectively if exposed to the same light dose. The principle of ALA PDT can be applied to the treatment of dysplasia in essentially all of the hollow organs of the body. PDT with other photosensitisers can be referred to as non-selective as the necrosis is similar in tumour and in all the layers of the normal wall of the gastrointestinal tract exposed to comparable light doses.

Looking outside the luminal gut, PDT experiments on transplanted cancers in the rat and hamster pancreas have shown better selectivity. It has proved possible to produce necrosis in the tumours without serious damage to the immediately adjacent normal pancreas with several sensitisers. Using pheophorbide A, some animals were tumour free at 120 days,[23] and using ALA, there was a significant increase in survival compared with untreated control animals.[24] Selectivity of uptake of sensitisers was comparable to the colon, but it was postulated that something in normal pancreas (perhaps glutathione), not present in the cancer, might quench the cytotoxic intermediary, singlet oxygen.[25] The normal tissues around the pancreas in hamsters are able to tolerate PDT, with the exception of the duodenum, although no problems have been reported treating the much thicker human duodenum.[26] This opens up exciting possibilities for a new approach to treating small cancers localised to the pancreas in patients unsuitable for surgery. Multiple fibres for light delivery could be positioned percutaneously with ultrasound or computed tomography guidance. PDT also has potential for tumours of the ampulla and bile duct.[26]

In theory, PDT is attractive as adjuvant treatment to pick up microscopic deposits of tumour left after surgery. As selectivity of tumour necrosis is so poor, this will almost certainly necessitate necrosis of a superficial layer of normal tissue as well, but as healing after damage to many normal tissues is so good with regeneration rather than scarring, this will often be acceptable. A randomised, controlled trial has been undertaken applying PDT to the tumour bed after resection of colorectal cancers, but unfortunately has shown no improvement in survival or local recurrence in the PDT group, perhaps because of caution on drug and light doses so as not to cause unacceptable damage to normal tissues.[27]

The first description of PDT nearly 100 years ago was of killing bacteria, and there is now interest in using PDT to treat localised infections. For gastroenterologists, the obvious target is *Helicobacter pylori*. Antibiotic regimens can eradicate *H pylori* in more than 90% of cases, but this is not without risk. The increasing use of systemic, broad spectrum antibiotics for treating such a common condition could lead to antibiotic resistance developing in an wide range of organisms at sites throughout the body. There is increasing pressure to find alternatives. Experiments have shown that *H pylori* can be killed by PDT with a range of photosensitisers in vitro[28] and *H mustelae* (which is very similar to *H pylori* and causes similar pathology in ferrets) can be killed locally in the ferret by filling the stomach with methylene blue and illuminating small areas ex vivo.[29] *H pylori* is usually found on the superficial mucosa of the upper gastrointestinal tract where it is readily accessible endoscopically. Thus it should be feasible to deliver appropriate light doses to all relevant areas, although it will require considerable technical ingenuity to get light to the base of all the folds in the stomach.

PDT is an exciting new way of producing localised tissue necrosis with light which heals remarkably well without cumulative toxicity. It has considerable potential, non-selectively, for treating small tumours that have not spread beyond the wall of the gastrointestinal tract in patients unsuitable for surgery, and selectively, using ALA, for the treatment of dysplasia, as in Barrett's oesophagus. PDT for palliation of advanced cancers, particularly of the oesophagus, is controversial. It is unlikely to become a treatment of choice as other options are simpler and highly effective, but it may have a role in the management of tumour overgrowth in metallic stents that cannot tolerate thermal treatment with the Nd:YAG laser.[30] Other applications to pancreatic and bile duct tumours, for adjunctive intraoperative use and for *H pylori* infection are more speculative at this time, but are certainly worthy of further study.

S G BOWN
C E MILLSON

National Medical Laser Centre,
Department of Surgery,
University College London Medical School,
Charles Bell House,
67-73 Riding House Street,
London W1P 7LD

Correspondence to: Professor S G Bown.

1 Pass HI. Photodynamic therapy in oncology: Mechanisms and clinical use. *J Natl Cancer Inst* 1993; **85:** 443–56.
2 Weishaupt KR, Gomer CJ, Dougherty TJ. Identification of singlet oxygen as the cytotxic agent in the photoactivation of a murine tumour. *Cancer Res* 1976; **36:** 2326–9.
3 Bown SG. Photodynamic therapy to scientists and clinicians – one world or two? *J Photochem Photobiol* 1990; **6:** 1–12.
4 McCaughan JS, Nims TA, Guy JT, Hicks WJ, Williams TE, Laufman LR. Photodynamic therapy for oesophageal tumours. *Arch Surg* 1989; **124:** 74–80.

5 Kashtan H, Papa MZ, Wilson BC, Deutch, Stern HS. Use of photodynamic therapy in the palliation of massive advanced colorectal cancer. Phase I/II study. *Dis Colon Rectum* 1991; **34:** 600–4.
6 Thomas RJ, Abbott M, Bhathal PS, St. John DJB, Morstyn G. High dose photoradiation of oesophageal cancers. *Ann Surg* 1987; **206:** 193–9.
7 Agrez MV, Wharen RE, Andersen RE, Laws ER, Ilstrup DM. Hematoporphyrin derivative quantitative uptake in DMH induced murine colorectal carcinoma. *J Surg Oncol* 1983; **24:** 173–6.
8 Barr H, Tralau CJ, Boulos PB, MacRobert AJ, Krasner N, Phillips D, Bown SG. Selective necrosis in dimethylhydrazine-induced rat colon tumours using phthalocyanine photodynamic therapy. *Gastroenterology* 1990; **98:** 1532–7.
9 Barr H, Tralau CJ, Boulos PB, MacRobert AJ, Tilly R, Bown SG. The contrasting mechanisms of colonic collagen damage between photodynamic therapy and thermal injury. *Photochem Photobiol* 1987; **46:** 795–800.
10 Chevretton EB, Berenbaum MC, Bonnett R. The effect of photodynamic therapy on normal skeletal muscle in an animal model. *Lasers Med Sci* 1992; **7:** 103–10.
11 Sibille A, Lambert R, Souquet JC, Sabben G, Descos F. Long term survival after photodynamic therapy for esophageal cancer. *Gastroenterology* 1995; **108:** 337–44.
12 Kato H, Kawaguchi M, Konaka C. Evaluation of photodynamic therapy in gastric cancer. *Lasers Med Sci* 1986; **1:** 67–74.
13 Barr H, Krasner N, Boulos PB, Chatlani P, Bown SG. Photodynamic therapy for colorectal cancer: A quantitative pilot study. *Br J Surg* 1990; **77:** 93–6.
14 Patrice T, Foultier MT, Yactayo S, Adam F, Galmiche JP, Douet MC, *et al.* Endoscopic photodynamic therapy with haematoporphyrin derivative for primary treatment of gastrointestinal neoplasms in inoperable patients. *Dig Dis Sci* 1990; **35:** 545–52.
15 Jin M, Yang B, Zhang W, Wang Y. Photodynamic therapy for upper gastrointestinal tumours over the past 10 years. *Semin Surg Oncol* 1994; **10:** 111–3.
16 Lightdale CJ, Heier SK, Marcon NE, McCaughan JS, Gerdes H, Overholt BF, *et al.* Photodynamic therapy with porfimer sodium versus thermal ablation therapy with Nd:YAG laser for palliation of esophageal cancer: a multicenter randomized trial. *Gastrointest Endosc* 1995; **42:** 507–12.
17 Heier SK, Rothman KA, Heier LM, Rosenthal WS. Photodynamic therapy for obstructing esophageal cancer: light dosimetry and randomized comparison with Nd:YAG laser therapy. *Gastroenterology* 1995; **109:** 63–72.
18 Schuitmaker JJ, Baas P, van Leengoed HLLM, van der Meulen FW, Star WM, van Zandwijk N. Photodynamic therapy: a promising new modality for the treatment of cancer. *J Photochem Photobiol B* 1996; **34:** 3–12.
19 Kennedy JC, Pottier RH. Endogenous protoporphyrin IX, a clinically useful photosensitiser for photodynamic therapy. *J Photochem Photobiol B* 1992; **14:** 275–92.
20 Loh CS, MacRobert AJ, Buonaccorsi G, Krasner N, Bown SG. Mucosal ablation using photodynamic therapy for the treatment of dysplasia – an experimental study in the normal rat stomach. *Gut* 1996; **38:** 71–8.
21 Barr H, Shepherd NA, Dix A, Roberts DJH, Tan WC, Krasner N. Eradication of high-grade dysplasia in columnar-lined (Barrett's) oesophagus by photodynamic therapy with endogenously generated protoporphyrin IX. *Lancet* 1996; **348:** 584–5.
22 Messman H, Mlkvy P, Buonaccorsi G, Davies C, MacRobert AJ, Bown SG. Enhancement of photodynamic therapy with 5-aminolaevulinic acid induced porphyrin photosensitisation in normal rat colon by threshold and light fractionation studies. *Br J Cancer* 1995; **72:** 589–94.
23 Evrard S, Keller P, Hajri A, Balboni G, Mendoza-Burgos L, Damge C, *et al.* Experimental pancreatic cancer in the rat treated by photodynamic therapy. *Br J Surg* 1994; **81:** 1185–9.
24 Regula J, Ravi B, Bedwell J, MacRobert AJ, Bown SG. Photodynamic therapy using 5-ALA induced PPIX for experimental pancreatic cancer – prolonged animal survival. *Br J Cancer* 1994; **70:** 248–54.
25 Chatlani PT, Nuutinen PJ, Toda N, Barr H, MacRobert AJ, Bedwell J, *et al.* Selective necrosis in hamster pancreatic tumours using photodynamic therapy with phthalocyanine photosensitisation. *Br J Surg* 1992; **79:** 786–90.
26 Abulafi AM, Allardice JT, Williams NS, Van Someren N, Swain CP, Ainley CA. Photodynamic therapy for malignant tumours of the ampulla of Vater. *Gut* 1995; **36:** 853–6.
27 Ansell JK, Abulafi AM, Allardice JT, De Jode ML, Grahn MF, Williams NS. Adjuvant intraoperative photodynamic therapy for colorectal cancer. *Br J Surg* 1996; **83:** 694.
28 Millson CE, Wilson M, MacRobert AJ, Bedwell J, Bown SG. The killing of Helicobacter pylori by low power laser light in the presence of a photosensitiser. *J Med Microbiol* 1996; **44:** 245–52.
29 Millson CE, Wilson M, MacRobert AJ, Bown SG. Ex vivo treatment of gastric helicobacter infection by photodynamic therapy. *J Photochem Photobiol* 1996; **32:** 59–65.
30 Raijman I, Lalor E, Marcon NE. Photodynamic therapy for tumour ingrowth through an expandable esophageal stent. *Gastrointest Endosc* 1995; **41:** 73–4.