ated total body irradiation (TBI) mice. *Int J Radiat Oncol Biol Phys* 1989, **17**, 1237–1245.
25. De Ruysscher D, Waer M, Vandeputte M, van der Schueren E. Mechanisms involved in the differential recovery of CD4 and CD8 T-lymphocytes after local irradiation in mice. *Radiother Oncol* 1990, **18**, 299–305.
26. Dutreix J, Girinski T, Casset JM, *et al.* Blood cell kinetics and total body irradiation. *Radiother Oncol* 1987, **9**, 119–129.
27. Manori I, Kushilevsky A, Segal S, Weinstein Y. Radiosensitivity of isolated subsets of human lymphocytes (E^+,$OKT4^+$,$OKT8^+$): protective role of monocytes and monokines. *Clin Exp Immunol* 1984, **58**, 453–461.

Eur J Cancer, Vol. 28A, No. 10, pp. 1734–1742, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Feature Articles

Photodynamic Therapy

Thomas J. Dougherty and Stuart L. Marcus

Photodynamic therapy (PDT) has been developed over the past decade into a useful treatment for several types of solid cancers in man. This unique therapy requires a photosensitiser accumulated in tumours and local activation by visible light generally delivered from lasers and delivered to the patient through various types of fibers and endoscopes. PDT appears to be most effective in treating certain superficial, difficult to treat cancers such as carcinoma *in situ* of the urinary bladder (here complete control is the intent), but also is effectively used in bulkier tumours obstructing bronchi or the oesophagus where palliation can be achieved. The primary mechanism of action is the *in situ* generation of an active form of molecular oxygen (singlet oxygen) which causes the rapid, local onset of vascular stasis and eventual vascular haemorrhage and tumour wall destruction. This process appears to be mediated through various cytokines such as prostaglandin, lymphokines and thromboxanes. The ultimate clinical value of PDT will be seen over the next few years following health agency approval worldwide.
Eur J Cancer, Vol. 28A, No. 10, pp. 1734–1742, 1992.

INTRODUCTION

WHILE MOST cancer deaths are a result of advanced metastatic disease, a considerable number of patients succumb due to inability to control local tumours (e.g. glioblastoma multiforme, certain intraperitoneal cancers). In some cases, potentially curable early stage cancers cannot be effectively treated by standard therapy because of mitigating clinical situations (e.g. early stage lung cancers or refractory carcinoma *in situ* of the urinary bladder in elderly patients with medical conditions precluding surgery). In still other situations, the therapeutic intent is palliation with as little adverse reaction as possible. Photodynamic therapy (PDT), a relatively selective, local treatment, has been examined in all these situations in order to define its role in cancer treatment, both for palliation and complete local tumour eradication. Several ongoing Phase III clinical trials for health agency approval in the USA, Canada, Europe and Japan are described below, along with clinical experience with PDT from certain earlier Phase I/II trials.

T.J. Dougherty is at the Division of Radiation Biology, Roswell Park Cancer Institute, Buffalo, New York, U.S.A.; S.L. Marcus is at the Medical Research Division, Lederle Laboratories, a Division of American Cyanamid Pearl River, New York, U.S.A.
Revised 27 Mar. 1992; accepted 1 Apr. 1992.

METHODOLOGY AND MECHANISMS

PDT requires a photosensitiser, localised with some degree of selectivity in the solid tumour and the means for its local activation. The latter is achieved generally by visible light derived from a laser and directed to the site by various fibre optics. The cytotoxic process which occurs with the porphyrin currently in clinical trials (Photofrin, porfimer sodium) as well as with most experimental new photosensitisers, is known as the photodynamic process, a type II photochemical reaction:

$$PS + h\nu \rightarrow PS^*(1)$$
$$PS^*(1) \rightarrow PS^*(3)$$
$$PS^*(3) + O_2 \rightarrow PS + O_2^*$$
$$^*O_2 + T \rightarrow \text{cytotoxicity}$$

where PS = photosensitiser, PS*(1) = excited singlet state of PS, PS*(3) = excited triplet state of PS, $h\nu$ = light quantum, O_2^* = excited singlet state of oxygen and T = cellular target.

In practice, the patient receives an intravenous injection of Photofrin (1–2 mg/kg) and 24–72 h later is treated with 630 nm light from a dye laser directed through single quartz fibers with a variety of speciality ends. Photofrin has no apparent pharmacological effect in the absence of light activation, although the spleen and bone marrow in mice demonstrate increased cellularity [1]. However, its retention in skin requires

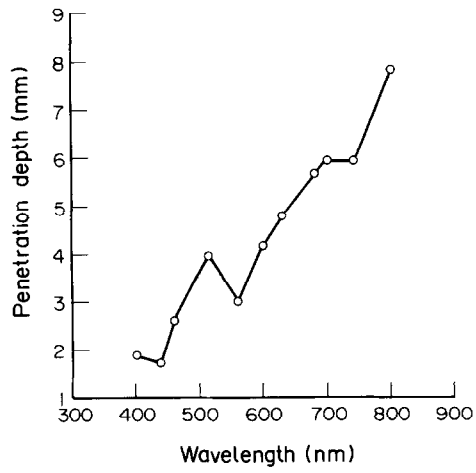

Fig. 1. Penetration of visible light at various wavelengths through bovine muscle where penetration depth is the 1/ε depth.

protection of patients from bright lights, especially bright sunlight, for a period of 4–6 weeks typically. While Photofrin has only a weak absorption band in the red region of the spectrum (15–20 times less than its blue absorption), this band is chosen for *in vivo* activation because of superior tissue penetrating properties (Fig. 1). Dosimetry and method of light delivery are dictated by the site and size of the tumour.

Many types of solid tumours have responsed favourably to PDT as discussed below. One of the major advantages of PDT appears to be the ability to use it repeatedly if necessary, to use it as adjunct to other treatments, and in patients who have been heavily pre-treated with other modalities.

Photofrin

Photofrin is a mixture of non-metallic oligomeric porphyrins linked primarily through ether bonds [2, 3]. The oligomers range in size from two to eight porphyrin units, although the major portion appears to be trimeric (Fig. 2). A small amount (5–10%) of haematoporphyrin (Photofrin precursor) and its dehydration products are present as well but are not retained in tissue and do not contribute to photosensitisation except possibly in the short term. In mice, oligomers demonstrate a complex serum clearance kinetics with a small fraction (<1%) retained for several weeks. Also, most tissues high in reticuloendothelial cells retain high levels of the drug for several weeks (e.g. kidney, adrenals, liver [4]). Interestingly, the ratio of Photofrin in subcutaneous transplanted mouse tumours relative to mouse skin is near unity, while in patients with cutaneous tumours (metastatic breast cancer, basal cell carcinoma) the tumour to skin ratio measured by fluorescence techniques is estimated to

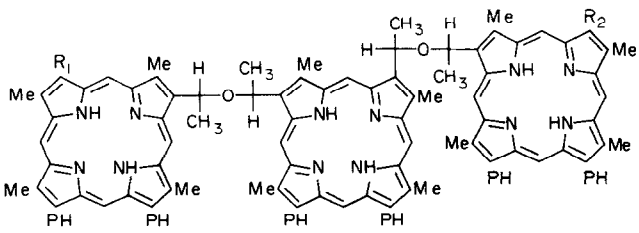

Fig. 2. Structure of a porphyrin trimer—a major component of Photofrin. $R_1 = R_2 = CH(OH)CH_3$ or $CH = CH_2$. PH = (CH_2) 2COOH. A major active component of Photofrin.

be 5–10 [5], thus predicting a much greater selectivity in treatment of humans than in mice which is, in fact, the case.

Light penetration into tissue

Although Photofrin is taken up by virtually all solid tumours as well as micrometastases, the therapeutic effectiveness of PDT is limited by the ability of the activating light to penetrate into tissues and tumours. Interstitial light delivery fibers have partly overcome this difficulty. Penetration of visible light into tissue is limited primarily by light scattering and absorption with the former dominating, except in highly pigmented tissues or tumours, e.g. liver and melanotic melanoma. The opacity of tissues is defined by the total attenuation coefficient, α (cm^{-1}), the inverse of which can be considered as a logarithmic penetration depth (δ, cm). Values of the exponential term δ, which is the depth at which the incident light density (not including reflection) falls to $1/\epsilon$ or approximately 37%, range from 1–2 mm (brain tissue) to nearly 5 mm (certain tumours, muscle [6, 7]). However, biological effects often occur at two to three times these depths (i.e. where the light flux is 3–10% of the incident intensity). If treatment of bulky tumour or deeper penetration is required, multiple interstitial fibres can be used. However, most PDT applications deal with tumours no more bulky than that of a totally obstructing bronchus or oesophagus (5–10 mm radius). In theory, treatment near 700–800 nm would approximately double these penetration depths, but new photosensitisers need to be developed in order to accomplish this (see below).

It should be noted that while the current PDT laser systems are based on various pumped dye lasers (continuous wave or certain pulsed systems), new advances in diode laser technology promise considerable simplification for PDT light delivery systems. These systems are compact, easily transportable, require only 108 V power, and are considerably less expensive than current PDT laser systems. Several watts of power from a diode laser are available near 800 nm and somewhat less developed systems can produce 2 W or more near 670 nm. There is also some expectation that diode lasers emitting near 630 nm will soon be available.

How does PDT work?

This discussion will focus mainly on Photofrin, since the bulk of investigations on both pre-clinical and clinical studies have been with this material.

Cells exposed *in vitro* to Photofrin for short periods of time (min) rapidly absorb the material onto the plasma membrane from which it can be removed readily by protein in fresh sera. Over time, however, the oligomers are slowly internalised in an irreversible fashion (i.e. cannot be removed by competitive binding with proteins) [8]. As it is internalised, Photofrin is diffusely distributed through the cytoplasm and then becomes bound primarily to mitochondrial membranes. It has been demonstrated that one of the earliest targets for PDT in such cells exposed to light are, in fact, the mitochondrial-bound enzymes such as cytochrome C oxidase and succinate dehydrogenase [9, 10]. While there is some conflicting data in the literature, in general, malignant and transformed cells *in vitro* do not appear to demonstrate selective or higher drug uptake than their normal counterparts. However, blastic cells such as leukaemia cells, appear to take up more material than normal lymphocytes and, in fact, can be selectively killed by light treatment [11]. This information should be cautiously extrapolated to the *in vivo* situation, however, where the vasculature appears to be the major initial target [12–14]. Photofrin, in the

SMT-F mammary tumour in mice is concentrated in the vascular stroma as well as in macrophages and mast cells within the tumour vascular stroma. The uptake in tumour cells is considerably less than in tissue phagocytic cells. Within the vascular stroma it is not known if most of the drug is in fibroblasts, endothelial cells, or in macrophages and mast cells within the stroma. The long-term retention of Photofrin in solid tumours may relate to leaky vasculature and poor lymphatic drainage in most tumours, allowing for relatively long exposure of tumour cells to plasma protein bound drug (primarily bound to high density lipoprotein and albumin) and thus longer time for internalisation as seen *in vitro*. This remains to be proven, however. What is clear is that shortly after initiation of the light treatment (e.g. approximately 5 min into a 30 min treatment), the vessels in the animal tumours undergo stasis followed shortly thereafter by complete collapse and extravasation of blood cells and fluid. If light treatment continues, similar effects occur within the entire light field. It appears that at least for these experimental rodent tumours, most of the tumour cells are sublethally damaged initially and die subsequently when vasculature collapse results in tumour hypoxia. For example, in the RIF fibrosarcoma subcutaneously implanted into C_3H mice tumour cell kill is only about 70% initially (determined by removing cells immediately after treatment and cloning for viability), but slowly progresses to several logs of kill over the next few hours [15]. The question of resistance or inadequate treatment due to PDT-induced or pre-existing tumour hypoxia has been addressed by Henderson and Fingar [16], who demonstrated that the use of Fluosol and increased oxygen during PDT delayed the vascular collapse and onset of hypoxia by several hours after treatment. Thus, photodynamic action, which requires oxygen, would take place throughout the entire time of the light treatment and throughout the entire treatment volume as compared to partial vascular shut down and induced hypoxia, which sets in immediately upon light treatment. However, tumour control and cure were essentially the same as in controls. Thus, while profound vascular effects set in early during PDT, thus inducing partial tumour hypoxia, this has not been shown to affect long-term tumour control in mice, perhaps because PDT is so effective at inducing complete tumour anoxia.

The vascular effects may be mediated by release of inflammatory agents and cytokines induced by PDT. Thus, Henderson has found that PGE_2 is readily released from tumour cells undergoing PDT *in vitro* and is inversely related to cellular survival [17]. Also, Nseyo, in preliminary studies of patients undergoing PDT for bladder cancer, has detected the local release of immunomodulators IL-2, IL-1β and TNF-α [18], for as long as 59 days following a single PDT treatment. This provides a possible explanation of long-term control of this disease in some of these patients. Tissues undergoing PDT ultimately become infiltrated by lymphocytes, plasma cells and histiocytes, again consistent with a possible local immunological response [19]. Further, Fingar and Wieman have measured various vaso-active eicosanoids (thromboxane, prostacyclin) in the circulation of rats undergoing PDT and found that serum levels of thromboxane were increased several fold. When the release of thromboxane was inhibited with indomethacin, vascular PDT effects were inhibited as well [20].

FUTURE DIRECTIONS IN PDT

As indicated, Photofrin may not be the optimum photosensitiser for PDT because of its persistent cutaneous photosensitivity requiring patients to protect themselves from sunlight for 4–6 weeks and lack of a maximum tissue penetrating wavelength. While some cite its complex structure as a deterrent, this is of less importance since it can be manufactured reproducibly to exact specifications and biological activity [21]. Further, all of the oligomers appear to have similar *in vivo* photosensitising ability [21]. Numerous investigators have reported potential new photosensitisers for PDT, all to one extent or another intended to address these disadvantages. Benzoporphyrin derivative mono-acid (BPD) is currently in phase I studies, and chlorin e_6 aspartate ester (NPe_6) will be in phase I clinical trials shortly. The former absorbs near 690 nm, which theoretically could increase the penetration depth in tissue from 30–50% compared with the Photofrin 630 nm wavelength, whereas the chlorin compound absorbs near 660 nm, offering a somewhat lower increase in penetration. However, to date, no photosensitiser has actually been demonstrated to improve depth of necrosis in experimental tumours relative to Photofrin, since many other factors enter into this parameter e.g. concentration of photosensitisers in tumour tissue required to achieve tumour control (high concentrations of strongly absorbing chromophores can actually reduce the depth of the biological effect, even at longer red wavelengths [22]), photobleaching (a property of Photofrin which actually allows much higher light doses to be used than would be expected, based on relative tissue levels between tumour and normal tissue [23]), pharmacokinetics, etc. Both BPD and the chlorins appear not to induce persistent skin photosensitivity in mice. However, this apparent advantage occurs due to rapid clearance from plasma, skin and other tissues, including tumours and/or rapid metabolism to an inactive form [24]. This may make it difficult to determine and deliver an optimum light dose, which depends not only on the delivered light dose, but on absorbed light dose, which in turn is dependent on the tissue drug level. If this changes during treatment, so too will the absorbed light dose. Perhaps compounds of intermediate pharmacokinetics will be most useful. For example, the zinc etioporphyrins [25], tetrahydroxyphenyl chlorins [26], and alkyl pheophorbide ethers [27] all appear to be retained at relatively constant levels for up to 24 h in mouse tumours, but clear skin over a period of a few days compared to several weeks for Photofrin. While the tetrahydroxyphenylchlorins have been examined in a few patients, it will be some time before these materials enter phase I trial in the USA. Other compounds examined experimentally include various sulphonated phthalocyanines [28], tetrahydroxyphenylporphyrins, all absorbing in the 650–700 nm range, and naphthalocyanines [29], sapphyrins [30], porphinones [31] and certain ether substituted porphyrins [27] absorbing in the 700–800 nm range. Cationic dyes such as the phenoxazines, absorbing in the 660 nm range and which may demonstrate enhanced selectivity for uptake in tumour cells have been studied by Cincotta *et al.* [32].

CLINICAL PHOTODYNAMIC THERAPY

At the present time, controlled clinical trials are being carried out for the purpose of product licensing in Europe and North America using PDT with Photofrin for the treatment of endobronchial lung cancer, oesophageal cancer and superficial bladder cancer. In Japan, these indications are also being developed, together with the additional indications of cervical dysplasia and early gastric cancer. Although PDT has been used to treat many types of solid tumours [33], this brief review will focus on the treatment of superficial bladder cancer, endobronchial cancer and oesophageal carcinoma. A recent report of intra-operative

PDT for intraperitoneal malignancy will also be reviewed as an example of the potential uses of PDT in oncology.

PDT in superficial bladder cancer

Because tissue necrosis resulting from Photofrin and 630 nm wavelength light can exceed 5 mm in certain tissues, PDT is considered to be able to eradicate most, if not all, superficial bladder cancer lesions extending into the mucosa or submucosal regions (<1 mm). Ablation of superficial bladder cancer papillary tumours has been attempted using front surface illumination with either a cleaved fiber or a microlens, and has been followed in some cases by whole bladder PDT using a spherical diffuser-tipped fibre optic in order to ablate micropapillary and remaining carcinoma *in situ* or severely dysplastic lesions. For focal therapy, light doses of 100–200 J/cm^2 have been used for papillary lesions. The overall response rate for such treatments varied from 70 to 100%, and the results of clinical trials published in the literature are summarised in Table 1 [18, 19, 34–45].

Although the incidence of side effects in bladder cancer PDT is not always reported, there appears to be a general 'post-PDT syndrome' characterised by irritative bladder symptoms of urinary frequency, urgency and dysuria which is transient but which may vary in duration from a few days to several weeks. Studies using 15 and 25 J/cm^2 for whole bladder PDT have been reported which suggest that light doses >15 J/cm^2 may be associated with severe treatment toxicities.

Lederle Laboratories are currently conducting a phase III, controlled clinical trial of whole bladder PDT for the prophylaxis of recurrent superficial bladder cancers (papillary type). After transurethral resection of bladder tumours (up to stage T1G3),

Table 1. Summary of published results with PDT in bladder cancer

Reference	Patients/ lesions	Description of disease	Therapy: Drug dose (mg/kg)	Therapy: PDT	Patient procedures	Patient response (lesions): CR	PR	NR	RE	Follow-up (months)
Benson [34, 35]	27/31	15-focal CIS	HPD 2.5	150 J/cm	Flat tip with	15	0	0	8	6–32
		12-diffuse			microlens	12	0	0	2	(mean 7)
		CIS	HPD 4–5	25–45 J/cm^2	Bulb diffuser	0	0	2	0	
		2-T_2		3 or 48 h	NS 150 to	0	0	2	0	
		2-T_a			250 ml					
Ha *et al.* [36]	6	Transitional cell	HPD 5			5	1	0	—*	1
Hisazumi *et al.* [37, 38]	9/48	T_a–T_1	HPD 2–3.2	150–300 mW/cm^2						1
				100–200 J/cm^2	200 ml NS					
		<1 cm			flat tip	22	6	5	—	
		1–2 cm				4	2	3	—	
		2–3 cm				0	1	2	—	
		>3 cm				0	0	1	—	
Nseyo and Dougherty [18]	10/13	4 T_{Is}	Photofrin 2	10–69 J/cm^2	Bulb diffuser;	4	0	0	—	2–12
		1 T_a			water or NS;	0	1	0	—	
		6 T_1			filling press	2	2	2	—	
		2 T_2			30–60 cm H_2O	0	0	2	—	
Shumaker and Hetzel [19]	16	12 T_{Is}	Photofrin 2	<20 J/cm^2	NS 150 Ml	7	2	0	—	6–24
		4 T_a				2		2		6–15
Tsuchiya *et al.* [39]	8 G HI	T_a–T_2	HPD 2.5	120–260 J/cm^2	Flat tip	8	0	0	2	6–18
Nseyo *et al.* [40, 41]	23	6 T_{Is}	Photofrin 2	16–200 J/cm^2	Bulb diffuser	4	1	1		2– >12
		8 T_a			Microlens or	3	3	2		
		8 T_1			cylinder	2	5	1		
		3 T_2				0	1	2		
		1 T_3				0	0	1		
Prout *et al.* [42, 43]	20/50	3 T_{Is}	Photofrin 2	5.5–10 J/cm^2	Bulb diffuser	3	0	0		3
		50 T_a			Microlens	12	25	13		
		or T_1		100–200 J/cm^2						
Harty *et al.* [44]	7	3 T_a	Photofrin 2	100 J/cm^2 focal	Microlens	3	0	0	1	
		2 T_1		+25 J/cm^2 whole	Bulb diffuser	1	0	1	0	
		2 T_{Is}		bladder		1	0	1	0	
Dugan *et al.* [45]	24	21 T_a, 3 T_1	Photofrin 2 after TUR	12 patients 15 J/cm^2 whole bladder	Spherical Bulb diffuser	Median time to recurrence 93 days—observation arm				
				12 patients observed		Not reached for PDT arm				

CIS = carcinoma *in situ*, NR = no response, CR = complete response, NS = normal saline, PR = partial response, RE = recurrence, TUR = transurethral resection. T_{Is}, T_a, R_1, T_2 = Clinical stage of bladder cancer from CIS to superficial muscle invasion.

* Data not provided.

patients are randomised to either a single course of PDT using Photofrin and a whole bladder light dose of 15 J/cm^2 or observation. Follow-up cytologies and cystoscopies are rigorously carried out every 3 months. An unscheduled interim analysis performed after accrual of 24 patients well matched in demography after 1 year of follow-up has revealed that the median time to recurrence for the observation group was 93 days, but has not yet been reached for patients receiving PDT [45]. No long-term symptomatic sequelae or bladder contraction has been observed in the PDT-treated patients. Recent studies have suggested that long-term prophylaxis of tumour recurrence in PDT may be the result of macrophage and lymphocyte stimulation within the bladder. Preliminary studies have shown that cytokines such as interleukin-1 and tumour necrosis factor appear in the bladder following PDT (but not TUR or infection) and may be detected in urine as long as 4 months after PDT, even though the patient is asymptomatic.

CIS, which is refractory to at least two courses of intravesical chemotherapy or immunotherapy has a strong potential for life threatening muscle or prostate invasion and subsequent or concurrent metastasis. Such patients may have also received radiation therapy in the course of therapy. Data from six studies reported from 1983 to 1988 has been recently reviewed [33]. All patients were reported to receive either Hpd (the earlier, less pure form of Photofrin), or Photofrin, and whole bladder radiation was given in all cases, the majority by spherical light diffusers. Light doses varied from 45 to 10 J/cm^2, and methods of determining fluence were not standardised. Of the 47 patients with refractory CIS reported in the literature, 46/47 (97.8%) were reported to have a complete response (negative cytology and/or biopsy) with follow-ups from a median of 3 to 12 months. Due to the small numbers of patients in this series, and the varied methods of treatment, a phase II study in North America in this indication as an alternative to cystectomy is also being conducted. All patients receive 2 mg/kg Photofrin, followed in 40–48 h by whole bladder PDT using a spherical diffuser-tipped fiber optic and a total light dose of 15 J/cm^2. The current controlled clinical trials will also provide information regarding the possible association of post-PDT side effects with (a) degree of mucosal involvement with disease, and (b) prior type and number of courses of intravesical therapy.

PDT in endobronchial non-small cell lung cancer

Since the early 1980's, nearly 500 patients have been reported in the literature with endobronchial lung cancer treated with PDT using either Hpd or Photofrin [33]. The results of individually published studies, when compared, are remarkably consistent in that local complete and partial response rates ranged from 70 to 100% [49–61], Table 2. Best results were obtained with mucosal tumours or early (stage 0) lung cancers [49, 51, 54, 60]. Hpd was used at a dose of 2.0–5.0 mg/kg intraveneously, and Photofrin at a dose of 2.0 mg/kg intravenously. Laser light doses ranged from 20 to 600 J/cm^2, with power intensity at the fibre tips ranging from 20 to 800 mW. One is struck by the wide range of light doses with which at least a partial response can be achieved.

It is important to note that, in certain studies, patients with very low performance status because of respiratory distress secondary to endobronchial obstruction were treated with PDT [61, 62]. Indeed, in the latter reference, 11/15 patients treated had a Karnofsky Performance Status <40. None of the patients died as a result of therapy, and 80% improved clinically, suggesting that the modality might be safe to use in patients too sick to be considered for the usual clinical trial population. In the studies, in which disease cure was the goal of therapy, follow-up of response ranged from 3 days to 41 months, with the average duration of follow-up approximately 12 months. The first patients with early disease who were inoperable have been reported surviving more than 5 years with no other treatment but PDT [49, 63]. When symptomatic improvement or improved operability was the therapeutic endpoint, a positive response was noted in 106/111 patients following PDT treatment [60, 62, 64, 65].

Controlled phase III studies in North America and Europe comparing the safety and efficacy of PDT with Photofrin with thermal ablation by the Nd:YAG laser in the palliative treatment of obstructing endobronchial lung cancer are in progress.

PDT for palliation of malignant dysphagia in esophageal cancer

Although PDT has been found useful for the potentially curative treatment of early (limited to mucosa) oesophageal adeno- and squamous cell carcinoma in various publications [33], lack of early screening methods in North America and Europe prompted us to pursue the use of PDT in palliation of malignant dysphagia caused by obstructing oesophageal lesions.

Thomas *et al.* [66] reported on the treatment of 14 patients with PDT for malignant dysphagia using Hpd as the photosensitiser. In this study, laser light of 627–630 nm was produced either by a continuous wave output argon pumped dye laser (APDL), 8 patients, or by a pulsed output gold metal vapour laser (GVL), 8 patients. Light was delivered by a cleaved fibre within a thin-walled balloon inflated with 0.5% lipid emulsion. 4 patients had adenocarcinoma, and 12 squamous cell carcinoma. Palliation of dysphagia was observed in all patients, with a median duration of response of 9.5 weeks (range, 1–28 weeks). Complications included sunburn (3 patients), fever resolving with antibiotic treatment (9 patients), and mediastinitis with pleural effusions (1 patient). A laser output of >1.5 W appeared to correlate with the development of complications. 2 patients, both >80 years old, died after therapy, one due to cardiac arrest and the other to pneumonia following bronchoesophageal fistula formation. Although both patients who died had been treated using the GVL, there is insufficient data available to determine whether continuous wave output APDL or pulsed output GVL laser treatments in PDT might differ in the nature or severity of treatment-related side effects.

McCaughan *et al.* [67] reported on the treatment of a total of 40 patients with oesophageal tumours (19 adenocarcinomas, 19 squamous cell carcinomas and two melanomas) who had failed conventional treatment. 4 patients were stage I, 17 stage II, 9 stage III, and 10 stage IV. 28 injections of Hpd and 45 injections of Photofrin were given. 85 PDT sessions were given, usually on the third day post-injection, and straight tipped or cylindrical diffusing fibres were used, both for surface and interstitial illumination. 3 patients in stage I exhibited 'no evidence of disease' status (NED). Of 35 patients who could be evaluated 1 month after the first PDT session, all were found to haave improvement in their oesophageal and diet grades. The improvement in diet was from a liquid to a soft diet. 9 patients with complete obstruction (inability to swallow even liquids) were treated, and the 7 who could be evaluated 1 month after treatment were all able to tolerate oral food intake with an average diet grade equivalent to a blenderised diet. One incident of mechanical perforation was observed after treatment, but was deemed unrelated to PDT by the investigator. 6 patients developed pleural effusions, with 5 resolving without definitive

Table 2. Summary of published clinical studies using PDT in lung cancer

Reference	Patients/lesions	Condition (no. patients)	Drug (mg/kg)	Method	Follow-up (months)	Response CR	PR	NR	Died	Side effects
Cortese and Kinsey [47, 48]	19/20 SC 17	Resected or inoperable	HPD 2.5–5.0	S/I	8–34	6	7	6	9	Phototoxicity cough obstruction
Edell and Cortese [49]	38/40 SC 37 SCC 1 Cylindroma 1 Fibrosarcoma 1	Resected or inoperable	HPD 2.0–5.0	S	6 days to 56 months	14	15	11	25	1° burn Hemoptysis Obstruction
Hayata *et al.* [50]	14/20 SC 6 AC 2 LC 3 SCC 2 Metaplasia	Early stage (1) Stage I (1) Stage II (0) Stage III (8) Stage IV (3) Metaplasia (1)	HPD 2.5–4.0	S	*	1 0 0 1 2 1	0 1 0 8 6 0	0 0 0 0 0 0	— — — — — —	Phototoxicity 1° burn
Hayata *et al.* [51, 52]	21 SC 20 LC 1	Early stage Unresected (8) Resected (5) Stage I (8)	HPD	S/I	 13–41 7–30 4–41	 8 2 2	 0 3 6	 0 0 0	 0 2 4	Photoxicity 1° burn Possible PDT complications
Kato *et al.* [53]	43/54 SC 29	23 obstructed Early stage (3)	HPD 2.0–5.0	S/I		 3	 0	 0	 —	36-phototoxicity 2 obstetric pneumonia
Kato [54]	AC 5 LC 4 SCC 2 Metaplasia 2 Other 1	Stage I (4) Stage II (8) Stage III (16) Stage IV (10) Met (2)				1 0 1 0 2	3 8 15 10 0	0 0 0 0 0	— — — — —	2 bronchial fistula 11/23 cleared Obstruction 6/9 pts operable after PDT
Keller *et al.* [55]	15	Obstructed	HPD 2.0–3.0 Photofrin 1.5–2.0	S/I	17	3	11	1	—	
Li *et al.* [56]	21/24 SC 18 AC 2 SCC 1	All advanced	HPD 5.0	S	3–7	3	17	4	1	Fever, hemoptysis, progression of in 8
Vincent *et al.* [57]	17 SC 11	Recurrent, advanced	HPD 2.5–3.0	S/I	5–210 days (mean 40)	0	13	4	8	Fever, pneumonia, hemoptysis
Vincent and Dougherty [58]	AC 5 LC 1	Obstructed								Candidiasis hypersecretion
Karanov *et al.* [59]	12	2 Stage II 10 Stage III	HPD 5.0		1–6	7	2	3	—	

CR = complete response, SC = squamous cell, SCC = small cell, PR = partial response, AC = adenocarcinoma, S = superficial, NR = no response, LC = large cell, I = interstitial.
*Data not provided.

treatment. Six strictures, all managed by dilatation, occurred in 5 patients. Three tracheoesophageal fistulas developed, one in a patient with prior surgery for laryngeal cancer, and one in a patient with tracheal invasion. 1 patient developed a third degree burn of a 2 cm diameter area of the hand 8 weeks after Photofrin injection and inadvertent exposure to sunlight, and 4 patients gradually developed a discoloration of exposed skin which lasted for several months.

Segalin *et al.* [68] reported recently on the treatment of 9 patients with oesophageal carcinoma using PDT with Hpd. Mean tumour length was 5.2 cm (range, 2–9 cm). 4 of the patients treated had severe dysphagia, and 3/4 obtained good palliation after a single course of PDT. No complications were observed in the PDT-treated patients. Patrice *et al.* [69] reported on the treatment of 24 patients with oesophageal squamous cell carcinoma, with PDT using Hpd, including 7 cases with malignant dysphagia. 11 of 24 patients responded to therapy, although as presented, the response of the patients with malignant dysphagia could not be determined. The most frequent complication, seen in 25% of patients, was painless tanning. Of five instances of post-treatment oesophageal stenosis, four were cured by dilatation and one required surgery. 2 patients with complete oesophageal obstruction so advanced that a guide wire could not be passed, rendering Nd:YAG treatment inadvisable, were treated with PDT with successful relief of their dysphagia [70].

Two protocols in this treatment indication are being conducted. In one protocol, patients with partially obstructing oesophageal lesions and malignant dysphagia are randomised to treatment with either Nd:YAG laser therapy or PDT with Photofrin. Patients in whom a guide wire cannot be passed (completely obstructing oesophageal lesions) are entered onto a phase II single-arm protocol for treatment with PDT and Photofrin.

Intra-operative abdominal or thoracic PDT

PDT has been used as an adjunct to surgical resection, for the prevention of recurrence as well as in the attempted conversion of partial to complete surgical responses [71–74]. In a study on 10 patients with retroperitoneal sarcomas [71], the patients received intravenous injections of either Hpd or Photofrin prior to laparotomy. If no extensive organ involvement was found during surgery, complete tumour resection was attempted. Following resection, the field was illuminated with 630 nm laser light using a microlens-tipped fibre optic to a total light dose of 30–288 J/cm^2; complete surgical resection and adjuvant PDT therapy occurred in 8/10 patients. No complications or side effects were noted except for photosensitivity.

The National Cancer Institute (NCI) of the United States recently reported on a phase I study of PDT with Photofrin for disseminated intraperitoneal neoplasms [74]. 23 patients were injected with Photofrin 48–72 h prior to laparotomy and debulking surgery to leave behind neoplastic nodules ≤5 mm in diameter. Treatment with 630 nm laser light was given intraoperatively, using a dilute lipid suspension (0.02–0.05% Intralipid) to enhance light diffusion. *In situ* measurement of fluence and light dose was carried out using sterile photodiodes sown into the peritoneal cavity. 13 patients with ovarian cancer, 8 with sarcoma, and 2 with pseudomyxoma peritoneii, underwent intra-operative PDT, and 5/8 patients cleared positive peritoneal cytologies after treatment. 6 patients remained free of disease for up to 18 months. The maximum tolerated dose of light for PDT (up to 2.8 J/cm^2 was given) was felt not to be reached at the time of this report. Studies are continuing at the NCI to improve methods of light delivery to large areas such as the intraperitoneal space.

Intra-operative PDT has also been used to treat pleural malignancies. At the NCI, a phase I study used PDT with Photofrin for intrathoracic treatment in patients with disease confined to one hemithorax, with light delivered after thoracotomy and debulking of gross tumour to ≤5 mm thickness [72]. Laser light dosimetry was performed *in situ* using seven photodiodes sewn into the chest cavity. All 3 patients reported treated were discharged 7–10 days after surgery without complications. Lofgren *et al.* [73] reported on the use of transthoracic endoscopic PDT to successfully treat a patient with malignant mesothelioma. The entire surface of the pleural cavity was exposed to a total laser light dose of 20 J/cm^2; *in situ* dosimetry was performed using a probe inserted via a separate puncture in the thoracic wall. Computed tomography revealed tumour response, and the patient was followed-up for 10 months without signs of tumour progression.

CONCLUSIONS

Controlled, randomised, comparative clinical trials in the treatment of superficial bladder cancer, endobronchial obstructive lung cancer, and oesophageal cancer are being carried out to determine the efficacy and safety of PDT in these indications. Initial results in the prophylactic treatment of superficial bladder cancer by PDT are encouraging. Phase I and phase II studies continue in many oncological indications [33], of which intraoperative PDT for tumours within large body cavities has been briefly discussed. Applications for product licensing of Photofrin and photodynamic therapy as an antineoplastic modality, to be used alone or in conjunction with established modalities, will be filed in certain countries during 1992.

1. Canti G, Franco P, Marelli O, Ricci L, Nicolin A. Hematoporphyrin derivative rescue from toxicity caused by chemotherapy or radiation in a murine leukemia model (L1210). *Cancer Res* 1984, **44**, 1551–1556.
2. Kessel D, Thompson P. Purification and analysis of hematoporphyrin and hematoporphyrin derivative by gel exclusion and reverse phase chromatography. *Photochem Photobiol* 1987, **46**, 1023–1026.
3. Dougherty TJ. Studies on the structure of porphyrins contained in Photofrin™ II. *Photochem Photobiol* 1987, **46**, 569–573.
4. Bugelski PJ, Porter CW, Dougherty TJ. Autoradiographic distribution of hematoporphyrin derivative in normal and tumour tissue of the mouse. *Cancer Res* 1981, **41**, 4606–4612.
5. Potter WR, Dougherty TJ. Author's unpublished results.
6. Svaasand LO. Optical dosimetry for direct and interstitial photodynamic therapy of malignant tumours. In: Doiron DR, Gomer CJ, eds. *Porphyrin Localization and Treatment of Tumors*. New York, AR Liss, 1984, 91–114.
7. Jacques SL, Prahl SA. Modeling optical and thermal distribution in tissue during laser irradiation. *Laser Surg Med* 1987, **6**, 494–503.
8. Henderson BW, Bellnier DA, Ziring B, Dougherty TJ. Aspects of the cellular uptake and retention of hematoporphyrin derivative and their correlation with the biological response to PRT *in vitro*. In: Kessel D, Dougherty TJ, eds. *Porphyrin Photosensitization*. New York, Plenum Press, 1983, 129–138.
9. Gibson SL, Murand RS, Chazen MD, Kelly ME, Hilf R. *In vitro* photosensitization of tumour cell enzymes by Photofrin II administered *in vivo*. *Br J Cancer* 1989, **59**, 47–53.
10. Gibson SL, Murant RS, Hilf R. Photosensitizing effects of hematoporphyrin derivative and Photofrin II on plasma membrane enzymes 5'-neucleotidase, Na+ K+-ATPase and Mg^{2+}-ATPase in RC3230AC mammary adenocarcinomas. *Cancer Res* 1988, **48**, 3360–3366.
11. Gulati S, Atzpodien J, Lemoli RM, Shimazaki C, Clarkson B. Photoradiation methods for purging autologous bone marrow grafts. *Prog Clin Biol Res* 1990, **333**, 87–102.
12. Star WM, Marijnissen JPA, van den Berg-Blok AE, Versteeg AAC, Franken KAP, Reinhold HS. Destruction of rat mammary tumor and normal tissue microcirculation by hematoporphyrin derivative photoradiation observed *in vivo* in sandwich observation chambers. *Cancer Res* 1986, **46**, 2532–2540.
13. Henderson BW. Significance of vascular photosensitization in photodynamic therapy. SPIE Inst for Adv Optical Technologies "Future Directions and Applications in Photodynamic Therapy". 1990, **IS6**, 153–166.
14. Henderson BW, Dougherty TJ. How does PDT work? *Photochem Photobiol* 1992, **55**, 145–157.
15. Henderson BW, Waldow SM, Mang TS, Potter WR, Malone PB, Dougherty TJ. Tumor destruction and kinetics of tumor cell death in two experimental mouse tumors following photodynamic therapy. *Cancer Res* 1985, **45**, 572–576.
16. Henderson BW, Fingar VH. Relationship of tumor hypoxia and response to photodynamic treatment in an experimental mouse tumor. *Cancer Res* 1987, **47**, 3110–3114.
17. Henderson BW, Donovan JM. Release of prostaglandin E2 from cells by photodynamic treatment *in vitro*. *Cancer Res* 1989, **49**, 6896–6900.
18. Nseyo UO, Dougherty TJ. Photodynamic therapy in the management of resistant bladder cancer. *Laser Surg Med* 1986, **6**, 228 (abstract).
19. Shumaker BP, Hetzel FW. Clinical laser photodynamic therapy in the treatment of bladder cancer. *Photochem Photobiol* 1987, **46**, 899–901.
20. Fingar VH, Wieman TJ. Studies on the mechanism of photodynamic therapy induced tumor destruction. *Proc SPIE "Photodynamic Therapy: Mechanisms II"* 1990, **1203**, 168–177.
21. Dougherty TJ. Author's unpublished results.

22. Dougherty TJ, Potter WR. Of what value is a highly absorbing photosensitizer in PDT? *J Photochem Photobiol B: Biol* 1991, **8**, 233–235.
23. Potter WR. The theory of photodynamic therapy dosimetry: Consequences of photodestruction of sensitizer. *Proc. SPIE "Lasers in Medicine"* 1986, **712**, 124–129.
24. Richter AM, Kelly B, Chow J, *et al.* Preliminary studies on a more effective phototoxic agent than hematoporphyrin. *J Natl Cancer I* 1987, **79**, 1327–1332.
25. Morgan AR, Garbo GM, Keck RW, Eriksen LD, Selman SH. Metallopurpurins and light: Effect on transplantable rat bladder tumors and murine skin. *Photochem Photobiol* 1990, **51**, 589–592.
26. Bonnett R, Berenbaum M. Porphyrins as photosensitizers. In: Bock G, Harnett S, eds. *Photosensitizing Compounds: Their Chemistry, Biology and Clinical Use*. Chichester, John Wiley and Sons, 1989, Ciba Foundation Symposium 146, 40–53.
27. Pandey RK, Bellnier DA, Smith KM, Dougherty TJ. Chlorin and porphyrin derivatives as potential photosensitizers in photodynamic therapy. *Photochem Photobiol* 1991, **53**, 65–72.
28. Brasseur N, Ali H, Langlois R, van Lier JE. Biological activities of phthalocyanines—IX. Photosensitization of V-79 Chinese hamster cells and EMT-6 mouse mammary tumor by selectively sulfonated zinc phthalocyanines. *Photochem Photobiol* 1988, **47**, 705–711.
29. Firey PA, Rodgers MAJ. Photo-properties of a silicon naphthalocyanine: A potential photosensitizer for photodynamic therapy. *Photochem Photobiol* 1987, **45**, 535–538.
30. Sessler JL, Hemi G, Maiya B, *et al.* Tripyrroledimethine-derived macrocycles. *Proceedings of SPIE "Optical Methods for Tumor Treatment and Early Diagnosis: Mechanisms and Techniques"* 1991, **1426**, 318–329.
31. Chang CK, Sotiriou C, Wu W. Synthetic approaches to long-wavelength-absorbing photosensitizers: porphyrinone and derivatives. *Proc SPIE "Photodynamic Therapy: Mechanisms II"* 1990, **1203**, 281–286.
32. Cincotta AH, Cincotta L, Foley JW. Novel benzophenothiazinium photosensitizers: Preliminary *in vivo* results. *Proc SPIE "Photodynamic Therapy: Mechanisms II"* 1990, **1203**, 202–210.
33. Marcus SL. Clinical photodynamic therapy: The continuing evolution. In: Henderson BW, Dougherty TJ, eds. *Photodynamic Therapy: Principles and Clinical Applications*. New York, Marcel Dekker, 1992, in press.
34. Benson RC Jr. Hematoporphyrin photodynamic therapy for transitional cell carcinoma of the bladder—an update. In: Kessel D, eds. *Methods in Porphyrin Photosensitization*. New York, Plenum Press, 1985, 3–12.
35. Benson RC. Treatment of diffuse transitional cell carcinoma in situ by whole bladder hematoporphyrin derivative photodynamic therapy. *Mayo Clin Proc* 1985, **134**, 675–688.
36. Ha XW, Sun XM, Xie JG, Fan XJ, Zhang YH, Mei QC, *et al.* Clinical use of hematoporphyrin derivative in malignant tumors. *Chin Med J* 1983, **96**, 754–758.
37. Hisazumi H, Misaki T, Miyoshi N. Photodynamic therapy of bladder tumors. In: Hayata Y, Dougherty TJ, eds. *Lasers and Hematoporphyrin Derivative in Cancer*. Tokyo, Igaku-Shoin, 1983, 85–87.
38. Hisazumi H, Misaki T, Miyoshi N. Photoradiation therapy of bladder tumors. *J Urol* 1983, **130**, 685–687.
39. Tsuchiya A, Obara N, Miwa M, Ohi T, Kato H, Hayata Y. Hematoporphyrin derivative and laser photoradiation in the diagnosis and treatment of bladder cancer. *J Urol* 1983, **130**, 79–82.
40. Nseyo UO, Dougherty TJ, Sullivan L. Evaluation of photodynamic therapy in the management of bladder cancer. *Laser Surg Med* 1987, **7**, 107 (abstract).
41. Nseyo UO, Dougherty TJ, Sullivan L. Photodynamic therapy in the management of resistant lower urinary tract carcinoma. *Cancer* 1987, **60**, 3113–3119.
42. Prout GR Jr, Griffin P, Daly JJ. The outcome of conservative treatment of carcinoma *in situ* of the bladder. *J Urol* 1987, **138**, 766–770.
43. Prout GR, Lin CW, Benson R, Nseyo UO, Daly JJ, Griffin P, *et al.* Photodynamic therapy with hematoporphyrin derivative in the treatment of superficial transitional cell carcinoma of the bladder. *N Engl J Med* 1987, **317**, 1251–1255.
44. Harty JI, Amin M, Wieman TJ, Tseng MT, Ackerman D, Broghamer W. Complications of whole bladder dihematoporphyrin ether photodynamic therapy. *J Urol* 1989, **141**, 1341–1346.
45. Dugan M, Crawford E, Nseyo U, *et al.* A randomized trial of observation vs photodynamic therapy (PDT) after transurethral resection (TUR) for superficial papillary bladder carcinoma. *Proc ASCO* 1991, **10**, 173.
46. Nseyo UO, Whalen RK, Duncan MR, Berman B, Lundahl SL. Urinary cytokines following photodynamic therapy for bladder cancer: A preliminary report. *Urology* 1990, **XXXVI**, 167–171.
47. Cortese DA, Kinsey JH. Bronchoscopic phototherapy using hematoporphyrin derivative. *Surg Clin N Am* 1984, **64**, 941–946.
48. Cortese DA, Kinsey JH. Hematoporphyrin derivative phototherapy in the treatment of bronchogenic carcinoma. *Chest* 1984, **86**, 8–13.
49. Edell ES, Cortese DA. Bronchoscopic phototherapy with hematoporphyrin derivative for treatment of localized bronchogenic carcinoma: A 5-year experience. *Mayo Clin Proc* 1987, **62**, 8–14.
50. Hayata Y, Kato H, Konaka C, Amemiya R, Ono J, Ogawa I, *et al.* Photoradiation therapy with hematoporphyrin derivative in early Stage I lung cancer. *Chest* 1984, **86**, 169–177.
51. Hayata Y, Kato H, Konaka C, Ono J, Saito M, Takahashi H, *et al.* Photoradiation therapy in early stage cancer cases of the lung, esophagus and stomach. In: Andreoni A, Cubeddu R, eds. *Porphyrins in Tumour Phototherapy*. New York, Plenum Press, 1984, 405–412.
52. Hayata Y, Kato H, Konaka C, Ono J, Takizawa N. Hematoporphyrin derivative and laser photoradiation in the treatment of lung cancer. *Chest* 1982, **81**, 269–277.
53. Kato H, Konaka C, Ono J, Matshushima Y, Nishimiya K, Tomono T, *et al.* Effectiveness of Hpd and radiation therapy in lung cancer. In: Kessel D, Dougherty TJ, eds. *Methods in Porphyrin Photosensitization*. New York, Plenum Press, 1983, 23–29.
54. Kato H. Lung cancer. In: Hayata Y, Dougherty TJ, eds. *Lasers and Hematoporphyrin Derivative in Cancer*. Tokyo, Igaku-Shoin, 1983, 39–56.
55. Keller GS, Doiron DR, Fisher GU. Photodynamic therapy in otolaryngology-head and neck surgery. *Arch Otolaryngol* 1985, **111**, 758–761.
56. Li JH, Chen YP, Zhao SD, Zhang LT, Song SZ. Application of hematoporphyrin derivative and laser-induced photodynamical reaction in the treatment of lung cancer: A preliminary report of 21 cases. *Laser Surg Med* 1984, **4**, 31–37.
57. Vincent RG, Dougherty TJ, Rao U, Boyle DG, Potter WR. Photoradiation therapy in advanced carcinoma of the trachea and bronchus. *Chest* 1984, **85**, 29–33.
58. Vincent R, Dougherty TJ. Photoradiation therapy in the treatment of advanced carcinoma of the trachea and bronchus. In: Doiron DR, Gomer CJ, eds. *Porphyrin Localization and Treatment of Tumors*. New York, AR Liss, 1984, 759–766.
59. Karanov S, Kostadinov D, Shopova M, Kurtov P. Photodynamic therapy in lung and gastrointestinal cancers. *J Photochem Photobiol B: Biol* 1990, **6**, 175–181.
60. Balchum OJ, Doiron DR. Photoradiation therapy of endobronchial lung cancer. *Clin Chest Med* 1985, **6**, 255–275.
61. McCaughan JS, Williams TE, Bethel BH. Photodynamic therapy of endobronchial tumors. *Laser Surg Med* 1986, **6**, 336–345.
62. Hugh-Jones P, Gardner WN. Laser photodynamic therapy for inoperable bronchogenic squamous carcinoma. *Quart J Med* 1987, **64**, 565–582.
63. Kato H, Konaka C, Kawate N, Shinohara H, Kinoshita K, Noguchi M, *et al.* Five-year disease-free survival of a lung cancer patient treated only by photodynamic therapy. *Chest* 1986, **90**, 768–770.
64. Lam S, Kostashuk EC, Coy EP, Laukkanen E, LeRiche JC, Mueller HA, *et al.* A randomized comparative study of the safety and efficacy of photodynamic therapy using Photofrin II combined with palliative radiotherapy versus palliative radiotherapy alone in patients with inoperable obstructive non-small cell bronchogenic carcinoma. *Photochem Photobiol* 1987, **46**, 893–897.
65. LoCicero J, Metzdorff M, Almgren C. Photodynamic therapy in the palliation of late-stage obstructing non-small cell lung cancer. *Chest* 1990, **98**, 97–100.
66. Thomas RJ, Abbott M, Bhathal PS, St. John DJB, Morstyn G. High-dose photoradiation of esophageal cancer. *Ann Surg* 1987, **206**, 193–199.
67. McCaughan JS Jr, Nims TA, Guy JT, Hicks WJ, Williams TE, Laufman LR. Photodynamic therapy for esophageal tumors. *Arch Surg* 1989, **124**, 74–80.
68. Segalin A, Little A, Ruol A, Ferguson MK, Bardini R, Norberto L, *et al.* Surgical and endoscopic palliation of esophageal carcinoma. *Ann Thoracic Surg* 1989, **48**, 267–271.
69. Patrice T, Foultier MT, Yactayo S, Adam F, Galmiche JP, Douet

MC, *et al.* Endoscopic photodynamic therapy with hematoporphyrin derivative for primary treatment of gastrointestinal neoplasms in inoperable patients. *Digest Dis Sci* 1990, **35**, 545–552.
70. Likier HM, Levine JG, Lightdale C. Photodynamic therapy for completely obstructing esophageal carcinoma. *Gastrointest Endosc* 1991, **37**, 75–78.
71. Nambisan RN, Karakousis CP, Holyoke ED, Dougherty TJ. Intraoperative photodynamic therapy for retroperitoneal sarcomas. *Cancer* 1988, **61**, 1248–1252.
72. Pass H, Tochner Z, DeLaney T, Smith P, Friauf W, Glatstein E. Intraoperative photodynamic therapy after resection of pleural malignancies. Presented at the 3rd Biennial Meeting of the International Photodynamic Association, Buffalo, New York, 1990, Abstract XX/5.
73. Lofgren L, Larsson M, Thaning L, Hallgren S. Transthoracic endoscopic photodynamic treatment of malignant mesothelioma. *The Lancet* 1991, **337**, 359.
74. Sindelar W, DeLaney T, Tochner Z, *et al.* Technique of photodynamic therapy for disseminated intraperitoneal malignant neoplasms. *Arch Surg* 1991, **126**, 318–324.

Eur J Cancer, Vol. 28A, No. 10, pp. 1742–1747, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00
Pergamon Press Ltd

Clinical Oncology: Case Presentations from Oncology Centres. Intensive Treatment of Poor Prognosis Gastrointestinal Lymphoma

R. Pettengell, P. W. Bishop and D. Crowther

CASE PRESENTATION

A 50-YEAR-OLD European engineer presented to his family doctor with intermittent right hypochondrial pain, diarrhoea and lethargy. These symptoms were initially managed with antacids and simple analgesics. His past history included a laparotomy 30 years ago for duodenal ulceration, followed by pyloroplasty and vagotomy 2 years later. Three years ago he had complained of right upper quadrant pain but a barium enema at that time was normal.

For 7 months his symptoms of dyspepsia persisted. He became anorexic and lost 19 kg in weight. In the final 3 months he developed drenching nocturnal sweats but no fever or pruritus. He returned to his general practitioner and on abdominal examination a right upper quadrant mass was felt.

His general practitioner referred him for upper gastrointestinal endoscopy which was normal. A barium enema showed narrowing of the hepatic flexure of the colon and was reported as a possible lymphoma. An ultrasound examination confirmed the presence of a solid mass in the upper abdomen.

He proceeded without delay to surgery. At laparotomy an advanced tumour was found at the hepatic flexure infiltrating the right mesocolon and the root of the small bowel mesentery. This was unresectable and a palliative ileo-transverse anastomosis was performed and a biopsy sample taken. The postoperative recovery was uneventful. A preliminary diagnosis of diffuse high grade non-Hodgkins' lymphoma was made and the patient was referred to the Department of Medical Oncology at the Christie Hospital.

Correspondence to R. Pettengell.
The authors are at the Department of Medical Oncology, Christie Cancer Centre, Wilmslow Road, Manchester M20 9BX, U.K.
Received 24 Feb. 1992 accepted 17 Mar. 1992.

Clinical assessment

The patient was thin, with a Karnofsky performance score of 60. Multiple 2–3 cm fixed lymph nodes were palpable in the right supraclavicular fossa. There was no other peripheral lymphadenopathy and Waldeyer's ring was normal. The abdomen was distended with a 20 cm × 11 cm right upper quadrant mass. The liver and spleen were not palpably enlarged.

Staging investigations

At presentation he had a normochromic, normocytic anaemia with a haemoglobin of 11.0 g/dl. His platelets were 532 × 10^9/l, white blood count 6.6 × 10^9/l (neutrophils 63%, lymphocytes 26%, monocytes 3%, eosinophils 7%, basophils 1%, no abnormal cells). The erythrocyte sedimentation rate (ESR) was 18 mm/h. Serum protein electrophoresis revealed a raised α_2 globulin but immunoglobulin levels were normal. Serum vitamin B_{12} was 457 ng/l (normal range 140–640) and serum folate 4.1 μg/l (2–8). Serum electrolytes were normal but liver function was deranged: serum alkaline phosphatase 244 U/l (25–110), gamma glutamyl transferase 165 U/l (5–65) and lactate dehydrogenase 635 U/l (200–500). Renal function was normal. Bone marrow aspirate and trephine showed normal cellularity and maturation with reduced iron stores but no evidence of malignant infiltration. Examination of the cerebrospinal fluid was normal.

Diagnostic imaging included radiographs of the chest, postnasal space and computed tomography (CT) the chest and abdomen. Right paratracheal, tracheobronchial and anterior mediastinal lymphadenopathy was evident on the chest radiograph. Postnasal space radiographs were normal. CT confirmed enlargement of mediastinal, right internal mammary, bilateral supradiaphragmatic and retrocrural lymph nodes. All abdominal lymph node groups were involved with bulky para-aortic and paracaval nodes extending from the level of the pancreas to the aortic bifurcation (maximum diameter of 10 cm). A conglomerate