tumours present higher numbers of peritumoral and intratumoral lymphoid cells, poorly demarcated tumours and, more so, diffuse or multiple tumours show lower numbers of lymphoid cells. Maybe the expanding or infiltrative tumour growth is related to a more or less pronounced immunological response.

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Acknowledgements—We thank Mrs Dolly Beghè and Miss Paola Mangiavacchi for their skilled assistance in histochemical and immunohistochemical preparations.

Eur J Cancer, Vol. 28A, No. 8/9, pp. 1370–1373, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

A Pilot Study of Photodynamic Therapy in Patients with Inoperable Non-small Cell Lung Cancer

Tom Sutedja, Paul Baas, Fiona Stewart and Nico van Zandwijk

26 patients with inoperable non-small cell lung cancer (NSCLC) were treated with photodynamic therapy (PDT) with intravenous Photofrin II 2 mg/kg. 10 out of 11 stage I patients achieved a complete response. The remaining patient, and 11 out of 15 stage III patients had a partial response. No response was seen in 4 patients, 2 of whom had inadequate illumination. Thus, the objective response rate was 85% (22/26). Although lung function did not improve, dyspnoea was ameliorated in 7 (58%) of the partial responders. 4 stage III patients had tumour progression and died of pulmonary haemorrhages 1.5–6 months after PDT. All had received external irradiation, Nd-YAG laser and/or brachytherapy before PDT. 4 patients had grade I–II skin photosensitivity. Although of value in stage I NSCLC, the clinical benefit of PDT in stage III disease was small.
Eur J Cancer, Vol. 28A, No. 8/9, pp. 1370–1373, 1992.

INTRODUCTION

PHOTODYNAMIC THERAPY (PDT) is based on the illumination of malignant tissue containing compounds (photosensitisers) activated by light. Illumination with light of an appropriate wavelength initiates a photochemical reaction and the formation of various radicals in the vicinity of the activated sensitiser molecule. This process leads to the disruption of biomolecular structures, causing vascular thrombosis and tissue necrosis [1–3]. PDT offers the possibility of selective tumour damage due to the local application of laser light and the relatively higher retention of photosensitisers in tumour stroma, in comparison to the surrounding normal lung tissue [3]. The experiences with PDT in lung cancer have suggested that palliation of locally advanced tumours is feasible [4–6], and that cure may be

obtained in superficial lesions [7, 8]. So far, skin photosensitivity is the only known side effect. This is due to the fact that sensitisers are also retained in the skin and strongly absorb ultraviolet light [9].

We report our first experience with PDT in 26 patients with stage I and stage III non-small cell lung cancer (NSCLC), judged to be inoperable for various reasons.

PATIENTS AND METHODS

From March 1989 to January 1991, 26 patients with inoperable NSCLC entered this study. All patients had a performance score of ≥70% and endobronchial tumours which were accessible to the fibreoptic bronchoscope. 11 patients presented with a stage I NSCLC and were judged inoperable due to poor pulmonary function. The remaining 15 patients had locally advanced stage III disease, 13 of them had recurrences after first or second line treatment (Table 1).

Photofrin II® (2 mg/kg; PII, Cyanamid) was given by intravenous bolus 48 h before illumination. Patients were instructed to avoid sunlight for a minimum period of 2 weeks after PII injection [1, 9]. Fibre optic bronchoscopy (Olympus) was performed using topical anaesthesia of 10 ml lidocaine 2%. 100% oxygen was routinely given using nasal prongs and oxygen saturation was monitored with a pulse oximeter (Datex Satlite). Interstitial or intraluminal illumination was carried out by positioning a laser fibre with a cylindrical diffusing tip of various length (1.5, 2.0 and 2.5 cm) in the centre of or adjacent to the malignant tissue, to transmit red laser light of [mean (S.D.)] 628 (2) nm wavelength from an argon-dye laser (Spectra Physics 171/375B). Light energy output was standardised at 400 mW/cm and the illumination time was 500 s. Light energy output from the cylindrical diffuser was measured using an integrating sphere (UDT-2500) connected to a power meter (UDT S371). Light energy output was checked again immediately after tumour illumination. Additional illumination was given to compensate for a more than 15% drift from the initial power setting. A "clean-up" bronchoscopy was performed within 2 days after treatment to remove necrotic tissue [4–5]. Additional illumination was also carried out if viable tumour tissue was still apparent at this time. Follow-up was scheduled 4–6 weeks after PDT and then at intervals of 3 months.

Table 1. Characteristics of 26 patients treated with PDT

Male/female	25/1
Stage I	11
Stage III	15
Median age (years)	64
Range (years)	49–83
Prior treatments	13
Surgery	1
RT	1
Surgery and RT	6
RT and HDR	1
RT and YAG	1
RT, YAG and HDR	1
YAG and HDR	1
Surgery, RT, YAG and HDR	1

HDR = High dose rate brachytherapy; YAG = yttrium aluminium garnet laser or Nd-YAG.

Table 2. Response, survival and cause of death in 26 patients with inoperable NSCLC treated with PDT

Status	Complete response	Partial response	No response
n = 26			
11 stage I	10	1	0
15 stage III	0	11	4
Follow-up (months)	6–18	1.5–16	5–14
n deceased	2	8	2
Survival (months)	2–18	1.5–10	4–10
Median survival	7	4	6
Cause of death			
Bleeding	0	4	0
Pneumonia	2	0	0
Pulmonary embolism	0	1	0
Progressive disease	0	3	4

Relief from dyspnoea was considered significant if there was a ≥2 grades improvement of the WHO symptom scale (0–4 scale: no dyspnoea to severe dyspnoea at rest).

A complete response (CR) was defined as no residual tumour seen on chest X-rays and computed tomography (CT) scan, and bronchoscopy with negative histology and cytology examinations. A ≥50% improvement of the airway lumen diameter or a ≥50% reduction of the intraluminal tumour size (assessed using the distance between the jaws of the biopsy forceps) was regarded as a minimum requirement for a partial response (PR). A <50% improvement of the airway lumen diameter was regarded as a treatment failure. Cutaneous side effects were graded according to WHO criteria.

RESULTS

A total of 43 illumination procedures were carried out using topical anaesthesia. No immediate treatment related complications were encountered. During the initial study period, we encountered problems in adequately transmitting the laser light due to the complicated coupling system from the argon-dye laser to the fibre, causing unstable light output. 2 patients therefore received an insufficient light dose and in another 2 patients tumour illumination was delayed. Additional illumination was necessary on nine occasions to compensate for inadequate light energy output during the first session. The total procedure usually lasted not more than 20 min. There were no treatment failures after the fibre-coupling system had been improved.

On one occasion the clean-up bronchoscopy had to be performed under general anaesthesia. This patient had a pneumonectomy prior to PDT and suffered from a subtotal obstruction of the trachea and the left main bronchus by necrotic tumour tissue.

Complete and partial responses were assessed in 22 out of the 26 patients (85%, see Table 2). CR was achieved after one treatment in 6 patients and after a second treatment in the remaining 4 patients. All 10 patients had stage I tumours. The only remaining patient with a stage I disease achieved a PR, still

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Revised and accepted 20 Feb. 1992.
EJC 28:8/9-D

Table 3. Vital capacity (VC) and forced expiratory volume 1 s (FEV1) in 17 patients before and after PDT treatment

Patient category and no. of patients (*n*)		Before PDT	After PDT
Stage I patients (10)	VC	3.3 (0.7)	3.2 (0.8)
	FEV1	2.0 (0.4)	2.0 (0.5)
Stage III patients (7)	VC	3.2 (0.9)	3.0 (0.8)
	FEV1	1.7 (0.7)	1.7 (0.8)
Partial responders in Stage III group (5)	VC	3.1 (0.9)	3.1 (1.1)
	FEV1	1.5 (0.3)	1.6 (0.4)

Mean (S.D.).

showing carcinoma *in situ* after three treatments. 11 of the 15 patients with stage III NSCLC showed a PR at the first evaluation. Retreatment in 2 patients did not lead to a CR.

2 of the 4 non-responders (two treatment failures) were given radiotherapy after PDT. The remaining 2 patients had previously been treated extensively and no further treatment was possible.

Although pulmonary function parameters (available for 17 patients) before and after PDT did not show large differences (Table 3), a significant improvement of dyspnoea score was noted for patients who attained a PR.

2 elderly patients, 79 and 83 years old, died with pneumonia 2 and 6 months after PDT. In one of them, bronchoscopy shortly before death confirmed a CR. Of the 11 patients with a PR, 8 died after a follow-up period of 1.5–10 months. The median survival of the PR group was 4 months.

4 patients with stage III disease and tumour progression 1.5 to 6 months after treatment, died because of pulmonary haemorrhage. Autopsy showed the bleeding site to be unrelated to treatment in 1 patient and in another patient a fistula was found between the left main bronchus and the left pulmonary artery, completely surrounded by tumour tissue.

Recurrent respiratory infections were seen in 5 patients, 2 of them had also been treated with brachytherapy prior to PDT. 1 patient died because of pulmonary embolus.

4 patients suffered from mild skin photosensitivity in the first 2 months after PII injection, 2 had erythema and 2 others, skin oedema. 2 of them had clearly neglected the instructions to avoid sunlight after PII injection. Skin photosensitivity in all 4 cases was self-limiting and did not cause late skin damage.

DISCUSSION

Our results confirm that PDT is easily performed as a routine fibreoptic bronchoscopic procedure and is well tolerated [4–8]. No immediate treatment related complication occurred. Difficulties with the laser equipment were the reason of treatment failure in 2 patients during the initial study period. Fortunately, additional illumination procedures could be performed following the clean-up bronchoscopy in the majority of cases. Adaptations of the fibreoptic coupling system have now greatly improved our illumination technique.

A complete and partial response rate of 85% confirms the efficacy of PDT as previously reported [4–6]. Complete responses, however, were only obtained in patients with stage I disease. Their tumour volume was estimated by bronchoscopy to be less than 2 cm^3 as CT scan did not reveal any peribronchial involvement. Tissue necrosis achievable by PDT with light of 628 nm wavelength is known to be 3–9 mm deep [1], so it is obvious that PDT can achieve cure only in patients with "early stage" or "superficial" tumours [7–8]. The use of tumour fluorescence for detection of "early" lung cancers in combination with PDT may therefore improve the chance of cure [4, 11,12]. The majority of patients with locally advanced tumours did show a PR, although it is difficult to quantify the benefit of PDT in this category of patients.

Our series showed a discrepancy between the subjective improvement of dyspnoea (noted by many patients) and the lung function parameters. This could be explained by the fact that patients with T1–2 tumours could not be expected to have a significant improvement of their lung function parameters as their tumour usually did not completely obstruct the bronchi. The majority of patients with locally advanced tumour had been previously irradiated, so improvement of dyspnoea and lung function parameters was limited.

PDT causes immediate vascular thrombosis and tissue hypoxia leading to secondary necrosis [1–3, 13]. The primary vascular effect of PDT could, theoretically, cause pulmonary haemorrhage. However, there was a relatively long time interval (of 1.5–6 months) between PDT and fatal bleeding in the 4 patients where this occurred. Tumour progression was clinically evident in all 4 cases and may also cause spontaneous bleeding [14]. Moreover, previous treatments such as surgery, radiotherapy, Nd-YAG laser and brachytherapy could have contributed to tissue damage. Considering all these factors, it is difficult to attribute the fatal bleeding seen in 4 of our patients to PDT alone.

Dougherty *et al.* reported skin photosensitivity to occur in 25–35% of the patients treated with PDT [9], and our experience in this regard was favourable. It was rather unfortunate that 2 of the non-responding patients became skin photosensitive.

We confirm that PDT is a valuable new technique in the treatment of patients with stage I NSCLC. PDT limitations are the uncertainties in dosimetry (particularly absorbed tumour light doses), poor penetration of 628 nm light, the complicated laser equipment and the skin photosensitivity associated with PII. Whether new photosensitisers and light of a longer wavelength can improve PDT efficacy, remains to be seen [1]. We believe that for patients with locally advanced tumours, PDT should be compared with other palliative techniques in a randomised fashion as an additional local treatment, prior to external irradiation [15, 16].

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Eur J Cancer, Vol. 28A, No. 8/9, pp. 1373–1379, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Malignant Mesothelioma: Clinical Characteristics, Asbestos Mineralogy and Chromosomal Abnormalities of 41 Patients

Lauri Tammilehto, Timo Tuomi, Marianne Tiainen, Jukka Rautonen, Sakari Knuutila, Seppo Pyrhönen and Karin Mattson

The clinical characteristics and the results of mineral fibre and cytogenetic analyses were coordinated prospectively for 41 patients with confirmed malignant pleural mesothelioma. A correlation was found between high total fibre concentration, and partial or total loss of chromosomes 1, 4 and 9 and chromosomal rearrangements involving a breakpoint at 1p11–p22. There was also a correlation between crocidolite/amosite as the main fibre type and partial or total loss of chromosomes 1, 3 and 4 and chromosomal rearrangements involving del (3p). Positive prognostic factors were female gender, low total fibre concentration (< 10^6 fibres per g dried lung tissue), anthophyllite as the main fibre type and normal chromosome 7. In addition, we found 4 patients with malignant mesothelioma who had been exposed mainly to anthophyllite fibres (total lung fibre concentrations of 1.2, 0.4, 0.2 and 0.1 × 10^6 fibres per g dried lung tissue). This would seem to indicate that there may be a carcinogenic role for anthophyllite.
Eur J Cancer, Vol. 28A, No. 8/9, pp. 1373–1379, 1992.

ASBESTOS EXPOSURE and possibly genetic susceptibility are considered to be contributing factors in the development of malignant mesothelioma [1, 2]. The latent period, between the first exposure to asbestos and the diagnosis of mesothelioma ranges from 20 to 40 years. This explains the increasing incidence of mesothelioma in industrialised countries, with the highest incidence occurring in people who suffered heavy occupational exposure between 1950 and 1970 [3]. In Finland, the annual incidence of mesothelioma in 1985 was 12 per million for males and 3 per million for females [4]; but as yet very little is known about the natural history and biology of the disease.

Amphibole fibres with a high length-to-diameter ratio such as crocidolite, amosite and tremolite are most often implicated in the development of mesothelioma [5, 6]. Chrysotile, by comparison, is less carcinogenic, and anthophyllite has not been shown to cause mesothelioma in exposed individuals [7]. In Finland, anthophyllite asbestos has been mined and used in exceptionally large quantities in the construction industry; it is estimated that 200 000 workers had significant exposure between 1918 and 1975 [7]. It was therefore of particular interest to study prospectively more Finnish mesothelioma patients, in order to elucidate further the possible relationship between anthophyllite and mesothelioma, and to characterise biologically such anthophyllite related tumours.

Experimental studies have shown that asbestos fibres cause cell transformation and chromosomal abnormalities in normal human mesothelial cells [8]. Non-random patterns of chromosome aberration have been detected in studies of human mesothelioma [9–11]. No specific chromosomal aberration has as yet

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Revised 9 Jan. 1992; accepted 15 Jan. 1992.