LUNG CANCER

Sequential photodynamic therapy (PDT) and high dose brachytherapy for endobronchial tumour control in patients with limited bronchogenic carcinoma

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Background: Bulky endobronchial tumours in patients with lung cancer are difficult to treat. Brachytherapy and photodynamic therapy (PDT) are variably effective, and the combination of these treatments is not often recommended. However, cell culture studies and animal studies indicate a possible synergistic effect of combining PDT with ionising radiation. We assessed the safety and effectiveness of combined brachytherapy and PDT in patients with bulky endobronchial lung cancer.

Methods: Patients with histologically proven non-small cell bronchogenic carcinoma and bulky endobronchial tumours were treated using a combination of PDT (Photofrin, 2 mg/kg) and brachytherapy. Six weeks after PDT, brachytherapy was applied with five fractions of 4 Gy at weekly intervals. Follow up was performed with standard and autofluorescence bronchoscopy and tissue biopsies every 3 months.

Results: Thirty two patients were treated. Tumours were extensive with lengths ranging from 10 to 60 mm along the bronchus and estimated volumes ranging from 40 to 3500 mm^3. At a mean follow up of 24 months, 26 patients were free of residual tumour and local recurrence. The remaining patients received a second treatment with PDT, brachytherapy, Nd:YAG laser coagulation, or external beam radiation. Distant metastases (lung, lymph node) developed in two of the six patients. Currently, all 32 patients are well. There is no evidence of residual or local recurrent endobronchial cancer in 28 patients and none had severe complications.

Conclusion: The combination of PDT and brachytherapy for treating patients with lung cancer and extensive endobronchial tumour is safe and, in this study, had excellent therapeutic efficacy.

Bronchogenic carcinoma is the most common cancer in the United States and Europe. Many patients suffer from marked endobronchial obstruction, either as a presenting symptom or as a recurrence of their malignancy. If the tumours are inoperable, various palliative treatments are usually pursued. Local treatment options are Nd:YAG laser coagulation, cryotherapy, electrocautery, brachytherapy, and photodynamic therapy (PDT).[1] Nd:YAG laser resection is the most common method of clearing the airways from exophytic bulky tumours. Photodynamic therapy has emerged as an alternative, with a slower but longer lasting effect.[2 3] Its use is considered to be limited to superficial tumours with limited mass and extension.[4] Intramural and peribronchial tumour growth can be managed by brachytherapy. In two studies we have reported prolonged survival with endobronchial high dose brachytherapy[5] and good responses to PDT in cases of postoperative cancer recurrence.[6] We postulated that combining PDT and brachytherapy could improve local tumour control and survival in patients with bulky endobronchial tumours. At the same time, we aimed to assess the safety of combining these treatments.

METHODS

Patients

Patients with technically inoperable primary bronchogenic carcinoma and patients with recurrent lung cancer in the airways were eligible for inclusion. Tumours had to be limited to the airways, without evidence of other chest or metastatic disease; otherwise, external beam radiation or chemotherapy would have been pursued. Primary radiation therapy of the airways is not uniformly successful, and therefore we believed that offering alternative therapeutic approaches to an individual patient, such as the one proposed in this study, was ethical. The Institutional Review Board approved the study, and written informed patient consent was obtained in all cases. Patients were followed prospectively to assess the feasibility and results of this approach.

Evaluation

After routine clinical tests including CT scans, all patients underwent standard bronchoscopy with conventional white light and autofluorescence examination. Biopsy specimens were taken from the tumour and sites proximal and distal to the neoplasm to confirm the diagnosis and tumour margins histologically. Tumour extensions were noted as visible length, width, and height over the bronchial surface level. Tumour volume was estimated as the cubic product of these three values.

Photodynamic therapy

Photofrin (QLT Pharmaceuticals, Susteren, The Netherlands, or Ipsen Pharma, Ettlingen, Germany) was injected intravenously at a dose of 2 mg/kg body weight. Patients were instructed to avoid exposure to direct sunlight for 4–6 weeks. Bronchoscopic examination with light activation of the drug was performed 48 hours after injection.

Red light was generated with an argon pumped dye laser (Lambda Plus, Coherent, Palo Alto) or a diode laser (Zeiss, Jena, Germany) adjusted to 630 nm. Optical fibres (400 μm) with cylindrical diffusers ranging from 1 to 3 cm long or microlens fibres were used to debulk the tumours. Tumour tissue was either impaled with the diffuser fibre for interstitial illumination or irradiated on the surface with the help of microlens fibres. Red light was applied at 200 J/cm for interstitial treatment or at 100 J/cm^2 for surface treatment. Forty eight hours after the first illumination

Table 1 Demographic and clinical characteristics of 32 patients with limited bronchogenic carcinoma treated with sequential photodynamic therapy (PDT) and high dose brachytherapy

						Tumour dimensions			
No	Age (years)	Sex	Histology	Tumour localisation	Indication for PDT	Length (mm)	Width (mm)	Depth (mm)	Volume (mm^3)
1	70	M	sq	rulb	Postop	10	10	2	200
2	68	M	sq	lulb	Postop	35	20	5	3500
3	66	M	sq	tra, rulb	Emphysema	30	5	2	300
4	49	F	adcy	bri, lulb	Postop	15	10	3	450
5	64	M	sq	rulb	Postop	20	10	3	600
6	65	M	sq	lulb, IIIb	Card	15	15	3	675
7	65	M	sq	rulb	Postop	10	2	2	40
8	67	M	sq	rmb	Card	10	10	3	300
9	68	M	sq	IIIb	Postop	10	10	3	300
10	71	M	sq	lulb, IIIb	Card	15	15	3	675
11	62	M	sq	carina	Emphysema	10	10	3	300
12	80	M	sq	bri	Card	20	15	3	900
13	81	M	ad/sq	tra, rulb	Card	15	15	2	450
14	68	M	sq	tra, stump	Postop	15	10	3	450
15	61	M	sq	rmb, rulb	Card	15	15	3	675
16	55	F	sq	L main, IIIb	Emphysema	50	20	3	3000
17	66	M	sq	IIIb	Card	50	6	2	600
18	52	M	sq	rIIb	Emphysema	20	5	3	150
19	59	M	sq	rIIb	Card	25	10	3	750
20	62	M	sq	IIIb	Postop	30	10	3	300
21	57	M	sq	rulb	Postop	20	5	3	150
22	63	F	sq	tra, bri	Postop	30	10	5	1500
23	69	F	sq	tra	Card	60	10	4	2400
24	62	M	sq	rIIb	Emphysema	20	5	4	400
25	76	M	sq	rulb	Postop	20	5	3	300
26	68	M	sq	tra	Postop	40	8	3	960
27	66	M	sq	lulb	Postop	5	5	3	150
28	78	M	sq	rul, lul carina	Postop	30	10	3	900
29	64	M	sq	tra	Postop	50	10	2	1000
30	51	M	sq	rulb	Postop	20	5	2	100
31	69	M	sq	lulb	Card	20	5	3	300
32	70	M	sq	rulb	Postop	15	10	2	300

lobectomy; XRT, external beam radiation therapy; res, resection; rulb, right upper lobe bronchus; lulb, left upper lobe bronchus; tra, trachea; bri,bronchus intermedius; rmb, right main bronchus; rIIb, right lower lobe bronchus; IIIb, left lower lobe bronchus; lmb, left main bronchus; lul, left upper lobe; sq, squamous cell carcinoma; adcy, adenoid-cystic carcinoma; ad, adenocarcinomas; postop, postoperative recurrence; card, inoperable due to cardiac insufficiency.

another bronchoscopic examination was performed for debridement and re-evaluation. If indicated, another illumination with 100 J/cm (or 50 J/cm^2) was applied. Therapeutic bronchoscopies were performed two or three times, depending on the tissue reaction.

Brachytherapy

Biopsy specimens were taken from the treated sites during bronchoscopy 5–6 weeks after PDT and high dose brachytherapy with iridium-192 was administered. A catheter (4 mm outside diameter) was introduced using the Seldinger technique with flexible bronchoscopy under local anaesthesia. If a carina was involved, two catheters were placed. A dose of 4 Gy, calculated at a distance of 10 mm from the source axis, was applied. Brachytherapy was repeated five times at weekly intervals until a total dose of 20 Gy had been administered.

Follow up

Follow up bronchoscopic examinations were performed every 3 months. Biopsy specimens of the treatment areas were examined by the same pathologist who examined the initial specimens. If tumour recurrence was noted, patients received additional local treatment.

Outcomes

Outcomes were the presence or absence of tumour as indicated by bronchoscopic inspection and histological analysis.

RESULTS

Between April 1995 and November 1998, 32 patients with technically inoperable (n = 15) or recurrent (n = 17) bronchogenic carcinomas were treated sequentially with PDT and brachytherapy (table 1). All tumours were functionally or technically unresectable. The tumours were limited to the bronchial wall and other metastatic disease was not evident.

Complete response was achieved in 24 patients (75%) after initial PDT, as indicated by negative histological results in multiple biopsy specimens from the original tumour site (table 1). In one patient squamous cell carcinoma cells were still found after brachytherapy; in all other patients the biopsy specimens became negative after brachytherapy. Thus, the combined treatment had a complete histological response rate of 97% (31/32). The remaining patient received additional brachytherapy with 8 Gy. Although the tumour is still present, he is alive and well 37 months after initial treatment.

Cancer recurred in six patients (19%) at 6, 9, 11, 12, 24, and 26 months after PDT (table 2). Five neoplasms were found at the original site. In one patient recurrence developed 2 cm distal to the original tumour. Using external beam radiation, brachytherapy, Nd:YAG laser coagulation, or additional PDT, tumours were eradicated in three of these six patients. In one patient pulmonary parenchymal metastasis was found 11 months after PDT, and in another patient lymph node metastasis was detected after 3 months. Both patients were successfully treated with external beam radiation and no tumour cells were found in the bronchus. At present, all 32

Table 2 Initial and current response of 32 patients with limited bronchogenic carcinoma treated with sequential photodynamic therapy (PDT) and high dose brachytherapy

No	Response to brachytherapy		Relapse (months since treatment)	Intervention after relapse	Current endoscopic status	Current histological status of airway	Months since first PDT
	Endoscopic	Histological					
1	Complete	Negative			No tumour	Negative	46
2	Complete	Negative			No tumour	Negative	43
3	Complete	Negative	9	Brachytherapy	No tumour	Positive	40
4	Complete	Negative			No tumour	Negative	39
5	Complete	Negative			No tumour	Negative	37
6	Complete	Positive		Brachytherapy, YAG laser	Visible tumour	Positive	37
7	Complete	Negative			No tumour	Negative	35
8	Complete	Negative			No tumour	Negative	34
9	Complete	Negative			No tumour	Negative	33
10	Complete	Negative			No tumour	Negative	31
11	Complete	Negative	11	XRT	No tumour	Negative	29
12	Complete	Negative			No tumour	Negative	27
13	Complete	Negative			No tumour	Negative	27
14	Complete	Negative	12	PDT	Visible tumour	Positive	25
15	Complete	Negative	24	YAG laser	Suspicious	Positive	24
16	Partial	Negative	26	PDT	No tumour	Negative	23
17	Partial	Negative			No tumour	Negative	23
18	Complete	Negative			No tumour	Negative	22
19	Complete	Negative		XRT	Pulm metastasis	Negative	22
20	Complete	Negative			No tumour	Negative	22
21	Complete	Negative			No tumour	Negative	20
22	Complete	Negative			No tumour	Negative	20
23	Complete	Negative			No tumour	Negative	19
24	Complete	Negative			No tumour	Negative	19
25	Complete	Negative			No tumour	Negative	16
26	Complete	Negative		XRT	Lymph node metastasis	Negative	16
27	Complete	Negative			No tumour	Negative	13
28	Complete	Negative			No tumour	Negative	10
29	Complete	Negative			No tumour	Negative	7
30	Complete	Negative			No tumour	Negative	6
31	Complete	Negative			No tumour	Negative	3
32	Complete	Negative			No tumour	Negative	3

XRT, external beam radiation; PDT, photodynamic therapy.

patients are alive and well after a mean follow up period of 24 months (range 3–46).

There were no severe complications such as haemoptysis, fistulas, or post-obstructive pneumonia. As expected, temporary mucosal swelling occurred in most cases. Necrotic tissue and fibrin commonly accumulated during the first week after PDT but were always easily cleared by bronchoscopy. Moderate scarring of the bronchus 2–3 months after treatment was usually observed in the radiated bronchial segment. None of the obstructions was severe enough to require intervention.

The patients were well informed about light protection and none experienced sunburn.

DISCUSSION

Photodynamic therapy with Photofrin is safe and effective,[2–4 6–9] but high efficacy has only been found when the tumour is smaller than 10 mm in diameter. Above this critical size the response rate falls from 98% to 43%.[4] Other factors determining the outcome are submucosal invasion and peribronchial extension.[10] Underestimating the extent of the tumour and undertreatment have been identified as reasons for treatment failure.[11]

Brachytherapy is also a well established method of palliation and works well in combination with Nd:YAG laser photoresection to control local tumour growth.[5 12] It is also effective in eradicating early cancer.[13]

Cell culture studies and animal studies indicate a possible synergistic effect of combining PDT with ionising radiation.[14 15] Both result in tumour cell apoptosis but probably via different pathways.[16] Other studies combining PDT and external beam radiation do not indicate a higher risk of complications.[17 18]

Theoretically, the order of treatment could be reversed, starting with brachytherapy and applying PDT later. However, ionising radiation affects tissue vascularisation. The impaired perfusion of the tumour might result in a lower uptake of the sensitiser, possibly compromising the effect of PDT.

We treated only patients whose tumours were inoperable, either for technical or functional reasons or because of recurrence after surgery. Also, all of our patients had a substantial tumour burden in the tracheobronchial tree. The prognosis for these patients is poor. The results in our study were surprisingly good, with a response rate of 97%. All patients are alive after a mean of 24 months, and the combined treatment failed to eradicate the tumour in only one patient. Relapse occurred at the treated site in five patients, and most of these tumours were successfully treated locally. Also encouraging is the fact that no serious side effects were observed during this aggressive treatment protocol.

Our main interest in this descriptive study was to acquire initial data regarding the feasibility and efficacy of this regimen. As a result, we did not use a randomised trial design. However, our results are extremely encouraging for these difficult to treat patients and we believe that further controlled trials of this treatment regimen are warranted.

We conclude that, in this carefully selected patient population, aggressive combined treatment with PDT and brachytherapy is safe and efficacious in achieving local tumour control.

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LUNG ALERT

Disease progression in COPD correlates with airway remodelling and inflammatory responses

▲ Hogg JC, Chu F, Utokaparch S, *et al.* The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;**350**:2645–53.

In this study the lung tissue obtained from surgical resection in 159 patients was examined to correlate pathological findings in the small airways with the severity of COPD using the GOLD classification. The percentage of airways containing polymorphonuclear neutrophils, macrophages, CD4 cells, CD8 cells, B cells, and lymphoid follicles increased with disease progression. The volume of B cells and CD8 cells also increased with increasing severity of COPD. The progression of COPD through GOLD stages 0–4 was most strongly associated with thickening of the airway wall and each of its components. This is a reflection of the repair or remodelling process within the lung. Disease progression was also associated with the degree of inflammatory response and occurrence of lymphoid follicles in the airway wall, and the presence of mucous exudates within the airway lumen.

This study shows that the adaptive immune response may play a key role in the persistent inflammation associated with COPD. This, and other factors such as infection, are likely to lead to changes in the airway wall that contribute to the small airways obstruction in COPD.

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