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Effects of Intensive Chemotherapy on Respiratory Function in Patients with Small Cell Carcinoma of the Lung*

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Abstract—*The lung function of 30 consecutive patients with small cell carcinoma of the lung was evaluated before and* 3 months *after initiation of intensive chemotherapy. Radiological evaluation of the therapeutic effect on the lung tumor was possible in 19 patients after* 3 months. *Six patients achieved complete normalization of the chest X-ray,* 10 *patients achieved more than* 50% *reduction of the tumor and no or minimal changes in the radiological image were observed in* 3 *patients. Before treatment a mixed pattern of obstructive and restrictive lung disease was observed in all patients. In the* 16 *patients who achieved partial or complete remission of the tumor normalization of the total lung capacity* ($P < 0.02$), *vital capacity* ($P < 0.02$), *FEV_1* ($P < 0.02$) *and PEF* ($P < 0.05$) *was observed independently of the degree of shrinkage of the tumor on chest roentgenogram, thus suggesting that the tumor was the major cause of the lung function impairment in these patients. The diffusion capacity and parameters reflecting the function of the small airways (RV/TLC% and MEF_{50}) remained abnormal after treatment. Improvement of the lung function did not predict the individual duration of survival. However, the study proved that roentgenological normalization is paralleled by physiological normalization with the current treatment of this disease.*

INTRODUCTION

BY APPLYING modern combination chemotherapy it is possible to obtain regression of tumor in 80% of patients with small cell carcinoma of the lung. These results have been reported with a variety of treatment regimens. In 40% of patients complete disappearance of the tumor is observed at the chest roentgenogram after combination chemotherapy [1]. Most small cell carcinomas are localized centrally in the bronchial tree and a pattern of mixed restrictive and obstructive lung function reduction is characteristic [2]. This is due partly to the obstructive effect of the tumor and partly to coexisting chronic pulmonary disease which is often present in these patients.

The present trial was initiated in order to evaluate the presumed improvement of lung function in patients with small cell carcinoma of the lung during combination chemotherapy. Variation of static and dynamic lung volumes and diffusion capacity were studied before and 3 months after initiation of combination chemotherapy including cyclophosphamide, vincristine, CCNU, methotrexate, adriamycin and VP-16. The degree of tumor reduction was compared to the improvement in pulmonary function.

MATERIALS

Patients

Thirty consecutive patients with histologically proven small cell carcinoma of the lungs referred to the department between December 1979 and July 1981 were included. Twenty-four were men (median age 64, range 42–76) and 6 were women (median age 62, range 52–68). To be included in this study the patient had to have a measurable lesion on the chest X-ray. Patients who were unable to cooperate for adequate lung function tests were also excluded. A patient was evaluable if

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re-examination was possible 3 months after initiation of chemotherapy. That excluded 9 patients who died early in the course, and 2 who did not want to have the lung function studies performed. Age, sex and history of lung diseases together with the smoking habits of the 19 evaluable patients are summarized in Table 1. The performance status (Karnofsky) at the time of initiation of treatment is shown in Table 2 together with the results of staging and bronchoscopy, localization of the tumor, response to treatment and patient survival.

Treatment

All the patients in this study were randomized to receive 1 of 5 different combination chemotherapeutic regimens consisting of cyclophosphamide, vincristine, CCNU, methotrexate, adriamycin and VP-16 (Table 3). No chest irradiation was given.

Before initiation of chemotherapy the extent of disease was evaluated by the use of a defined set of staging procedures including chest X-ray, bilateral bone marrow examination from the iliac crest and peritoneoscopy with liver biopsy.

Table 1. Pretreatment data of 19 evaluable patients

Patient No.	Age	Sex	Prior pulmonary disease	No. of cigarettes per day
1	65	M*	asthma	40
2	54	F	N	30
3	65	M	N	15
4	61	M	N	15
5	57	F	bronchitis	20
6	47	F	N	15
7	68	F	bronchitis	30
8	54	M	N	20
9	39	M	bronchitis	30
10	61	M	N	20
11	58	M	tuberculosis	20
12	76	M	N	30
13	60	M	bronchitis	15
14	58	M	N	10
15	56	F	N	20
16	62	M	N	40
17	58	M	bronchitis	20
18	72	M	N	20
19	55	M	bronchitis	10

*M: Male; F: female; N: no prior disease.

Table 2. Results of staging procedures in 19 evaluable patients

Patient No.	Performance status	Bone	Liver	Affected lung	Bronchoscopy	Response	Survival (weeks)
1	2	-	+	L*	CS	CR	21
2	1	-	-	R	CS	CR	84+
3	2	-	-	R	CS	CR	45
4	2	-	-	R	CS	CR	42
5	2	-	-	R	CS	CR	58
6	1	-	-	R	CS	CR	73
7	2	+	-	R		PR	26
8	2	-	-	R	CS	PR	54
9	1	-	-	R	CS	PR	39
10	2	-	-	R	CS	PR	56
11	3	-	-	L	L	PR	56
12	1	-	-	R	CS	PR	52
13	3	-	-	L	O	PR	45
14	3	-	-	R	CS	PR	58
15	1	-	-	L	CS	PR	79
16	1	-	-	L	CS	PR	30
17	3	-	-	R	O	NC	32
18	1	-	-	L	CS	NC	38
19	3	-	-	R	CS	NC	81+

*L: left; R: right; CS: central stenosis; N: no visible tumor; CR: complete response; PR: partial response.

Table 3. The chemotherapeutic treatment regimens for the 5 regimens

	Time (weeks) →																							
Regime 1	L*				L			L			L													
	C		M		C		M	C		M	C													
	V	V	V	V	V			V			V													
Regime 2	L						L																	
	C		M		A		C		M		A													
	V	V	V	V	F		V				E													
Regime 3	L				L			L			L													
	C		E		C		E	C		E	C													
	V	V	V	V	V			V			V													
Regime 4	L				L			L			L													
	C				C			C			C													
	VE	V	V	V	VE			VE			VE													
Regime 5	L							L			L			E		C		M					L
	C		M		C		E			M	C													
	V	V	V	V	V			V			V					V							V
					A			A								A							A
	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	-

*Agents and doses: L = CCNU, 70 mg/m² p.o.; C = cyclophosphamide, 700–1000 mg/m² i.v.; V = vincristine, 1.3 mg/m² i.v. (max: 2 mg); M = methotrexate, 20 mg/m² p.o. (days 15 and 18); A = adriamycin, 30–35 mg/m² i.v.; E = VP-16-213, 100 mg/m² p.o. (days 1–4).

Response evaluation

Based on changes in the chest roentgenogram, the antineoplastic effect of the treatment was evaluated according to the recommendations given by the World Health Organization [3]; complete remission (CR): total disappearance of all visible tumor tissue; partial remission (PR): decrease in the measurable lesion of more than 50%; no response (NR): less than 50% decrease of the measurable lesion; progressive disease (PD): more than 25% increase of the measurable lesion.

Pulmonary function

Lung function was examined by means of a Hewlett-Packard computing pulmonary system prior to treatment and 3 months after initiation of treatment. At each examination the following variables were calculated from the best of 3 flow volume curves: the peak flow (PF), forced expiratory volume in one second (FEV_1) and the mid-expiratory flow rate (MEF_{50}). Total lung capacity (TLC), vital capacity (VC) and residual volume (RV) were measured using a helium dilution technique. The diffusion capacity (DL_{CO}) was determined using the single-breath method described by Mitchell and Renzetti [4]. The DL_{CO} values were corrected according to hemoglobin concentration [5]. The determination of DL_{CO} was repeated until the differences between 2 readings did not exceed 2 ml/min/mm Hg.

Statistical analysis of the variance of the lung function variables was performed according to the method of Rodbard [6]. Student's *t* test for paired samples was used to analyse the effect of the chemotherapy on the different lung function variables.

RESULTS

Of the 19 evaluable patients 6 obtained complete roentgenological remission, 10 had a partial remission and 3 were non-responders.

Table 4 shows the results of the lung function tests before and 3 months after initiation of treatment. Before treatment the TLC, VC and DL_{CO} values of the complete responders and partial responders were almost equally reduced, as were the PEF, FEV_1 and the MEF_{50} values of the two groups, indicating restrictive as well as obstructive pulmonary dysfunction. Three months after initiation of treatment the TLC of both complete and partial responders had significantly improved, whereas minor changes or further deterioration was observed in non-responding patients. The VC values improved significantly, but remained subnormal. A significant increase in RV was seen in both groups after treatment and this was paralleled by a similar increase in TLC. Thus the RV/TLC ratio remained significantly elevated after treatment. There was no difference between the DL_{CO} values in the two groups before and after treatment. Before treatment there was a slight though not significant difference between the complete and the partial responders with regard to PEF and

Table 4. Lung function before and after treatment

Function	Change in function	Complete responders ($n = 6$) Before treatment	3 months after initiation of treatment	Effect of treatment	Partial responders ($n = 10$) Before treatment	3 months after initiation of treatment	Effect of treatment
PEF	%predicted	48***	73**	$P < 0.02$	37***	57***	$P < 0.05$
	(S.D.)	(18)	(20)		(19)	(12)	
FEV_1	%predicted	61**	85	$P < 0.01$	49***	62***	$P < 0.02$
	(S.D.)	(15)	(20)		(14)	(18)	
MEF_{50}	%predicted	52*	65	N.S.	46***	50**	N.S.
	(S.D.)	(29)	(33)		(19)	(23)	
TLC	%predicted	74*	91	$P < 0.02$	78**	106	$P < 0.01$
	(S.D.)	(20)	(15)		(24)	(12)	
VC	%predicted	66***	71***	$P < 0.02$	65***	81**	$P < 0.01$
	(S.D.)	(15)	(12)		(6)	(11)	
RV	%predicted	108	129**	N.S.	128	154*	$P < 0.01$
	(S.D.)	(71)	(29)		(37)	(41)	
RV/TLC%	%predicted	131*	142**	N.S.	138***	137***	N.S.
	(S.D.)	(26)	(26)		(24)	(17)	
DL_{CO}	%predicted	63**	71*	N.S.	75*	74*	N.S.
	(S.D.)	(14)	(17)		(19)	(26)	

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.01$ for the difference between the observed and the predicted values.

FEV_1, but the increase of the variables after the treatment was almost identical. The PEF of both groups remained subnormal after treatment and so did the FEV_1 of the partial responders. The FEV_1 of the complete responders normalized. The decreased MEF_{50} values remained subnormal during treatment in both groups.

The 'within' variance of the different variables was less than 4%.

The mean survival of the complete responders was 53.8 weeks (S.D. = 9.0). The mean survival of the partial responders was 46.9 weeks (S.D. = 17.2). There was no correlation between the change of the various lung function variables and the survival of the patients.

DISCUSSION

In the treatment of small cell carcinoma of the bronchus 2 different modalities are employed: irradiation and chemotherapy. In both cases the response of treatment is seen as a shrinkage of the tumor on the chest roentgenogram. In 1979 Fazio *et al.* [7] evaluated the effect of irradiation on the lung function of 45 patients with lung cancer of whom 22 had small cell carcinoma. He found no significant improvement in the conventional lung function values after treatment, but there was a marked and significant improvement of ventilation and of perfusion in the affected lungs after treatment evaluated by isotope $^{81m}Kr/^{99m}Tc$-scans. It was not mentioned whether this improvement was related to the histological diagnosis of the patients' tumor. Because small cell carcinoma is the most radiosensitive type of lung cancer, with a response rate of 75–80% [1], while the response rate among the other cell types of lung cancer is only 30–50% [8], an improvement in conventional lung function variables could be concealed by the lack of response in patients who had other cell types.

As for the combination chemotherapy, Bake *et al.* [9] found some improvement of perfusion as

well as ventilation evaluated by ^{133}Xe-scans and conventional lung function variables in 3 of 11 patients with small cell carcinoma who obtained complete remission during combination chemotherapy. The small number of patients, however, precluded definitive conclusions.

The pretreatment lung function status of the 19 evaluable patients of this study shows a mixed pattern of restrictive and obstructive lung disease. Three months after initiation of treatment there was a normalization of TLC values in patients obtaining both complete or partial remissions. This increase was paralleled by an increase in VC and RV values so that the RV/TLC ratio remained persistently elevated throughout the study. These results indicate that tumor infiltration is largely responsible for the pretreatment restrictive impairment of lung function. On the other hand, diffusion capacity remained subnormal during treatment. As it is known that cyclophosphamide, methotrexate and CCNU can induce pulmonary toxicity [10], it is possible that absence of any increase in diffusion capacity can be attributed to drug-induced pulmonary toxicity combined with the effect of life-long smoking, which also impairs carbon monoxide diffusion capacity [11].

The large airways are the major contributors to airways resistance. Involvement of the larger airways of the lungs is a characteristic feature of small cell carcinoma of the lung [12]. It is not surprising, therefore, that there is an increase of FEV_1 and PEF after treatment in complete and partial responders of 45 and 51% respectively. These findings are in agreement with the findings of Østerlind *et al.* [13], who reported a median improvement in peak flow of 58% in patients responding to combination chemotherapy and chest irradiation. They did not find any statistical difference in PEF between patients with complete or partial tumor remission judged from the chest roentgenogram. Of course, it is possible to attribute some of the increase in FEV_1 and PEF in this study to the improved physical performance of the patients during treatment, but a 'within' coefficient of variation of less than 4% among the patients makes this explanation less likely.

In accordance with the smoking habits of the patients, the variables monitoring the function of the small airways (RV/TLC% and MEF_{50}) remained abnormal and unchanged throughout the investigation. The lung function of these heavy smokers is very likely to have been impaired before the small cell carcinoma arose. It could hardly be expected, therefore, that improvement in all different lung function variables resulting from chemotherapy and the duration of survival in these patients would be well correlated. There was a correlation between improved lung function and the shrinkage of the tumor during treatment judged from the roentgenogram. However, the correlation was not simply reflected by the degree of improvement in lung function variables.

As different chemotherapeutic regimens become increasingly effective, the quality of life in connection with this kind of therapy becomes an evermore significant problem. It is therefore important that the lung function in these patients improves significantly after treatment.

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