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Small Cell Carcinoma of the Lung: a Combined Modality Treatment*†

P. VAN HOUTTE,‡ G. TANCINI,§ R. DE JAGER,¶ J. LUSTMAN-MARÉCHAL,‡ F. MILANI,§ G. BONADONNA§ and Y. KENIS¶

‡*Service de Radiothérapie, Institut Jules Bordet* 1, *rue Héger. Bordet*, 1000 *Bruxelles, Belgium*
§*Istituto Nazionale per lo Studio e la Cura dei Tumori*, 1, *Via Venezian*, 20133 *Milano, Italy*
¶*Service de Médecine et Laboratoire d'Investigation Clinique, Institut Jules Bordet*, 1, *rue Héger-Bordet*, 1000 *Bruxelles, Belgium*

Abstract—*Between* 1973 *and* 1977, 84 *patients with small cell anaplastic bronchogenic carcinoma underwent staging procedure including brain, liver and bone scan, bone marrow biopsy and peritoneoscopy.*

Fifty-eight patients with limited disease were treated with concomitant radiation therapy to the primary site and the combination of vincristine and cyclophosphamide (VCR–CPA). Two maintenance chemotherapy schedules were used: methyl CCNU, cyclophosphamide, vincristine and bleomycin (COMB) or VCR–CPA. The median survival was 11 months. *No statistical difference could be observed in survival and relapse rates between these two treatments.*

Twenty-six patients with extensive disease were treated with methyl CCNU, cyclophosphamide, vincristine with or without bleomycin. Median survival was 7 months *and the use of bleomycin did not improve the response rate.*

INTRODUCTION

UNTREATED small cell anaplastic carcinoma of the lung is a rapidly fatal disease: median survival from the time of diagnosis is 3 months for patients with limited disease receiving a placebo, to 6 months after surgical resection in a selected group of patients [1, 2]. The use of combination chemotherapy with or without radiation therapy has significantly improved the prognosis [3, 4].

This study was initially planned as an E.O.R.T.C. Lung Cancer Group trial, but it rapidly appeared that it was run almost exclusively in two institutions (more than 90% of the cases were treated in Brussels and Milan). The induction treatment was identical in both institutions but maintenance therapy varied. Despite this, there was no difference between the two populations considering response rate, toxicity, relapse and survival. As an example Fig. 1 shows the actuarial survival curves of the patients of Milan and Brussels. This allowed the pooling of data (Fig. 1).

The COMB combination which consisted of semustine (MeCCNU), cyclophosphamide (CPA), vincristine (VCR) and bleomycin (BLM) was chosen for the following reasons: this combination was devised by combining the two two-drug sequential associations of MeCCNU-cyclophosphamide and vincristine–bleomycin [5]. MeCCNU and cyclophosphamide were synergistic in the experimental Lewis lung carcinoma [6] and showed interesting activity in a pilot study. Vincristine produces a marked increase in mitotic index 4–12 hr after its administration, achieving temporary synchronization of the cells in M and G_2 phases [7], when cells are more sensitive to the cytotoxic effect of bleomycin [8, 9].

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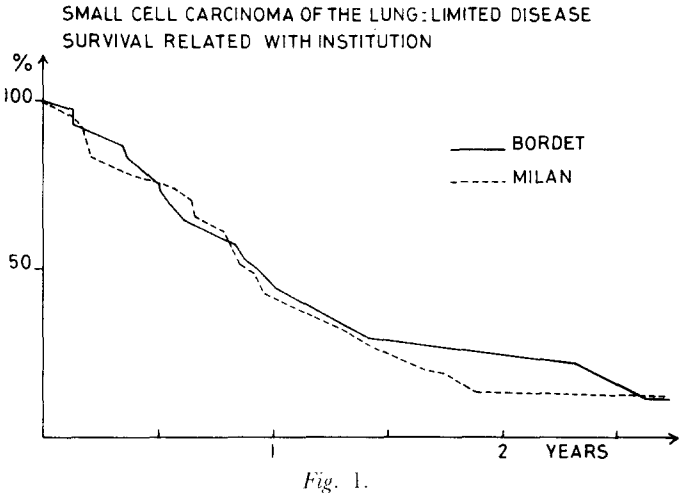

Fig. 1.

MATERIALS AND METHODS

Between April 1973 and December 1977, 84 patients with biopsy proven small cell anaplastic carcinoma of the lung were admitted to this clinical trial if they fulfilled the following criteria: no prior treatment with surgery, radiation therapy or chemotherapy; no history of other malignant disease excluding skin cancer; a performance status (Karnofsky) >40%; age below 72 yr.

Diagnosis was obtained through biopsy taken at fiberbronchoscopy, mediastinoscopy or thoracotomy. Staging included bone, liver and cerebral scintigraphies, peritoneoscopy with liver biopsy and bone marrow biopsy.

The stage of the disease at onset of therapy was classified as limited disease (disease confined to one hemithorax, mediastinum and homolateral supraclavicular nodes) and extensive disease [1]. Patients presenting with brain metastases at the time of diagnosis were excluded. Evaluation of response: a complete response corresponds to a complete disappearance of all tumor lesions. Partial response corresponds to a decrease of more than 50% of the sum of the products of the two largest perpendicular diameters of all measurable lesions without appearance of other tumors.

The actuarial method of Kaplan–Meyer was used. The statistical significance between curves was determined by the Mantel–Haenszel test [10].

Therapeutic regimens

(*a*) *Limited disease* (*Fig.* 2). Induction treatment consisted of 2 courses of chemotherapy at a 3-week-interval: vincristine 1.5 mg/m^2 i.v. days 1 and 8 and cyclophosphamide 1.2 g/m^2 i.v. day 1 (VCR–CPA) and radiation therapy: 4500 rad through megavoltage equipment in $4\frac{1}{2}$ weeks to the primary tumor, mediastinum and involved supraclavicular nodes.

Maintenance chemotherapy followed 2 weeks after the completion of radiation therapy. Patients received either COMB (MeCCNU–CPA–VCR–BLM) or VCR–CPA

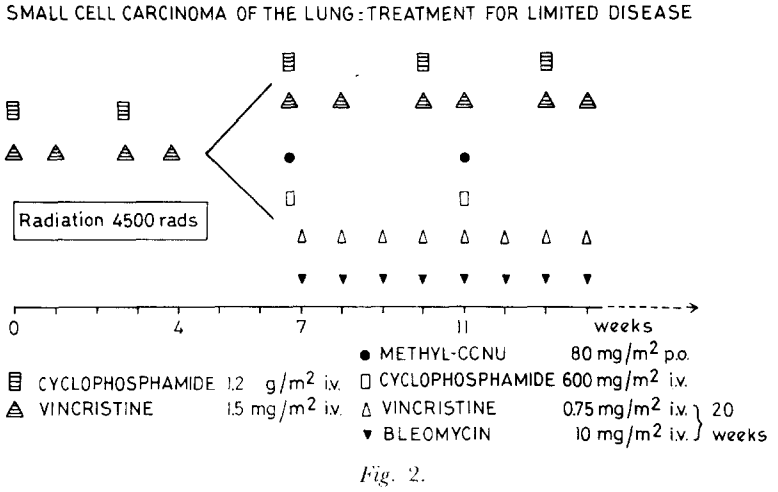

Fig. 2.

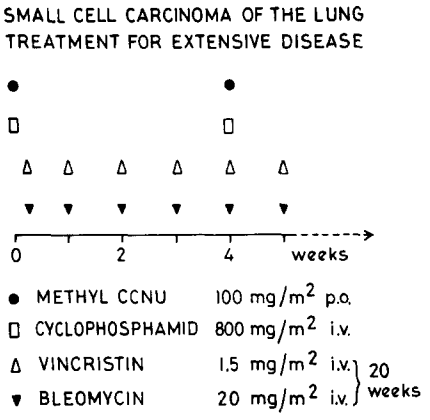

Fig. 3.

for 24 months or until time of relapse. The COMB regimen was given every 4 weeks as follows: CPA 600 mg/m^2 i.v., and MeCCNU 80 mg/m^2 orally on day 1, VCR 0.75 mg/m^2 i.v. and BLM 10 mg/m^2, 6 hr after VCR, on day 2. VCR and BLM were repeated every week up to a total of 20 doses. The combination VCR–CPA was given every 3 weeks as follows: CPA 1.2 g/m^2 i.v. on day 1 and VCR 1.5 mg/m^2 i.v. on days 1 and 8.

(*b*) *Extensive disease* (*Fig.* 3). Combination chemotherapy with COMB or COM (the same combination without BLM) was administered at monthly intervals. The dosage of the drug was higher than in the limited disease group: MeCCNU 100 mg/m^2, CPA 800 mg/m^2, VCR 1.5 mg/m^2 and BLM 20 mg/m^2.

(*c*) *Progression of disease.* In both limited and extensive disease, treatment after relapse consisted of adriamycin (ADM) 45 mg/m^2 i.v. and methotrexate (MTX) 40 mg/m^2 i.v. every 3 weeks. After failure of this regimen, hexamethylmelamine (HMM) 150 mg/m^2 was administered orally, once a day.

RESULTS

Fifty-eight patients with limited disease and 26 with extensive disease were entered into the study. Median age was similar (55 and 56 yr) in the two groups. The sites of metastases are shown in Table 1. Actuarial median survival was 344 days in limited disease and 210 days in extensive disease respectively. In the latter group all patients were dead at 18 months from starting treatment. Seven patients with limited disease survived more than 2 yr (Fig. 4). This difference in survival is statistically significant ($P<0.01$).

In limited disease, 10 patients did not receive maintenance chemotherapy because of early death (5 cases), refusal of further treatment (3 cases) or excessive toxicity (2 cases). Nineteen patients received COMB and 29 VCR-CPA with a median survival of 468 and 333 days, respectively. There was no statistical difference between these two survival curves ($P=0.20$) (Fig. 5). In addition, the duration of remission was similar.

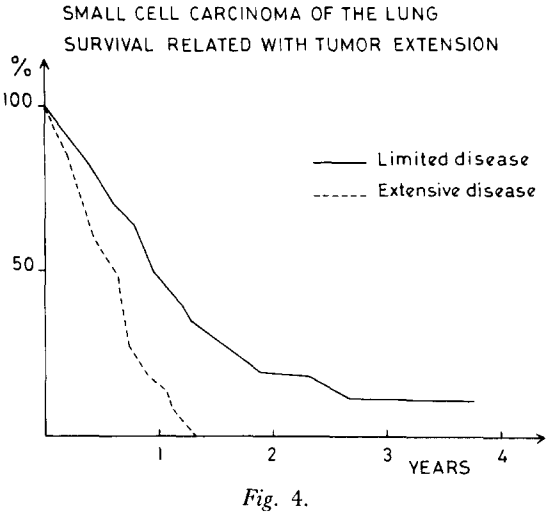

Fig. 4.

Table 1. *Patients' characteristics*

Involved site	Limited disease	Extensive disease
Total No. of patients	58	26
Supraclavicular nodes		
ipsilateral	6	
contralateral		8
Axillary nodes		2
Liver		6
Bone		2
Skin		1
Parotid		1
Bone marrow		5
Pleura		2
Contralateral lung		3

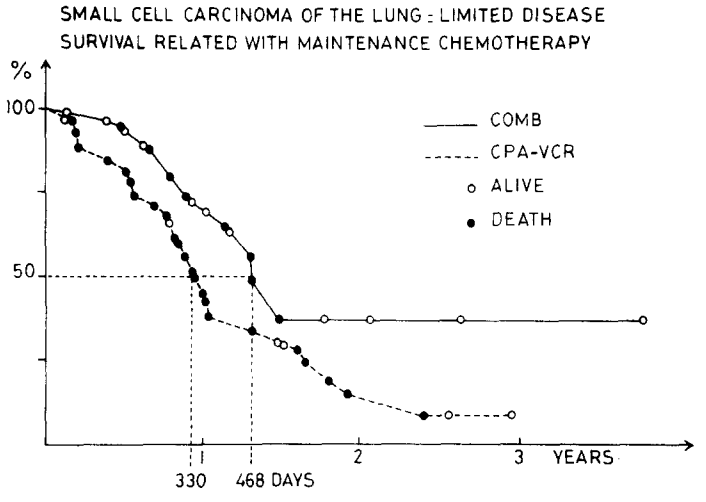

Fig. 5.

Table 2. *Response analysis to treatment*

	Response CR	PR	No response	Not evaluable	Total
Limited disease					
Initial treatment	26	24	7	1	58
ADM–MTX for relapse	2		2	3	7
Extensive disease					
COMB		10	6	1	17
COM		7	2		9
ADM–MTX		3	7	3	13
Hexamethylmelamine			4		4

CR = complete response, PR = partial response.

Table 3. *Small cell carcinoma of the lung with limited disease, site of disease progression*

	COMB	CPA–VCR	None	
Local	3	3	3	
+supraclaviculaire node	1			
+brain	1	1		
Thoracotomy scar		1		
Contralateral lung	1			
Cervical nodes	1	2		
Liver			1	1*
Bone		2	2	
Brain	1	7	3	
Skin		1		
Bone marrow		2		
Stomach	1			
Toxicity	2	2		
Unknown		3		
Total	11/19	24/29	10/10	

*1 patient had bone and brain metastases.

Table 4. Toxicity in limited disease

	Induction treatment	Maintenance chemotherapy COMB	CPA–VCR
Number of patients	58	19	29
Hematological toxicity			
leukocytes $<3000/mm^3$	20	2	5
platelets $<100{,}000/mm^3$			
Peripheral neuropathy	7	7	17
Pulmonary fibrosis		4	
Skin toxicity	1	3	
Severe nausea/vomiting		1	3

Table 5. Toxicity in extensive disease

	COMB	COM
Hematological toxicity		
leukocytes $<3000/mm^3$	8	5
platelets $<100{,}000/mm^3$	2	1
Peripheral neuropathy	12	4
Severe nausea/vomiting	1	
Skin toxicity	4	

Initial treatment with the combination of radiotherapy and chemotherapy resulted in 50/58 (86%) objective responses: 26 (45%) complete responses and 24 (41%) partial responses (Table 2). In addition, 3 patients showed stable disease lasting over 1 yr. Intrathoracic disease and cerebral metastases were the two most common sites of failure (Table 3).

In extensive disease, 17/26 (65%) partial responses were obtained: 10/17 with COMB and 7/9 with COM. No complete response could be documented. Secondary treatment with ADM–MTX resulted in 5/14 objective responses. In this group, 2 patients with intrathoracic relapse after primary treatment for limited disease achieved a complete response and are alive more than 2 yr later (Table 2). Hexamethylmelamine was given to 4 patients after failure to ADM–MTX and no response was observed.

Dose limiting toxicity was hematological and possibly contributed to death in three cases (major pulmonary infection in severely leukopenic patients: leukocyte count below $1000/mm^3$). In addition, one patient died of BLM induced pulmonary fibrosis. VCR neurotoxicity necessitating discontinuation of the drug occurred in 31/58 patients (Tables 4 and 5).

DISCUSSION

Small cell carcinoma of the lung is a very malignant tumor because of rapid proliferation and early metastatic spread [11]. This explains the failure of local regional treatments such as surgery and radiation therapy and the necessity of systemic treatment [12].

For limited disease, the actuarial survival time at 2 yr reaches a plateau at 37% for COMB and 12% for VCR–CPA, although no statistical difference in survival time and duration of remission could be observed with the two different maintenance regimens. The median survival of 67 weeks with radiotherapy and COMB and 49 weeks for radiotherapy plus VCR–CPA compares favorably with the good results reported in the literature with other treatments [3, 4, 13]. Two common causes of failure were local relapse and brain metastases. Nitrosourea does not appear effective in preventing brain metastases [2/11 for the COMB and 8/24 for the VCR–CPA ($P=0.27$)]. This does not support the conclusion of Bunn [13] that the administration of nitrosourea affords a good protection against brain metastases compared to other types of chemotherapy (4.9% brain metastases with nitrosourea vs 25.8% without nitrosourea). This conclusion was obtained by the pooling of data from different non-randomized trials and must be therefore considered with some reservations.

Prophylactic brain irradiation does not change significantly the survival over that expected with chemotherapy alone although the incidence of brain metastases is reduced [14–16]. Many of these patients never achieve a complete response and relapse systematically within a few months after onset of treatment. Prophylactic brain irradiation should improve survival only if a high percentage of long

standing complete responses is obtained by new chemotherapy regimens.

Bleomycin was incorporated in COMB for cell kinetic reasons but did not contribute to improve therapeutic activity (COMB 10/17 partial responses and COM 7/9). These results are in accordance with those of the literature [17]. Furthermore, there is no evidence of bleomycin activity as a single agent in lung cancer [18] and it contributed to one toxic death. In our opinion, it should be deleted in subsequent studies.

Maximum benefit from initial therapy both in limited and extensive disease was obtained within the first 3 months [19]. Control fiberbronchoscopy at that time is desirable to define the quality of response as precisely as possible since radiation therapy may induce changes on conventional X-ray examination that may render difficult the evaluation of tumor regression.

Our results confirm the validity of maintaining the distinction between limited and extensive disease since this remains the single most important prognostic factor in small cell carcinoma. All patients alive over 2 yr show no evidence of disease. They had limited disease and achieved complete remission under treatment. This raises some hope of permanent control of this disease with combination therapy. COMB is one of the many effective multiple drug combinations in small cell carcinoma. Better results could be anticipated with dose modification or replacing bleomycin by a more active drug.

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