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Etoposide, Cisplatin and Doxorubicin in Patients with Small Cell Lung Cancer: Tumor Response and Long Term Survival

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Abstract—*One hundred and fourteen patients with small cell lung cancer received a combination of etoposide* 80 mg/m^2 IV days 1,2,3,15,16,17, *cisplatin* 20 mg/m^2 IV days 1,2,3 *and doxorubicin* 40 mg/m^2 IV day 1, *repeated every* 4 *weeks. The observation time from the initiation of treatment is longer than* 4 years *for all patients. An* 85% *response rate* (38% *complete responses*) *was obtained after* 1–4 cycles *in* 105 *evaluable patients* (96 *without prior antitumour treatments*). *The response rate was not influenced by initial performance status and minimally by disease extension, whereas the same prognostic factors correlated significantly with complete responses. For limited disease and WHO performance* 0 *all responses were complete. For extensive disease and performance* 3 *no complete response was obtained. Various chemotherapy regimens with or without radiotherapy were used during the maintenance phase. Forty five per cent of first relapses were in the lung or mediastinum and* 18% *in the nervous system* (20% *without and* 7% *with prophylactic cranial irradiation*). *The median survival was* 13.4 months *for limited and* 8.5 months *for extensive disease, and correlated with performance and response. Only* 2 *patients survived free of disease after* 4.8 *and* 5.5 years. *We conclude that the induction treatment as used here produces a high rate of partial and complete responses but a low rate of long survivors.*

INTRODUCTION

SMALL cell lung cancer (SCLC) is highly responsive to multiple drug chemotherapy. However, the influence of treatment on survival is still disappointing with 15% or less patients alive 2 years or more after the initial tumor regression. In a recent review concerning the role of chemotherapy in the treatment of SCLC, a panel of investigators of the International Association for the Study of Lung Cancer stressed the significance of prognostic factors such as performance status, disease extension and quality of tumor response in the probability of long term survival [1]. It is a general observation that only early complete responders have a chance of surviving 2 years or more. In order to achieve a high rate of early complete responses, the most active agents should be used simultaneously for the initial treatment of SCLC, particularly in patients with limited disease and good performance status.

Response rates in excess of 40% have been reported with single drug etoposide in SCLC either by i.v. or oral routes in non-pretreated and pretreated patients [2–8]. Tumor responses have also been observed with single drug cisplatin in heavily pretreated patients [9–12]. A synergistic or more than additive activity has been observed in animal tumor models [13–15] with a combination of these two agents. Doxorubicin is another active drug in SCLC [16]. In 1979–80 the Swiss Group for Clinical Cancer Research (SAKK) conducted a pilot study of a combination of etoposide, cisplatin and doxorubicin in patients with SCLC with two objectives: to define the response rate and survival as related to prognostic factors and to provide an active non-cross resistant combination to be alternated in a further study with another drug combination. Preliminary results of this study have

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been reported earlier [17,18]. In this final report the observation time is in excess of 4 years for all treated patients.

MATERIAL AND METHODS

One hundred and fourteen patients with histological or cytological diagnosis of SCLC [19] were registered between January 1979 and July 1980. All had one or more measurable and progressive tumor manifestations. Eligibility criteria included a WHO performance status of 0–3, no chemotherapy or radiation treatment in the last 3 weeks, no prior exposure to etoposide, cisplatin and doxorubicin, normal serum creatinin, bilirubin, alkaline phosphatase, leucocyte and platelet counts.

Pretreatment staging included physical examination, diagnostic radiology, isotopic imaging and ultrasonography. Bone marrow aspiration and bone marrow and liver biopsies were optional. Chemotherapy consisted of etoposide, 80 mg/m^2 by slow direct i.v. injection on days 1, 2, 3 and 15, 16, 17; cisplatin 20 mg/m^2 in 1000 ml isotonic NaCl in water on days 1, 2, 3 and doxorubicin 40 mg/m^2 i.v. push on day 1 (AVP). The treatment cycles were repeated every 4 or more weeks, depending on the intensity and duration of toxicity. A dose modification schedule was provided with a 50% reduction of all three drugs for leucocyte counts 2000–3500/mm^3 and platelet count 70,000–120,000/mm^3, a temporary discontinuation of treatment for leucocyte 0–1999/mm^3 and platelet counts 0–69,999/mm^3 and temporary discontinuation of cisplatin for serum creatinine 130 μmoles/l or more, and of doxorubicin for abnormal values of serum bilirubin and/or alkaline phosphatase. After a maximum of four cycles all patients were evaluated for tolerance and tumor response. For further treatment, participating institutions selected independently one of the following attitudes: no maintenance chemotherapy, continuation of the same AVP combination, combination of other agents. Participating institutions could similarly select independently whether the patients should have a prophylactic irradiation of the brain or a complementary irradiation of the primary tumor site and mediastinum as well as the dose, portals and fractionation of this treatment.

Tumor response and toxicity were evaluated according to the WHO guidelines [20]. Complete responses were assessed clinically without pathological restaging. All patients were followed up until they died. The study documentation was separately reviewed by the SAKK central office and by the study chairman (P.A.).The chi-square test, the log rank test and the test for trend were used for the comparison of response rates and survival. In all patients evaluable for toxicity the percentage of the drug dose actually administered was computed separately for each agent and for treatment cycles 1–4. The results were expressed as the mean per cent per cycle and per agent.

RESULTS

Nine patients were excluded from analysis. One had a performance status 4 at start, one received a concurrent radiotherapy on the mediastinum and primary tumor, one was treated with doses different from those defined in the protocol and six had tumor criteria that could not be used for the evaluation of tumor response. Table 1 summarizes the characteristics of the 105 evaluable patients. Ninety-six patients had no prior antitumor treatment. The data of 110 patients were used for the evaluation of drug toxicity.

Tumor response

The overall response rate observed during treatment cycles 1–4 was 85% with 38% complete responses. Table 2 shows the correlation of responses and complete responses with disease extension and patient performance status. For limited disease and performance status 0, 100% of tumor responses were complete responses, whereas for extensive disease and performance status 3, no complete response was obtained. The correlation of complete response with performance status is significant (test for trend) in all evaluable patients and in patients with limited disease but not in patients with extensive disease. The overall response rates vary from 87 to 92 for limited disease and from 69 to 80 for extensive disease and show no correlation with performance status. For male patients the complete responses were 39% and overall responses 82%. Corresponding figures for female

Table 1. Characteristics of 105 evaluable patients

Male/female ratio	93/12
Mean age (years)	59
No. of patients with:	
Prior antitumor treatment:	
Surgery	1
Chest radiotherapy	5
CNS radiotherapy	1
Chemotherapy	6
Limited/extensive disease	55/50
Extensive disease sites:	
Liver	28
Bone	21
CNS	2
Pleura	11
Skin	3
Others	7
Performance status 0/1/2/3	24/37/31/13
Months from initial diagnosis: 1	74
2	16
More than 2	13
Unknown	2

Table 2. Therapeutic response according to disease extension and performance status

Performance status	Limited disease			Extensive disease		
	N.Pat.	CR (%)	CR + PR (%)	N.Pat.	CR (%)	CR + PR (%)
0	15	13 (87)	13 (87)	9	3 (33)	7 (78)
1	24	11 (46)	22 (92)	13	2 (15)	9 (69)
2	13	4 (31)	12 (92)	18	5 (28)	14 (78)
3	3	2	3	10	0 (0)	8 (80)

patients were 25% and 100%. In the 96 patients without prior antitumor therapy, the complete and overall response rates were 56% and 91% for limited disease and 22% and 85% for extensive disease. In the nine patients with prior treatment one had a complete response and three a partial response.

Maintenance phase

Of 88 responders 23 relapsed shortly after induction treatment. Sixty-five patients were eligible for analysis of the maintenance phase. Twenty-two had no further chemotherapy following an induction treatment of 4 cycles in 18 patients and three cycles in four patients. Seven patients received one to four additional cycles of AVP with the same dose. In one of them, the initial partial response was transformed into a complete response after the sixth cycle. The other patients received a different drug combination, 14 of them cyclophosphamide 1000 mg/m^2/day 1, methotrexate 20 mg/m^2/days 14 and 17, vincristine 1.4 mg/day 1 and lomustine 40 mg/day 1 (CyMOC). One patient in this group had a complete response after two additional cycles of this regimen. Twenty-three patients had a complementary radiotherapy of the primary lung tumor and mediastinum and 14 patients received a prophylactic irradiation of the brain. Median survival for patient subgroups according to the therapeutic attitude in the maintenance phase is shown in Table 3. No significant difference was observed between patients with or without maintenance chemotherapy and with or without prophylactic brain irradiation. The significance of the difference observed between patients with or without thoracic irradiation is questionable in a study where patients with radiotherapy have been arbitrarily selected.

Site of first failure

The distribution of sites of first failure for partial and complete responders with limited or extensive disease is shown in Table 4. In 44% of responders, the site of first tumor relapse was the primary tumor site and/or mediastinum. This proportion of local failures is not significantly different for complete or partial responders. There is a trend for patients with limited disease to fail more often in the primary site and mediastinum than patients with extensive disease ($P = 0.096$). The central nervous system was the second most frequent site of failure, representing 20% in responding patients without prophylactic brain irradiation. One patient only out of the 14 with prophylactic brain irradiation had a first relapse in the brain, i.e. 7%. Due to the small number of observations, this difference is not significant. Six patients died without tumor relapse: two because of pulmonary embolisms, the others because of congestive heart failure, myocardial infarction, decompensated diabetes mellitus and ulcerative colitis. No correlation could be established between death due to cardiopathy and the previous administration of doxorubicin. Two patients remain without evidence of tumor recurrence.

Table 3. Median survival according to therapeutic attitude in 65 responders eligible for maintenance treatment

Post-induction treatment	N. Patients	Survival (days)	
Maintenance chemotherapy			
None	22	396	
Etoposide single drug	11	356	
Etoposide + cisplatin + doxorubicin	7	279	
Cyclophosphamide + methotrexate + vincristine + lomustine	14	369	
Other combinations	11	381	
Lung + mediastinum radiotherapy			
Yes	23	433	*
No	42	357	*
Prophylactic cranial irradiation			
Yes	14	400	
No	51	370	

* $P = 0.06$.

Survival

The median survival was 13.4 months for patients with limited disease and 8.5 months for patients with extensive disease. The survival time correlates with performance status and tumor response (Table 5). Concerning performance status, significantly different survival times were obtained for patients with good (WHO 0–1) or poor (WHO 2–3) performance, but no difference was observed

Table 4. Sites of first failure in 88 responders according to disease extension and treatment response

Site of failure	% Patients with failure: Limited disease CR	Limited disease CR + PR	Extensive disease CR	Extensive disease CR + PR	All responders CR	All responders CR + PR
Lung + mediastinum	50	52	30	34	45	44
Nervous system	23	20	20	16	22	18
Nervous system (no PCI*)	27	22	29	18	28	20
Liver	3	4	10	13	5	8
Others & unknown	13	14	20	32	15	22
Deceased without failure	10	8	10	3	10	6
Alive without recurrence	0	2	10	3	3	2

* PCI = Prophylactic Cranial Irradiation.

Table 5. Median survival time in days for 105 evaluable patients according to disease extension, performance status and therapeutic response

	Days Survival	(95% Confidence Interval)	
Limited disease	402	(336–429)	$P = 0.0008$
Extensive disease	254	(217–318)	
Performance status 0	347	(283–403)	
1	373	(318–419)	$P = 0.056$
2	255	(197–373)	
3	234	(200–258)	
Complete response	411	(380–489)	
Partial response	275	(241–353)	$P = 0.004$
Stable disease	315	(206–406)	
Progression	86	(5–126)	

within these two groups (WHO 0 vs 1 or 2 vs 3).

The survival of partial responders and patients with stable disease was practically identical and significantly shorter than that of complete responders. As previously mentioned, no difference in survival was observed for responding patients with or without maintenance chemotherapy. Five patients only survived longer than 2 years (Table 6). Three died of tumor progression after initial complete response and loco-regional tumor recurrence. Two were still alive and free of disease after 1757 and 2014 days. Interestingly, these long term survivors did not belong to the best prognostic subgroup. One was classified as having extensive disease on the basis of a liver ultrasonogram showing liver metastases without confirmation by laparoscopy or needle biopsy. The other one was evaluated as partial response because of the persistence of a residual enlargement of the mediastinum. The initial performance status was quoted as 2 because of severe dyspnea due to the mediastinal tumor.

Toxicity

Table 7 indicates the WHO grading of treatment related toxicity during induction treatment. The most frequently encountered side effects were leucopenia, thrombopenia, nausea and/or vomiting and alopecia. Leucopenia was often dose limiting and is responsible for the reduction of the etoposide dose. Grade 3–4 thrombopenia was less frequently observed and the nadir counts for platelets appeared later. Nausea and vomiting were generally recorded as mild or moderate. However, the analysis of the intensity of nausea and vomiting is rendered difficult by the fact that various antiemetic treatments were used. The grading for alopecia was considered by many investigators as difficult and many cases of alopecia were not graded. Renal toxicity was mild, reversible and observed in 8% of patients only. It never exceeded WHO grade 1. Other toxic effects were rare. Neurological toxicities were recorded in four patients: two were mild peripheral motor or sensitive neuropathies, one consisted of convulsions and one of a progressive loss of consciousness. In this latter patient the brain CT scan did not reveal brain metastasis and the cerebrospinal fluid did not contain tumor cells but an increased protein

Table 6. Characteristics of patients with survival longer than 2 years

Initials	Disease extension	Performance status	Tumor response	Survival (days)	First failure	Cause of death
R.D.	Limited	0	Complete	746	Local	Cancer
G.B.	Limited	1	Complete	803	Local	Cancer
W.H.	Limited	1	Complete	920	Local	Cancer
H.S.	Extensive	1	Complete	1757+	—	—
B.W.	Limited	2	Partial*	2014+	—	—

* See text.

Table 7. Toxicity of induction treatment

	% Patients with toxicity (WHO grading)				
	0–1	2	3	4	Not graded
Nadir leucocyte count* (Median day nadir: 39)	19	35	39	11	0
Nadir platelet count† (Median day nadir: 66)	72	18	8	1	0
Serum creatinine‡	100	0	0	0	0
Alopecia	13	9	33	21	25
Nausea, vomiting	31	47	20	2	0
Neurologic	96	0	0	0	4
Cardiac	97	0	0	0	3
Sepsis	96	1	0	2§	1
Hemorrhage	99	0	0	1§	0
Local irritation	99	1	0	0	0

* 0–1 = 3000 or more, 2 = 2000–2999, 3 = 1000–1999, 4 = 0–999/mm^3.
† 0–1 = 75,000 or more, 2 = 50,000–74,999, 3 = 25,000–49,999, 4 = 0–24,999/mm^3.
‡ 8% of patients with grade 1 (145–290 μ mol/l.
§ 2 toxic deaths (days 13 and 166).

concentration. Treatment consisted of corticosteroids and brain irradiation. The patient died 2 months after discontinuation of treatment. Unfortunately, the diagnosis remained unclear and no post-mortem was performed. Brain metastases or a neurological paraneoplastic syndrome could not be excluded. A possible cardiac toxicity was recorded in three patients consisting of mild reversible supraventricular arrhythmias. A mild local irritation at the injection site was noted in one patient. Two patients died of drug related toxicity on day 13 and 166 after initiation of treatment. The second was in complete remission at the time of death due to myelosuppression, sepsis and massive bronchial hemorrhage.

Drug dose, response and survival

The analysis of the percentage of full drug dose is shown on Table 8. No dose reduction was necessary for cisplatin and doxorubicin. The dose of etoposide decreased from 85 to 90% in cycles 1–2 to 75% in cycles 3–4. This reduction consisted mainly of the suppression of treatment on days 15, 16, 17 because of persistent leucopenia.

Forty-eight patients received three or four AVP courses with 80% or more of the theoretical etoposide dose. From the others, 15 were treated for one or two courses only due to early death (3), tumor progression (8), toxicity (1), refusal (1) or protocol violation (2). No significant difference was observed in terms of response, complete response or survival between patients treated for more than two cycles with more than 80% etoposide or with a lower dose.

DISCUSSION

A high activity of etoposide combined with cisplatin has been previously reported in small

Table 8. Median percentage of full dose in induction treatment

Agent	Cycle			
	1	2	3	4
Etoposide	85	90	75	75
Cisplatin	100	100	100	100
Doxorubicin	100	100	100	100

series of patients, generally after failure of primary chemotherapy [22–28]. Porter *et al.* [29] have observed 60% of objective tumor responses in patients with prior exposure to etoposide, a result suggesting a synergism between cisplatin and etoposide. Klastersky and the EORTC Lung Cancer Working Party [30] treated 36 SCLC patients without prior chemotherapy with a combination including the three drugs used in the present report and obtained a response rate superior to 80% with 64% complete responses in limited disease and 23% complete responses in extensive disease. Their follow-up time was too short for an analysis of survival. The present study confirms the high activity of a combination including etoposide, cisplatin and doxorubicin in a larger series of SCLC patients without prior chemotherapy. Other authors have used a cisplatin-etoposide based regimen in alternance with a different drug combination [31,32], or combined with radiotherapy [33].

Aisner *et al.* [1] have stressed the importance of a sufficiently long follow-up in SCLC studies regarding the significance of survival curves and the analysis of long term survival. In the present series the follow-up is longer than 4 years for all patients and the analysis is based on the actual survival curve. From the initial 88 responders, 23 had already relapsed shortly after completion of an induction treatment made of four monthly cycles. The median survival was 402 days or 13.4 months for patients with limited disease and 254 days or 8.5 months for patients with extensive disease. Five patients only survived more than 2 years and three of them died eventually of tumor recurrence. This final result is inferior to the 15% long term survival expected from highly active treatment programs [1]. All patients did not receive the same maintenance treatment and a part of them had no maintenance chemotherapy. In our opinion, this could not explain these negative results. Other authors have shown that maintenance chemotherapy has no significant influence on survival [33,34]. Although adjuvant radiotherapy to the primary tumor and mediastinum may have improved long term survival in published series [35,36], these results are still controversial and the absence of thoracic radiotherapy in the majority of our patients could not explain the low fraction of long term survivors. The proportion of limited disease, the mean age and sex distribution and the proportion of first relapse in the CNS are in agreement with what is generally observed. The results of this study suggest that AVP, at least in the form used here, induces a high proportion of responses and complete responses but has a limited value in terms of prolonged survival. A possible explanation could be the inadequate dose schedule of etoposide. With 480 mg/m^2 per treatment cycle, the dosage of this agent corresponds to what is generally used in combination chemotherapy. However, only 50% of this dose was administered on days 1, 2, 3, the second half of the dose being postponed to days 15, 16, 17. In practice, leucopenia prevented this second half to be administered to many patients and the actual etoposide dose received was only a fraction (90–75%) of the one defined in the study program. In a further study of the Swiss Group for Clinical Cancer Research SAKK, AVP with a modified schedule is used in alternation with a non-cross resistant combination in patients with SCLC.

The results of this study are particularly illustrative of the relationship of complete response with disease extension and performance status, whereas the overall response rate seems much more independent of these prognostic factors. All responders in the category with limited disease and performance status 0 were complete responders. On the contrary, of an equal percentage of responders in the category with extensive disease and performance status 3, none had a complete response.

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