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VINCRISTINE, DOXORUBICIN AND CYCLOPHOSPHAMIDE WITH AND WITHOUT ETOPOSIDE IN LIMITED SMALL CELL LUNG CANCER

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Abstract

A total of 80 patients with limited disease of small cell lung cancer were randomized to receive either vincristine 1 mg/m^2 (max. 2 mg), doxorubicin 50 mg/m^2 and cyclophosphamide 750 mg/m^2 (VAC) i.v. on day 1, or the same drugs and etoposide 80 mg/m^2 i.v. daily for 3 days (VACE) every 3 weeks for nine courses. Chest irradiation was given in both regimens after the second course. The response rate was 84% for VAC (41% complete responses) and 75% for VACE (46% complete responses). The median survival time was 10 months with VAC regimen, and 14 months with VACE (difference statistically not significant). The median duration of remission was 8 months with VAC and 14 months with VACE ($p = 0.03$), and the median survival for complete or partial responders was 12 months and 20 months respectively ($p = 0.006$). Myelosuppression was significantly greater in the VACE group, and there was one treatment related death in the group receiving VACE. In this study the addition of etoposide to VAC improved the duration of response, but did not lead to longer survival of patients with limited disease of small cell lung cancer.

Key words: Small cell lung cancer, chemotherapy, vincristine, doxorubicin, cyclophosphamide, etoposide.

Treatment results of small cell lung cancer (SCLC) have improved significantly since the early 1970s, following the introduction of combination chemotherapy (CT), with 70–90% response rate in limited disease (LD), and median survival time ranging from 12 to 16 months (1). However, the long-term results are less encouraging, only about 7% of patients in LD survive for five years, and there has been only minimal improvement in the therapeutic results during the 1980s (2).

The role of radiotherapy (RT) as an adjuvant to CT is still controversial. Thoracic RT reduces chest failures and improves 2-year survival by 5–10%, but at the price of increased toxicity (2, 3).

The best results with CT are obtained by combining three or four drugs (1). The drugs most widely used are vincristine (V), doxorubicin (Adriamycin, A), cyclophosphamide (C), and etoposide (E), and the combination VAC has become the standard regimen (2). The aim of this multicenter study was to compare VAC with and without etoposide (VACE) combined with chest RT in LD of SCLC.

Material and Methods

The study was carried out in six departments of radiotherapy and diseases of the chest in Finland between December 1983 and April 1987. The eligibility requirements were: no previous malignant disease (except skin basalioma), no previous chemotherapy or radiotherapy, presence of measurable disease, Karnofsky performance status (K) ≥ 60, no cardiac, hepatic or renal disease preventing chemotherapy, and age ≤ 72 years. SCLC was considered as limited, if cancer was only found in one lung, the mediastinum, or supraclavicular lymph nodes. The presence of ipsilateral pleural effusion was also allowed.

Pretreatment staging included clinical examination, chest radiography, bronchoscopy, bone marrow aspiration biopsy, ECG, white blood cell count (WBC), blood

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haemoglobin, platelet count, liver and renal function tests, bone scan if skeletal symptoms were present, and ultrasonography of the liver in selected cases. Haemoglobin, WBC, and platelet counts were repeated before each cycle of CT.

Patients were randomized into two groups receiving either VAC or VACE combined with chest irradiation. VAC consisted of vincristine 1 mg/m^2 (max. 2 mg), doxorubicin 50 mg/m^2 and cyclophosphamide 750 mg/m^2, i.v. on day 1. In the VACE regimen vincristine, doxorubicin and cyclophosphamide were administered as in VAC on day 1, and etoposide was given 80 mg/m^2 i.v. on days 2–4. In both regimens the courses were given q. 3 weeks × 9, or until progression. Appropriate dose modifications due to myelosuppression, neurotoxicity and gastrointestinal toxicity were done routinely.

Radiotherapy (RT) of the primary tumour and the mediastinum was started 14 days after the second cycle of CT. Total tumour dose of RT was 48 Gy in 20 fractions given over six weeks. The split course technique was used with a 2-week rest interval. RT was always given with megavoltage equipments. An appropriate spinal shielding was employed after 40 Gy. No prophylactic cerebral irradiation was given. CT was continued two weeks after the completion of RT.

Objective response was determined according to the criteria of WHO, and it was based on chest radiography and clinical findings (4). Control bronchoscopy was recommended, but not required for patients in complete response after all CT courses. Patients who received at least two courses of CT and RT were considered evaluable for response. The acute and subacute toxicity was evaluated according to the criteria of WHO (4).

Statistical methods. Response rates and toxicities in both treatment groups were compared using the χ^2-test. All patients were included for survival analysis. The survival rate was calculated from the day of randomization by the Kaplan-Meier method. The survival curves for VAC and VACE regimens were compared using the Mantel-Breslow test. The effects of age, Karnofsky's status, sex and treatment on survival were estimated with Cox's proportional hazard model.

Results

Altogether 80 patients entered the study. The follow-up of all patients was complete by the closing date (1st of September 1988). The characteristics of the patients are presented in Table 1. Eight patients were not evaluable for response but they were evaluable for survival and toxicity: five patients (four on VAC and one on VACE) had progression after two courses of CT, two patients on VACE refused to continue the treatment after the first course, and one patient on VACE did not receive RT for an unknown reason.

Table 1

Patient characteristics

	VAC	VACE
No. of patients	41	39
Male	35	35
Female	6	4
Median age (years)	62	61
Range	40–72	41–72
Karnofsky performance status (median)	80	80
No. of patients evaluable for response	37	35

The response rate for the evaluable patients was 84% with VAC and 75% with VACE (Table 2). The maximal response occurred after two courses of CT and RT in 27 (87%) out of 31 patients on the VAC regimen, and 24 (92%) out of the 26 patients on the VACE regimen. If the maximal response took place later, it was achieved between the fifth and eight course in 4 patients in the VAC arm, and between the third and fifth course in 2 patients in the VACE arm.

The crude survival of all randomized patients is presented in the Figure. The 2-year survival rates of patients

Table 2

Response rates of evaluable patients

	VAC		VACE	
	n	(%)	n	(%)
Complete remission (CR)	15	(41)	16	(46)
Partial remisssion (PR)	16	(43)	10	(29)
No change (NC)	2	(5)	5	(14)
Progressive disease (PD)	4	(11)	4	(11)
Total	37		35	

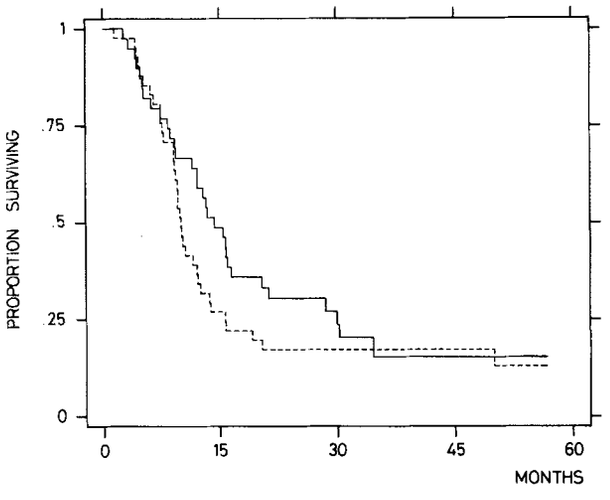

Figure. Survival of patients after the two treatment regimens. —— VACE; - - - VAC.

with VAC and VACE regimens were 17% and 30% respectively. The median survival time (MST) was 10 months with VAC, and 14 months with VACE. The difference in survival between the arms was not statistically significant ($p = 0.16$). At the closing date of the study 5 patients were still alive and free from the disease in both treatment groups. Karnofsky's performance status was the only statistically significant prognostic factor. In both treatment groups the survival rate was significantly poorer in patients with $K \leq 70$ than in patients with $K > 70$ ($p = 0.009$). Age and sex did not have any significant impact on prognosis.

The median duration of remission was 8 months for the VAC, and 14 months for the VACE regimen ($p = 0.03$), and the median survival of the complete or partial responders was 12 months with VAC and 20 months with VACE ($p = 0.006$).

The whole planned treatment (including 9 courses of CT and RT) could be given to 13 (32%) patients with the VAC, and to 18 (46%) patients with VACE regimen. The most important reason for the reduced number of CT courses was progression of the disease (in 15 cases with the VAC and in 11 with the VACE regimen).

The site of the first relapse is presented in Table 3. There was no difference in the site of such relapse between two treatment groups.

Toxicity. Two hundred and thirty-eight courses of VAC and 240 of VACE were given. All patients were included in the analysis of acute and subacute toxicity (Table 4). Leukopenia and thrombocytopenia were significantly more common in the VACE regimen. There were no life-threatening complications due to myelosuppression. One treatment related death occurred in the VACE arm. The patient died immediately after the ninth course of CT with cardiac arrhythmia and severe lung fibrosis probably caused by the combined toxicity of CT and RT. Unfortunately, autopsy was not carried out. Prophylactic antiemetic treatment was not used during the first course, but since then antiemetic drugs were given individually. Seven patients (four on VAC and three on VACE) refused to continue the treatment because of nausea and vomiting. Lung fibrosis probably related to RT was detected radiologically in 41% and 51% of the patients on the VAC and VACE regimens respectively.

Table 3

Site and frequency of the first relapse among the responders (CR + PR) on the VAC and VACE regimens

	VAC		VACE	
	n	(%)	n	(%)
Primary tumor	9	(35)	5	(25)
Central nervous system	6*	(23)	2**	(10)
Liver	2	(8)	1	(5)
Osseous	1	(4)	4	(20)
Extrapulmonary lymph nodes	1	(4)	2	(10)
Multiple	7	(26)	5	(25)
Other	—		1	(5)
Total	26		20	

*) Includes 2 patients with CR.
**) Includes 1 patient with CR.

Discussion

Many agents, e.g. vincristine, doxorubicin, cyclophosphamide, etoposide, cisplatin, carboplatin, methotrexate, CCNU, teniposide, and ifosfamide have been shown to be effective as single agents against SCLC (1, 5). The best results have been obtained with a combination of three to four drugs. The response rate for untreated patients in LD of SCLC varies from 70 to 90% with about 50% complete responses, but the long-term survival rate still remains poor. On the basis of literature reviews (1, 2) the 2- and 5-year survival rates are 20% and 7% respectively. Several recent studies suggest that alternating treatment with different drug combinations is more effective than sequential use of VAC (2, 6, 7).

Table 4

Acute and subacute toxicity encountered (WHO grade 1–4)

	VAC (n = 41)				VACE (n = 39)				
Grade	1 + 2		3 + 4		1 + 2		3 + 4		
	n	(%)	n	(%)	n	(%)	n	(%)	
Cardiac	2	(5)	2	(5)	5	(13)	0		ns*
Neurotoxicity	4	(10)	0		7	(18)	1	(3)	ns
Alopecia	8	(20)	30	(73)	6	(15)	30	(77)	ns
Nausea and vomiting	24	(59)	10	(24)	22	(56)	7	(18)	ns
Leukopenia	16	(39)	7	(17)	8	(21)	19	(49)	$p = 0.009$
Thrombocytopenia	5	(12)	0		8	(21)	7	(18)	$p = 0.007$
Anaemia	9	(22)	0		15	(39)	2	(5)	ns

*) ns = not significant

The VAC combination has been considered to be the standard regimen for comparison with new regimens (2). In the present study there was no statistically significant difference in the response rate, overall survival, or MST between VAC and VACE. Our results are in agreement with other studies with the same drug combinations (8–10). There seems, however, to be some benefit from combining etoposide with VAC. Both the median survival and the median duration of response were significantly longer among responders on the VACE than on the VAC regimen. The reason for not obtaining statistically significant differences between the two regimens may be the fact that the number of patients was rather small in the trial. It should be noted that in one trial (11) the response rate, time to progression and 2-year survival were significantly better with the combination VACE than with VAC alone.

Since the 1980s about 80% of patients with LD of SCLC have received chest irradiation in randomized trials (12), but its role is still controversial (13, 14). The frequency of local recurrence decreases significantly, but only 10 to 15% of patients achieve a long-term benefit, if chest irradiation is given (2). The risk of pulmonary toxicity increases markedly with combined modality treatment (2). RT is most effective in LD if it is given early, if alternated with CT cycles, and if given with a sufficiently high dose (12).

Prophylactic cerebral irradiation (PCI) is commonly given to patients who have achieved a complete response, but its role is still controversial. PCI reduces the rate of cerebral relapses significantly, but it has no significant impact on survival (2). In the present study PCI was not used and its role seems to be limited, since brain metastases were diagnosed as the first relapse only in 2 of the 31 complete responders with VAC, and in 1 of the 26 complete responders with VACE.

The length of CT varied in our study, and the results appeared to be similar if the duration of treatment was 6 months, or as long as 12 to 24 months (2). The optimal duration of CT when CR has been achieved is uncertain (15). In this study, only one-third of the patients treated with VAC and half the patients treated with VACE received all nine courses. Our results indicate that two courses of CT combined with local irradiation give maximal response in about 90% of patients.

The overall toxicity was acceptable. There was one treatment-related death due to severe lung fibrosis after RT, and with concomitant cardiac arrhythmia. Myelosuppression was significantly more common in the VACE regimen, but life-threatening infections or bleeding were not encountered. The other side-effects were almost similar in the two regimens. Seven patients (9%) suffering from nausea and vomiting refused to continue therapy. This indicates that effective prophylactic antiemetic drugs should be recommended from the beginning of CT.

In conclusion, the two multidrug regimens studied were similar concerning response and survival rates. The addition of etoposide to VAC improved the survival rate of the responders, but caused more severe haematologic toxicity. The maximal response was usually obtained after two courses of CT and RT. Central nervous system relapses were uncommon in this study. Finally, high response rates give only little hope for cure, and therefore the long-term survival should be the most important parameter when judging the efficacy of treatment in LD of SCLC.

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