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Two randomized trials for alternating polychemotherapy of small cell lung cancer

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Summary. Patients with small cell carcinoma of the lung (SCCL) were treated in two multicenter trials with different cytostatic drug regimens including ifosfamide.

In the first randomized study, including 306 patients, alternating chemotherapy with VP 16, ifosfamide, vindesine (VPIV), adriamycin, cisplatinum, vincristine (APO), and cyclophosphamide, methotrexate, CCNU (CMCC) was compared against standard treatment with ACO (adriamycin, cyclophosphamide, vincristine).

It was shown that the alternating therapy resulted in a higher response rate (88% vs 78%) and a longer median survival time (11 months vs 10 months). Regarding toxicity, VPIV was similar to ACO, whereas APO and CMCC had more side-effects, leading to an increase in the number of drop-outs.

In the second randomized study 144 patients were treated either with ifosfamide/VP 16 (IVP) or with cisplatinum/VP 16 (PVP). In the case of no further response, no change, or progression the induction therapy was changed to ACO. Interim analyses show that both regimens have similar therapeutic effects; but higher toxicity was observed in patients treated with *cis*-platinum/VP 16 than in patients treated with ifosfamide/VP 16.

According to the response rate in patients treated with ACO after first-line therapy there was less cross-resistance of IVP than of PVP to ACO.

Introduction

Despite the high remission rates achieved with various forms of treatment in small cell lung cancer (SCLC), the remissions are short-lived and death from tumor progression is the rule.

A number of attempts have been made during recent years to change this situation; however, many of these efforts cannot be difinitively evaluated.

Results published by Cohen et al. [1] indicate that patients who have achieved only partial remission with one combination can obtain a complete remission with a second non-cross-resistant combination. This report gave rise to a series of randomized trials to test the value of early addition of alternative non-cross-resistant combinations. The results of the published trials are conflicting, showing either an increase in survival [3, 6] and complete remission [6] or longer response duration [2], or no benefit from the non-cross-resistant therapy [4, 5]. It must be mentioned that in none of these trials was the non-cross-resistance of the multiple-drug combinations tested in pilot studies. Therefore the term "cyclic alternating chemotherapy" should be used for this type of polychemotherapy.

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Results and discussion

We started two multicenter trials, one in July 1981 with 306 patients, and one in December 1983 with 144 patients, to test the value of a cyclic alternating chemotherapy in a randomized fashion. Only patients with histologicaly confirmed SCLC with a performance status of 50% or more, who were aged 70 years or less, and had no severe heart or kidney disease were included.

In the first study, patients with SCLC from 14 participating institutions were randomized for the two treatment arms, A and B. Patients in A received ACO (adriamycin, cyclophosphamide, vincristine) as the standard therapy, while patients in B were treated with an alternating chemotherapy according to Fig. 1. Responding patients received prophylactic cranial irradiation after three cycles and chest irradiation after eight cycles. No maintenance therapy was given to patients in complete remission. A complete restaging (chest X-ray, bone scan, bone biopsy, abdominal sonography, laboratory parameters) was performed after four and eight cycles of chemotherapy. The patients were stratified according to the prognostic factors performance status, weight loss, and limited/extensive disease. The final analysis of the trial (excluding long-term survivors) performed in January 1985 gave the following results:

1. The given prognostic factors showed a good balance in both treatment arms, indicating comparability of the two chemotherapy regimens.
2. The alternating chemotherapy resulted in a higher response rate (according to chest X-ray after two cycles of therapy) of 88% vs 78%. Again, the complete remission rate after 6 (23% vs 17%) and 12 (11% vs 7%) months was higher in arm B than in arm A. The difference in remission rate was statistically significant at the 5% level (Table 1).
3. Treatment arm B induced a higher median survival than the standard therapy A (11 vs 10 months) (Fig. 2). The same was true for patients surviving 1 (43% vs 32%) and 2

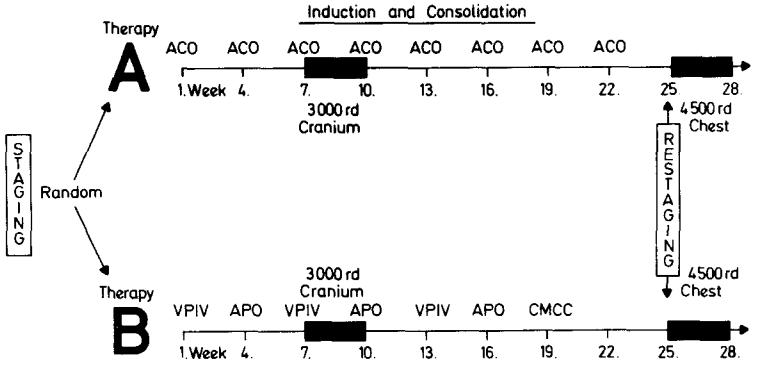

Fig. 1. Treatment plan of the multicenter trial with SCLC patients randomized to receive treatment A or B. *ACO*, adriamycin 50 mg/m² on day 1 + cyclophosphamide 1000 mg/m² on day 1 + vincristine 2 mg/day 1; *APO*, adriamycin 60 mg/m² on day 1 + cisplatin 90 mg/m² on day 1 + vincristine 2 mg/day 1; *VPIV*, etoposide 120 mg/m² i.v./day on day 5 1–3 + ifosfamide 1.5 g/m² i.v./day on days 1–5 + vindesine 3 mg/m² per day on day 1; *CMCC*, cyclophosphamide 1 g/m² per day on days 1 and 22 + methotrexate 15 mg/m² p.o. per day on days 1, 2, 8, and 11 + *CCNU* 100 mg/m² p.o. per day on day 1

Table 1. Therapy results

	Therapy A	Therapy B	Total
Response rate, primary tumor	78%	88%	83%
CR rate after 6 months	17%	23%	20%
CR rate after 12 months	7%	11%	9%
No progession			
After 6 months	47%	62%	54%
After 12 months	9%	21%	15%
Median survival (months)	10	11	10.5
One-year survivors	32%	43%	38%
Two-year survivors	5%	8%	6%

Table 2. Survival by prognostic factors

	Median survival	One-year survival	Two-year survival
Stage			
Limited	12.5 months	52%	9%
Extensive I	11.5 months	47%	3%
Extensive II	7.5 months	22%	3%
Karnofsky index			
80%–100%	11 months	42%	8%
50%– 70%	7 months	23%	3%
Sex			
Female	12.5 months	56%	14%
Male	10 months	34%	3%
Smoking			
Yes	10 months	35%	5%
No	14 months	53%	5%

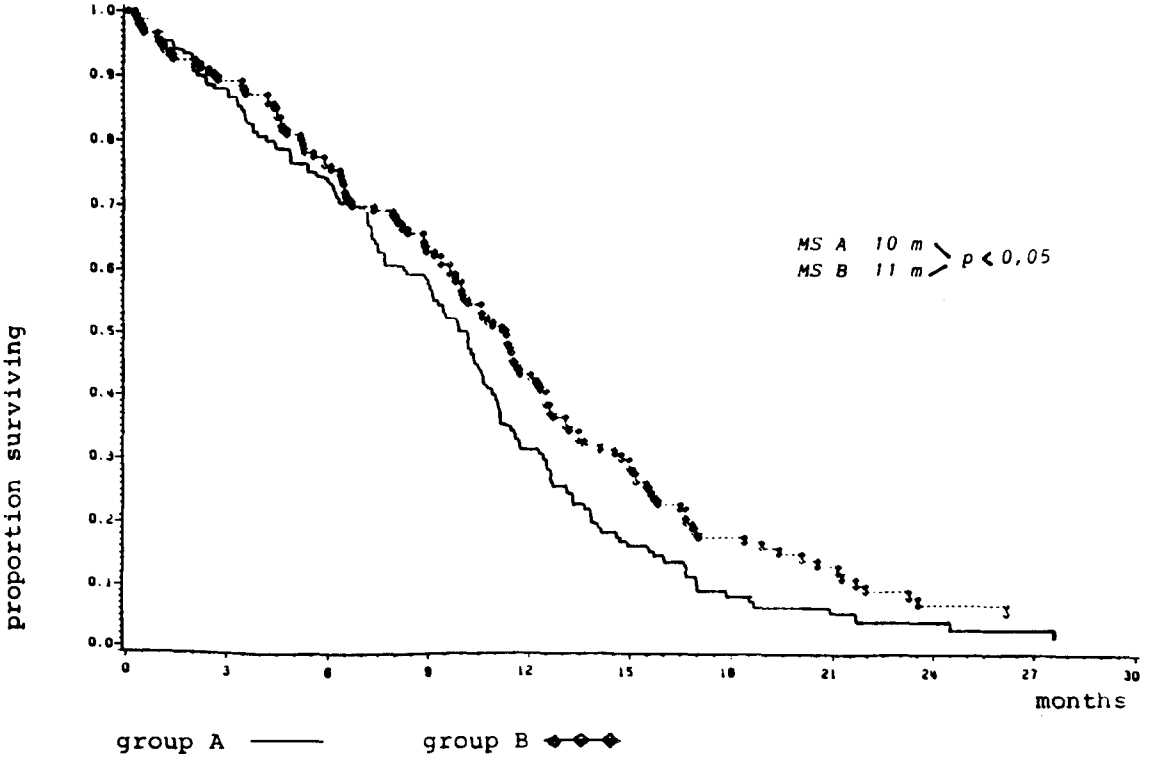

Fig. 2. Survival in groups A and B. For treatment plan see legend to Fig. 1

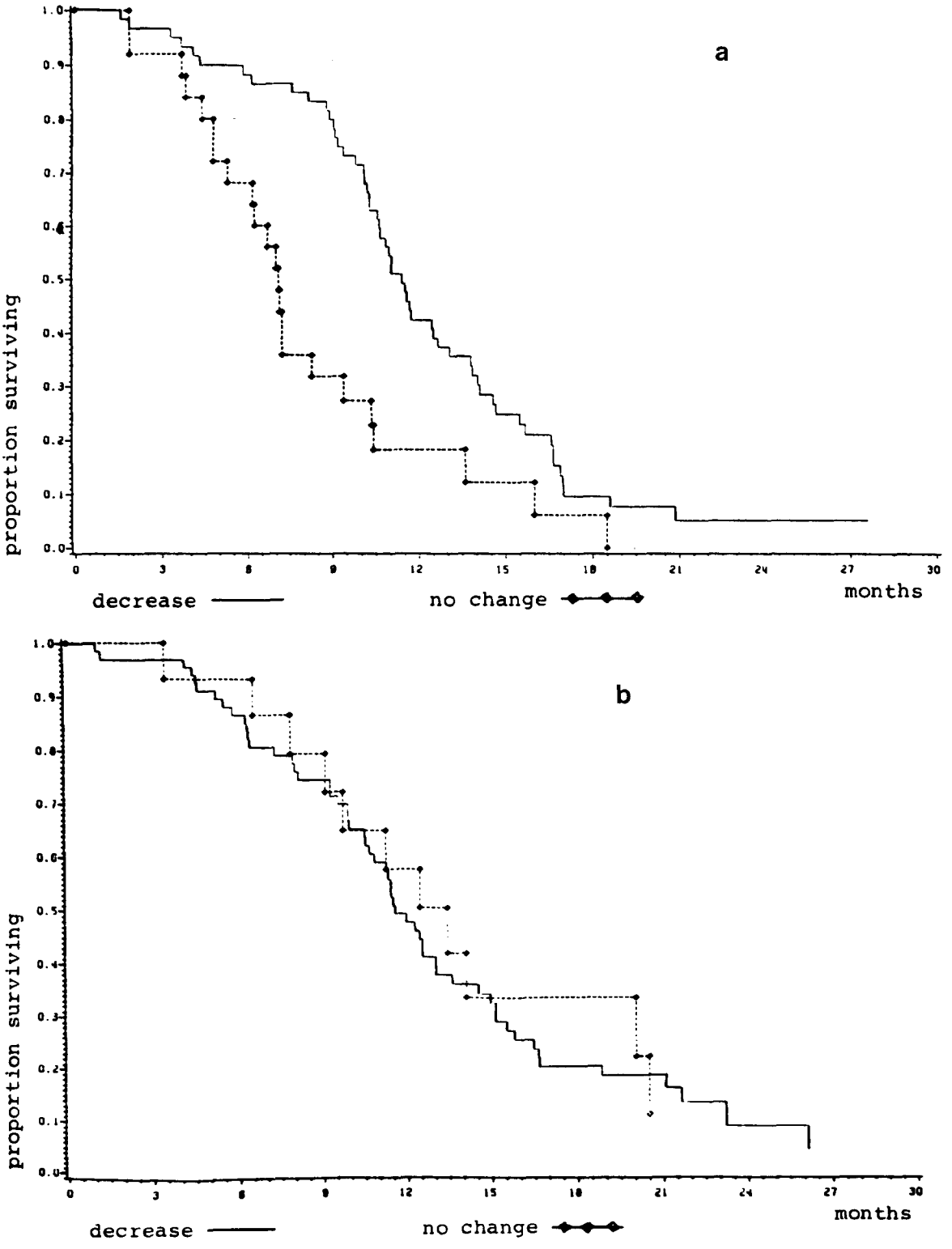

Fig. 3 a, b. Survival at chest X-ray after the first treatment cycle in groups A *(a)* and B *(b)*

(8% vs 5%) years. The differences were statistically significant ($P \leq 0.05$), except for 2-year survival.

4. Side-effects of therapy A and B were comparable. However, therapy B was somewhat less well tolerated and the rate of drop-outs due to refusal of therapy was higher.

5. A number of prognostic factors, such as extent of disease, performance status, sex, and previous history of smoking showead heavy influence on survival (Table 2).

When extensive disease was subgrouped into extensive I (limited to the chest) and extensive II (distant metastases), limited disease and extensive I were seen to involve a very similar prognosis, whereas patients with distant metastases had a much worse prognosis. This was especially true for patients with bone marrow, liver, and bone metastases, whereas brain metastases, surprisingly, had no influence on survival.

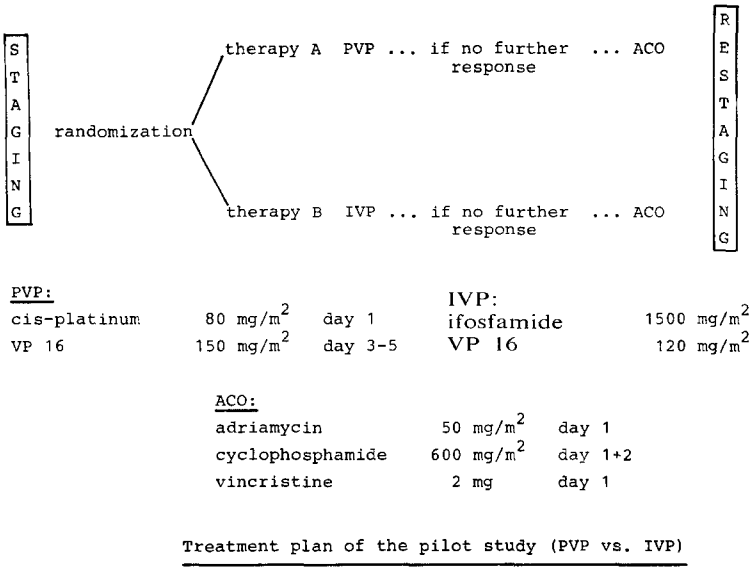

Fig. 4. Treatment plan for the pilot study of ifosfamide/VP 16 *(IVP)* against cisplatin/VP 16 *(PVP)*

Table 3. Response rates in the pilot study after three and six cycles of chemotherapy

	PVP/ACO		IVP/ACO	
	3 cycles ($n = 47$)	6 cycles ($n = 35$)	3 cycles ($n = 53$)	6 cycles ($n = 35$)
Complete remission	11%	23%	11%	23%
Partial remission	49%	26%	49%	20%

One major outcome of the trial was that response during the first two cycles according to chest X-ray had a great impact on survival in arm A, but not in arm B (Fig. 3 a, b).

These results are in accordance with those of large multicenter trials of combined chemo- and radiotherapy in SCLC. In addition, they indicate that cyclic alternating chemotherapy given as described is of some advantage, although the side-effects were somewhat more pronounced with the alternating treatment. This trial also suggests that

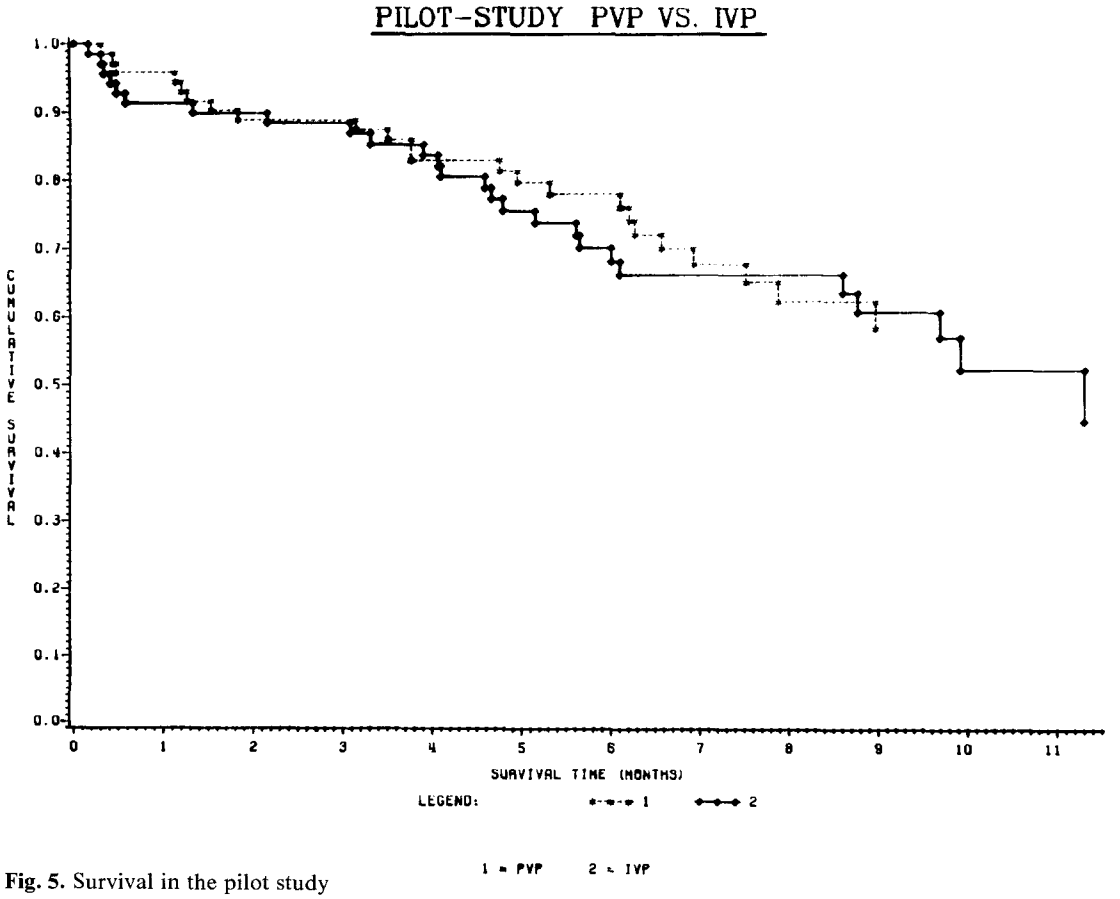

Fig. 5. Survival in the pilot study

the prognosis of nonresponders to the first and second cycle could be improved by an immediate switch to a non-cross-resistant second-line therapy, which would be a response-oriented individualized treatment form.

In preparation for a large randomized multicenter trial testing this hypothesis, we performed a pilot study in 144 patients with SCLC, in which cross-resistance against the second-line therapy with ACO and side-effects of the two polychemotherapy combinations were evaluated. The treatment plan is given in Fig. 4.

Patients in arm A received the combination ifosfamide/VP 16 (IVP), and those in arm B, *cis*-platinum/VP 16 (PVP). Nonresponders according to chest X-ray (taken immediately before each cycle) were switched to second-line therapy with ACO. Responding patients received a total of six cycles with no maintenance therapy. Chest irradiation was performed after six cycles and brain irradiation only if patients developed complete remission. The entrance criteria, staging, and stratification for prognostic factors were the same as in the preceding trial.

The interim analysis of February 1985 showed the following results:

1. Again, the prognostic factors were balanced between both treatment arms, indicating good comparability.
2. The two chemotherapy protocols led to identical response rates (87% vs 87%) after two cycles of chemotherapy. The therapy results (complete restaging) after three and six cycles of chemotherapy are given in Table 3.
3. The median survival was 11.2 months with IVP, and has not yet been reached with PVP (Fig. 5); it seems it may be similar.
4. Of the 58 patients who were switched to the second-line protocol because of progression, 20 (34%) had an additional response to ACO. Patients who received IVP as the first-line therapy showed a more pronounced secondary response to ACO (13 of 30 patients) than patients with PVP as the first-line therapy (7 of 28 patients).
5. Side-effects according to the WHO classification were significantly less pronounced with IVP (less nausea, vomiting and leukopenia) than with PVP.

From these preliminary results it is concluded that therapy A (IVP), because of a probably higher non-cross-resistance against ACO and because of less pronounced side-effects, is preferable to treatment B (PVP).

In May 1985 we therefore started a large multicenter trial comparing a fixed alternation (IVP/ACO/IVP/ACO/IVP/ACO) with a response-oriented alternation (IVP until progression, then ACO). The results will show whether this type of individualized treatment has any advantage over a fixed alternating chemotherapy.

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