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A Comparison of *Cis*-platinum–Vindesine and *Cis*-platinum–Etoposide Combined with Radiotherapy for Previously Untreated Localized Inoperable Non-small Cell Lung Cancer

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Abstract—*Seventy-two previously untreated patients with localized inoperable non-small cell lung cancer were randomized to a study comparing the efficacy of* cis-*platinum–vindesine (P-VDS) and of* cis-*platinum–VP*16 (*P–VP*16), *both combined with split-course radiotherapy. Fifty-nine patients were evaluable for response after the minimum requirement of two chemotherapy cycles. Both arms were further randomized to two split intervals,* 3 *or* 5 *weeks. The response rate to chemotherapy only (three cycles) was* 66% *for P–VDS and* 50% *for P–VP*16. *Radiotherapy increased the response rates to* 83 *and* 67%, *respectively. A Karnofsky score of* 80% *or more and the* 3*-week split interval were significant positive prognostic factors. Of all patients,* 66% *had local or combined recurrences and* 17% *relapsed at a distant site only. Since the* 2*-year survival rates are not strikingly better than those obtained by radiotherapy alone, we feel that these regimens should be restricted to further investigations of the role of chemotherapy in the treatment of different clinical presentations of NSCLC.*

INTRODUCTION

THERE EXISTS reliable evidence that radiation can sterilize non-small cell lung cancer (NSCLC). Like surgery, irradiation comprises local treatment for a disease, which in many instances either is already systemic or rapidly becomes so. Efficacious systemic therapy would be of significant therapeutic value. Clinical trials which make use of chemotherapy for the treatment of NSCLC have not consistently demonstrated clinical benefit to patients with this disease, although recent studies have indicated some progress in the development of new, moderately effective drugs such as vindesine (VDS) [1–5], *cis*-platinum (P) [6–10] and podophyllotoxin (VP16) [11–14].

This study was initiated primarily to investigate the effectiveness of P–VDS and P–VP16 against previously untreated, localized inoperable NSCLC; secondly to determine whether the combination of this chemotherapy with locoregional radiation improves the response rate, survival and local relapse rate compared with those reported solely with radiation; and thirdly to evaluate the treatment morbidity and interactions of the treatment modalities.

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MATERIALS AND METHODS

Patients

Previously untreated patients with histologically or cytologically confirmed inoperable NSCLC, limited to one hemithorax, were eligible for this study. All patients had either measurable or evaluable disease, and a performance status of 60% or more according to the Karnofsky scale. The upper age limit was 75 years. Disabling coronary insufficiency, the coexistence of severe pulmonary disease, preexisting neuropathy and impaired renal function were criteria for exclusion. Staging procedures included clinical examination, chest X-rays and tomograms of the mediastinum, bronchoscopy and a blood chemistry panel. Bone and liver scans were performed as routine measures, brain scans only when clinically indicated.

Study design and treatments

Eligible patients were randomized to receive either P–VDS or P–VP16 as systemic chemotherapy combined with local radiotherapy. Both chemotherapy arms were randomized to one of two

split intervals, 3 or 5 weeks. The P–VDS regimen originally comprised VDS 4 mg/m^2 i.v. once weekly for 4 weeks, every 2 weeks for 16 weeks, and subsequently only in conjunction with *cis*-platinum. P 120 mg/m^2 was administered with mannitol-induced forced diuresis before radiotherapy on days 1, 28 and 70, and again, beginning 28 days after the completion of radiotherapy, every 6 weeks to a total treatment time of approximately 1 year (seven or eight cycles in total), VP16 was given on days 1–5 at a dosage of 60 mg/m^2 i.v., always in conjunction with *cis*-platinum. Because of severe adverse effects in the first nine patients, the doses were reduced to VDS 3 mg/m^2, P 90 mg/m^2 and VP16 50 mg/m^2 (see Toxicity). Chemotherapy was discontinued at all events in cases of progressive disease, moreover after three cycles in cases of no change. If pretreatment WBC counts were between 3000 and 4000, 75% of the total dose was given; if they were between 2000 and 3000, 50% was given. The dose was omitted with counts of less than 2000. If troublesome or progressive paresthaesia occurred, VDS dose was reduced to 75%; in cases of motor weakness only 50% of the dose was given, and with progressive motor weakness VDS was stopped. Haemoglobin, WBC and platelet count were always obtained before the administration of chemotherapy and again 8–14 days after each treatment. Patients who on relapse were eligible for further chemotherapy treatment were administered cyclophosphamide 500 mg/m^2 day 1, Adriamycin® 40 mg/m^2 day 1 and etoposide 60 mg/m^2 days 1–3.

Radiotherapy, beginning 4 weeks after the start of the third chemotherapy cycle, was administered to the mediastinum and the primary tumour from two opposite portals as a split-course regimen: 55 Gy in 22 fractions over 7–9 weeks.

A complete response (CR) was defined as the total radiographic disappearance of all tumour for at least 30 days, partial response (PR) as at least 50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions, and progressive disease (PD) as an increase of at least 25% in any measurable lesion. All other responses were classified as no change (NC). Patients were evaluated for response after two and three cycles of chemotherapy, after radiotherapy, and again after every third course of chemotherapy following radiotherapy. Patients who had been administered at least two cycles of chemotherapy were considered evaluable for response. Patients who had been given at least one dose of any of the drugs were evaluable for toxicity.

Statistical methods

Survival curves and the duration of response were calculated from the day of randomization by the product limit method, and the level of significance was based on the log-rank test [15] with an adjustment as required for other factors [16]. Multiple regression analysis of the importance of a number of simultaneous factors was carried out by application of the Cox regression model. In the analysis, the factors were represented by indicator variables.

RESULTS

Patient entry

Fifty-nine of the 72 patients randomized were regarded as evaluable for chemotherapy response, 29 in the P–VDS and 30 in the P–VP16 group. Of the remaining 13 patients, eight in the P–VDS group and five in the P–VP16 group were administered less than two complete chemotherapy cycles.

Table 1 provides a summary of clinical patient characteristics.

Responses and survival

Among the 59 patients evaluable for chemotherapy response, three achieved CR (one large cell, two squamous cell) and 16 PR in the P–VDS arm after three cycles; the corresponding figures for the P–VP16 arm were one CR (squamous cell) and 14 PR, giving objective response rates of 66 and 50%, respectively (Table 2).

Radiotherapy further increased the tumour response of five patients in the P–VDS arm (two CR, three PR), and four patients in the P–VP16 arm (four CR). The maximum response to the combined treatment was 83% in the P–VDS arm, and 67% in the P–VP16 arm; the difference is not significant. Only after the third cycle were complete responses to chemotherapy registered. Most PRs occurred as early as after two cycles.

Table 1. Clinical characteristics of the 72 patients randomized to receive either cis*-platinum–vindesine (P–VDS) or* cis*-platinum–etoposide (P–VP16)*

	P–VDS	P–VP16
Number of patients	37	35
Median age (years)	66	67
Sex		
male	32	34
female	5	1
Karnofsky(%)		
range	60–100	60–100
median	80	80
Cell type		
epidermoid	29	25
adeno	4	2
large cell	4	8
Stage (UICC, 1978)		
I	1	3
II	19	12
III	17	20

Table 2. Tumour response achieved after chemotherapy alone, and after additional radiotherapy (RT)

	P–VDS (n = 29)			P–VP16 (n = 30)		
	CR	PR	Overall response (%)	CR	PR	Overall response (%)
After two cycles	0	16	16/29 (55)	0	15	15/30 (50)
After three cycles*	3	16	19/29 (66)	1	14	15/30 (50)
After two or three cycles and RT†	5	19	24/29 (83)	5	15	20/30 (67)

*Earlier discontinuation of chemotherapy without response counted as failure.
†Eight patients did not complete the third cycle.

The median duration of remission for all patients randomized to the P–VDS arm was 280 days, and the median survival was 383 days. The corresponding figures for the P–VP16 arm were 241 days and 409 days. The differences are not significant (Fig. 1).

Patients with a Karnofsky performance score of 80% or more had a median survival time of 408 days compared with 232 days for those with performance scores of 60–70% (P = 0.042). Age, stage or failure pattern or the use of second-line chemotherapy did not influence survival.

In the multifactorial step-wise regression analysis, it was found that three factors significantly influenced survival: pretreatment performance status, the 3-week (as opposed to the 5-week) split-interval, and the overall maximal response to therapy.

In regard to the patients in the P–VDS arm, the first site of relapse was local in 38% (11/29), combined in 21% (6/29) and distant in 21% (6/29); the corresponding figures for the patients in the P–VP16 arm were 60% (18/30), 13% (4/30) and 13% (4/30), respectively. Six patients in the P–VDS arm and four patients in the P–VP16 arm had no clinical evidence of tumour relapse at death.

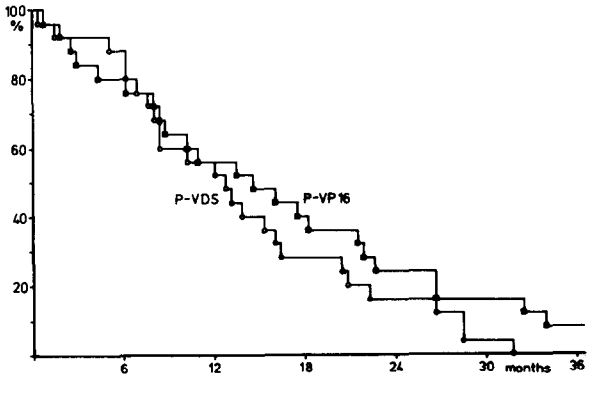

Fig. 1. All 72 randomized patients, survival by treatment, ■ P–VP16, ○ P–VDS. The difference shown is not statistically significant.

Toxicity

The first nine patients in the study (12 cycles) were administered chemotherapy at a dosage of VDS 4 mg/m^2, P 120 mg/m^2 and VP16 60 mg/m^2. Four of the five patients in the P–VDS arm showed a moderate to severe rise in serum creatinine (190–580). One patient experienced a complete loss of hearing, and one presented with progressive motor weakness. Vomiting was severe. These side-effects were reversible. Two of the four patients in the P–VP16 arm receiving this higher dosage died after the first cycle of chemotherapy. In neither case was death directly attributable to drug toxicity (myocardial infarction 25 days after chemotherapy, intestinal bleeding 36 days after chemotherapy).

Subsequent to reduction of the dosages to 3 mg/m^2 of VDS, 90 mg/m^2 of P and 50 mg/m^2 days 1–5 of VP16, the haematological, nephro- and neurotoxicities in both groups were mild to moderate.

When the lower dosages of chemotherapy were employed, nausea and vomiting were manageable. However, a deterioration of the patients' well-being prompted the discontinuation of chemotherapy before the planned 1 year (seven or eight cycles) in all but five cases in the P–VDS and six cases in the P–VP16 group. The mean number of cycles given were 3.3 in the P–VDS arm and 4.6 in the P–VP16 arm.

DISCUSSION

The objective of the current study was to test the efficacy and feasibility of combination chemotherapy with *cis*-platinum–vindesine and *cis*-platinum–VP16, combined with radiotherapy in previously untreated, limited NSCLC. The long-term results of radiotherapy as applied in our department for more than 20 years have been reported previously [17].

Long-term survival in inoperable cases of NSCLC is attained in a very limited number of patients by the use of radiotherapy alone. Most patients die

from their disease, by reason of either haematogenous dissemination or local relapse.

In 1979, when it was reported that new drugs such as *cis*-platinum and VP16 exhibited activity in NSCLC, it seemed logical to combine the experience gained from radiotherapy with modern 'more effective' combination chemotherapy with a view to the achievement of greater tumour responses, better local control, and possibly increased survival.

In the present study the objective response rate after chemotherapy alone was 66% for the P–VDS regimen, and 50% for the P–VP16 regimen. Three radiographic complete responses were observed with P–VDS, and one with P–VP16. Response rates to modern chemotherapy reported by others vary according to the selection of patients from 27 to 51% [18–24]. Our favourable response rates imply that suboptimal chemotherapy cannot be held responsible for the lack of a survival benefit for our patients.

Trovo *et al.* [25] have reported a 62% major objective response following the combination of radiotherapy and chemotherapy with cyclophosphamide, Adriamycin®, methotrexate and procarbazine (CAMP) in a non-randomized trial. In our series, radiotherapy administered after induction chemotherapy increased the overall response rates to 83% in the P–VDS arm and to 67% in the P–VP16 arm. The figures are very similar to those recently reported by Blum *et al.* [26], whose *cis*-platinum–VBL induction chemotherapy in locally advanced NSCLC resulted in a 69% response rate which was increased to 82% after consolidation radiotherapy.

Although response rates for radiotherapy are lower than attained by combined therapy, long-term survival figures, not differing strikingly from ours, have been reported with radiotherapy alone [17, 27].

Of the generally acknowledged prognostic factors, only a good initial performance score (Karnofsky at least 80%) indicated improved survival. There were only three patients with stage I disease in this study, but the survival curves of the stage II and III, M0 disease patients are almost identical. It is probable that the separation of N1 and N2 patients by the staging methods used did not yield reliable results.

In the present series, 17% of the evaluable patients had a distant site as the initial site of progression. A failure of the combined modality therapy to control local disease occurred in a total of 66% of cases (49% local only, and 17% combined). Following definitive radiotherapy with 50–60 Gy in operable stage I–III, M0 NSCLC, Perez *et al.* [28] reported a relapse rate of 32–33% at only distant sites. Stanley *et al.* [29] reported a relapse rate at distant sites of 40% for adeno- and large cell undifferentiated carcinoma and of 20% for squamous cell carcinoma after treatment of local NSCLC by irradiation alone. Consequently, the assumption that combined modality therapy yields less local relapses could not be confirmed.

The 3-week split was a significant prognostic factor in our study. There were 24 local relapses in the 5-week split group, as compared with only 17 in the 3-week split group. Possibly the prolonged overall treatment time (9 weeks) in the former group allowed repopulation of the tumour, resulting in more local relapses. Both regimens were equally effective in inducing objective responses irrespective of the cell type of the cancer.

Subsequent to the decreases in the planned dosages of all three study drugs, the side-effects of chemotherapy became clinically manageable. Nevertheless, of the 59 patients who received the protocol minimum requirement of at least two cycles of chemotherapy, only five in the P–VDS arm and six in the P–VP16 arm could complete the planned 1-year treatment (3 chemotherapy cycles—radiotherapy—4–5 chemotherapy cycles). Eleven patients refused further treatment, mainly because of nausea and deterioration of their clinical condition. Among these were patients who had achieved good responses.

We found that radiotherapy did not increase the side-effects induced by chemotherapy, but rather seemed to provide a good 'rest period' for the patients. It has also been reported by others [25, 26] that the combination of similar chemo- and radiotherapy regimens is feasible.

We conclude that the favourable responses attained confirmed the antitumour effect of P–VDS and P–VP16. Nevertheless, these chemotherapy regimens used in combination with radiotherapy resulted in a survival similar to, but not better than, that reported after radiotherapy alone. In NSCLC this type of chemotherapy is of doubtful value and should be restricted to carefully conducted clinical trials.

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