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# *cis*-Platinum (DDP) and VP 16-213 (Etoposide) Combination Chemotherapy for Advanced Non-small Cell Lung Cancer. A Phase II Clinical Trial

P. S. MITROU,* M. GRAUBNER,† W. E. BERDEL,‡ S. MENDE,§ C. GROPP,|| V. DIEHL¶ and T. H. KLIPPSTEIN*

*Zentrum der Inneren Medizin, Abteilung für Hämatologie/Onkologie der Universitätskliniken, Frankfurt/Main, F.R.G., †Zentrum der Inneren Medizin der Justus Liebig-Universität, Giessen, F.R.G., ‡Klinikum rechts der Isar, Abteilung für Hämatologie, Müchen, F.R.G. §St. Elisabethen-Krankenhaus, Ravensburg, F.R.G., ||Zentrum der Inneren Medizin, Abteilung für Hämatologie/Onkologie, Marburg, F.R.G. and ¶Medizinische Hochschule, Abteilung für Hämatologie, Hannover, F.R.G.

**Abstract**—*Forty-six patients with non-small cell lung cancer were treated with a combination of* cis-*platinum,* 90 mg/m² *i.v. on day* 1 *and VP* 16-213, 100 mg/m² *i.v. on days* 1, 3 *and* 5. *The overall remission rate was* 22%, *with a median duration of* 7 months. *Squamous cell and large cell undifferentiated carcinomas responded in* 27 *and* 22% *of patients, and seven patients with adenocarcinoma did not respond to chemotherapy. Survival was* 7 months *for all patients,* 11.5 months *for responders* (7–27+), 8.5 months *for patients with stable disease* (3–27+) *and* 5 months *for progressive tumours* (1–9). *Prognosis was adversely influenced by a performance status of less than* 80%, *a weight loss of more than* 10 kg *during the last* 3 months *before start of treatment and a radiologically demonstrable 'major' atelectasis (collapse of at least one superior or inferior lobe of the lung). Only one out of* 31 *patients with one or more poor prognostic factors came into remission. In contrast, nine out of* 15 *patients without poor prognostic factors showed objective tumour regression* (60% *remission rate). Stage and age did not affect the results. Haemotologic and renal toxicity were mild, but poor subjective tolerance (nausea, vomiting, loss of appetite) was prominent.*

## INTRODUCTION

THE DIAGNOSIS of non-small cell bronchogenic carcinoma is most frequently established in an unresectable advanced stage [1, 2]. The high incidence of disseminated surgically incurable tumors requires effective chemotherapy regimens. Based on the generally poor results with conventional chemotherapy, investigations have concentrated on the development of new agents. Encouraging results have been reported in recent trials with *cis*-platinum (DDP) and VP 16-213 (etoposide) [3, 4]. High-dose DDP produced an overall response rate of 24% in previously untreated patients, with a slight advantage for adenocarcinomas [2, 5, 6]. The cumulative response rate for VP 16-213, a semi-synthetic epipodophyllotoxin derivative, is about 19% [7–9]. However, results in patients with squamous cell cancer were slightly superior to those achieved in adenocarcinomas (25 vs 12%) [7]. Evidence of a possible synergistic antineoplastic effect of both drugs has been reported in murine tumors [10]. We therefore designed a phase II clinical trial to assess the antineoplastic activity of the two-drug combination DDP + VP 16-213 in all histologic types of non-small cell lung cancer (NSCLC). Preliminary results have already been published elsewhere [11].

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## MATERIALS AND METHODS

Since January 1980, 51 patients with histologically confirmed squamous cell or large cell undifferentiated carcinoma or adenocarcinoma of the lung were entered into the study. Evaluable patients were required to have received at least two complete cycles of chemotherapy with adequate documentation of the measurable lesions. Thus 46 patients were evaluable. Their characteristics are outlined in Table 1. The median age was 59 yr

*Table 1. Characteristics of the patients*

| | |
|---|---|
| Age (yr), median | 59 (41–67) |
| Male | 40 |
| Female | 6 |
| Performance status (PS) (%), median | 80 (60–100) |
| Limited disease | 14 |
| Extensive disease | 32 |
| Histology | |
| squamous cell carcinoma | 26 |
| adenocarcinoma | 7 |
| large cell, undifferentiated carcinoma | 13 |
| Weight loss (in the last 3 months) (kg) | |
| <5 | 16 |
| 5–10 | 20 |
| >10 | 10 |
| Atelectasis* | 12 |

*See text for explanation.

and the mean performance status according to the Karnofsky scale was 80%. Fourteen patients had 'limited disease' and thirty-two 'extensive disease'. Limited disease was characterized by one-side intrathoracic lesions with possible infiltration of the mediastinal lymph nodes but without pleural effusions, vena-cava-superior syndrome, paralysed recurrence nerve and no 'major' atelectasis, i.e. collapse of at least an inferior or superior lobe of the lung. Criteria for 'extensive disease' were the appearance of one of these symptoms or distant metastases.

Concerning the histologic type, squamous cell carcinoma was most frequent (26/46 cases), followed by large cell undifferentiated carcinoma and adenocarcinoma (Table 1). Thirty patients had a weight loss of more than 5 kg during the last 3 months before diagnosis was established. Twelve patients presented a radiologically demonstrable 'major' atelectasis of the lung. Two patient had received previous irradiation but none prior chemotherapy. Etoposide, 100 mg/m$^2$, was administered intravenously over 30–60 min on days 1, 3 and 5. *cis*-Platinum, 90 mg/m$^2$, was given i.v. on day 1 with enforced diuresis using 3 l/m$^2$ saline. Treatment was repeated after a 4-week interval.

Therapeutic responses were defined as follows: complete remission (CR) was the disappearance of all evidence of tumor. Partial remission (PR) was coded when the sum of the products of the two greatest perpendicular diameters of all measurable lesions decreased by more than 50% for at least 4 weeks. A tumour regression of less than 50% was defined as stable disease or no change. The measurement of tumour size was not possible in all cases with a 'major' atelectasis due to the difficulties in distinguishing between the tumour and the related collapse of the lung. As suggested by Eagan *et al.* [12], the resolution of the atelectasis was therefore accepted as a valid criterion for tumour response.

Survival and duration of remission were recorded from the first day of treatment. The statistical significance of observed differences in remission rates was assessed by Fisher's exact test, and for the difference in survival the Kaplan–Meier test [13] and the Gehan test [14] were performed.

## RESULTS

### *Toxicity*

Nausea, vomiting, loss of appetite and alopecia occurred in all patients. In most cases these individual signs of toxicity, especially prolonged inappetence, were severe. Bone marrow toxicity was generally mild, involving erythropoiesis predominantly. A progressive fall in creatinine clearance was observed in three patients, but serum creatinine did not rise above 2 mg/dl. In one patient platin-induced signs of ototoxicity occurred (Table 2).

*Table 2. Side-effects in 37 fully evaluable patients (%)*

| | |
|---|---|
| Haemoglobin decline >2 g/dl | 31 (86) |
| Blood transfusions necessary | 10 (27) |
| White cell count | |
| $<2 \times 10^9$/l | 5 (13) |
| $<1 \times 10^9$/l | 2 (5) |
| Platelets | |
| $<100 \times 10^9$/l | 6 (16) |
| $<50 \times 10^9$/l | 3 (8) |
| Serum creatinine >1.5 mg/dl | 3 (8) |
| Irreversible renal function impairment | 2 (5) |
| Ototoxicity | 1 (2) |

### *Remissions*

Overall, ten patients (22%) experienced complete or partial remission (1 CR and 9 PR). The CR was achieved in a patient presenting only lymph node metastases as the measurable tumour manifestation. Squamous cell carcinoma and large cell undifferentiated carcinoma responded with similar remission rates (Table 3). Patients with high performance status (80–100%) entered remission more often than those with lower performance status, the difference being statistically significant ($P < 0.02$). The prior weight loss seemed to influence tumour response because none of the ten patients, who lost more than 10 kg before start of the treatment, showed an objective tumor regression (Table 3). In twelve patients presenting a 'major' atelectasis no tumour response was observed, eight of them even having a progression of the carcinoma. The difference between the two groups with and without a collapse of a lobe of the lung was statistically

significant ($P < 0.03$). At least one of the three poor prognostic factors described above was noted in 31 of 46 patients; only one of them did respond to chemotherapy. In contrast, nine remissions occurred in 15 patients without poor prognostic factors (60%). The difference was statistically highly significant ($P < 0.001$). The overall response rate appeared to be independent of age and tumour stage (Table 3). The afore-mentioned poor prognostic clinical features occurred in 50 or 55% of the patients with limited or extensive disease respectively.

*Duration of response and survival*

The median remission duration was 7 months. All 46 patients had a median survival of 7 months. Responders (CR and PR) survived a median time of 11.5 months; this was significantly superior to the median 5 months time for patient with progressing carcinomas ($P < 0.001$), but compared to the median 8.5 months of those with stable disease, no statistical significance was demonstrable ($P > 0.08$). The duration of survival (9 months) for patients without a 'major atelectasis' appeared to be significantly longer than that for patients with a collapsed lobe of the lung (5 months) ($P < 0.02$). Comparing patients presenting one or more clinical features of poor prognosis (Karnofsky status of less than 80%, weight-loss of more than 10 kg within 3 months, 'major atelectasis') to those without negative prognostic factors differences as regards tumour response (60 vs 3%) and median survival (10 vs 4 months) were statistically significant ($P < 0.001$ for both).

All the patients having progressive disease died during the period of observation. In all, seven patients are still alive: three patients since 5, 9 and 14 months and four patients—two responders and two with stable disease—for more than 2 yr after start of treatment.

*Table 3. Response to the chemotherapy*

| | No. of patients | CR+PR (%) | NC | PGR |
|---|---|---|---|---|
| All patients | 46 | 10(22) | 16 | 20 |
| Squamous cell carcinoma | 26 | 7(27) | 8 | 11 |
| Adenocarcinoma | 7 | 0(—) | 5 | 2 |
| Large cell carcinoma | 13 | 3(23) | 2 | 8 |
| PS ≥ 80% | 27 | 9(33) | 8 | 10 |
| PS < 80% | 19 | 1( 5) | 8 | 10 |
| Limited disease | 14 | 3(21) | 5 | 6 |
| Extensive disease | 32 | 7(22) | 11 | 14 |
| Weight loss (kg) | | | | |
| <5 | 16 | 6(38) | 9 | 1 |
| 5–10 | 20 | 4(20) | 6 | 10 |
| >10 | 10 | 0(—) | 1 | 9 |
| Atelectasis | 12 | 0(—) | 4 | 8 |
| Age (yr) | | | | |
| <60 | 24 | 5(21) | 8 | 11 |
| ≥60 | 22 | 5(23) | 8 | 9 |

*Table 4. Remission duration and survival* (months)

| | Median | Range |
|---|---|---|
| Remission duration | 7 | 4–27+ |
| Survival | | |
| all patients | 7 | 1–27+ |
| CR + PR | 11.5 | 7–27+ |
| NC | 8.5 | 3–27+ |
| PGR | 5 | 1–9 |

## DISCUSSION

The systemic treatment of advanced non-small cell lung cancer with DDP and VP 16-213 either in single drug therapy or combination chemotherapy has produced very different results. Response rates varied in a range from 8% to 55%. Overall remission rates with DDP single agent therapy have been obtained in 8% [5] to 26% [6]. About 9% [9] to 19% [7] response rates have been reported with VP 16-213 used as a single drug. Combinations containing both drugs in different dose and schedule produced remissions in a range from 33% to 55% [4, 15–19] with a median remission duration from 3 [16] to 7 [4, 15] months.

Our major finding was the fact that tumour response and survival were a function of certain prognostic factors. These characteristics, which substantially influenced the remission rate and the median survival, were a reduced performance status of less than 80%, a weight-loss of more than 10 kg during the last 3 months before starting treatment and a 'major' atelectasis of the lung, i.e. a collapse of a superior or inferior lobe demonstrable in chest roentgenogram. Among our 46 patients only 15 presented none of these poor prognostic factors. In this selected group nine patients responded to chemotherapy, i.e. had a remission rate of 60%. The difference to the overall response rate of 22% is statistically significant ($P < 0.001$). All the patients surviving for more than 2 yr belong to this group.

Usually, the frequency of response to chemotherapy is reported as higher in patients with limited disease [3, 4, 7, 16–20]. Surprisingly, in our study a difference in remission rate for limited vs extensive disease could not be demonstrated. A possible explanation for this discrepancy may lie in the fact that neither limited nor extensive disease consists of a homogenous group of patients. The frequency of poor prognostic

factors in these two clinical categories may therefore vary considerably among the different studies. In this trial the distribution of negative prognostic features was similar in patient with limited or extensive disease (50 vs 55%). The patient population entered into this trial obviously was a negative one, largely (68%) consisting of patients presenting one or more poor prognostic factors. It remains speculative whether a negative selection of patients occurred. However, a possible selection of patients with far-advanced progressive tumours could be related to a widespread scepticism towards a chemotherapeutic approach to NSCLC, which is generally considered to be rather insensitive to cytotoxic drugs.

The median duration of tumour responses was rather short, comparable to previously reported results [4, 7, 15, 16]. The median survival of patients with objective tumour regression was not much superior to that observed in patients with stable disease (11.5 vs 8.5 months). This finding is already known from conventional chemotherapy trials and may be caused by an *a priori* less malignant growth of the tumour [11, 20]. This hypothesis is additionally confirmed by the fact that in two of four patients surviving for more than 2 yr only stable disease was achieved.

It is yet to be resolved whether an increased dose of DDP and VP 16-213 or a different schedule would improve our rather disappointing results. DDP 90 mg/m$^2$ seems to be sufficient, since Gralla *et al.* [16] observed similar remission rates with either high- or low-dose *cis*-platinum (120 vs 60 mg/m$^2$). However, remission duration and survival of responding patients are prolonged by high-dose *cis*-platinum [16]. Subjective toxicity of the regimen was prominent. In most cases nausea, vomiting and a prolonged loss of appetite were severe. Comparing the subjective intolerance with the overall remission rate obtained in this trial, we feel that the combination DDP and VP 16-213 cannot generally be recommended for the treatment of advanced NSCLC. But it must be pointed out that a high remission rate (60%) was achieved in certain patients who did not share any of the poor prognostic factors. Therefore the combination of *cis*-platinum and etoposide can be of benefit in good-risk patients.

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