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A phase II study of carboplatin and vincristine in previously treated patients with small-cell lung cancer

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Summary. A total of 28 previously treated patients with small-cell lung cancer were treated at relapse with 400 mg/m^2 carboplatin and 2 mg vincristine on days 1 and 8, every 4 weeks. Ten partial responses (PRs) (37%) but no complete responses (CRs) were seen. Median survival after the start of second-line treatment was 120 days (range, 39–503 days). Toxicity of this regimen was moderate, including WHO grade 3/4 myelosuppression in 26% of courses (n = 66). Eight PRs were seen in a subgroup of 22 patients who relapsed <3 months after first-line treatment. The responses seen in this group of patients may be due to the absence of cross-resistance between the regimens used.

Introduction

Small-cell lung cancer (SCLC) is a rapidly progressive and ultimately fatal disease. Combination chemotherapy is the treatment of choice, resulting in response rates of up to 95%; however, only 5%–15% of the patients with limited disease (LD) survive beyond 5 years [8], and patients with extensive disease (ED) are rarely cured [10, 12]. This depressing fact is caused by the development of resistance to the initially effective drugs in relapsing patients. Therefore, there is a great need for active second-line combinations of cytotoxic agents.

Carboplatin (CBDCA) is a second-generation platinum analogue with little evidence of nephrotoxicity at the dose levels used in phase II studies [19]. Compared with its parent compound, cisplatin, it is less emetogenic, neuro- and ototoxic, although myelosuppression (particularly thrombocytopenia) was found to be dose-limiting [2, 3, 6]. In contrast to cisplatin [4], carboplatin given either as a single agent or in combination chemotherapy has shown high activity against SCLC, with response rates ranging from 62% to 95% in previously untreated patients [1, 9, 16, 18].

In this study we report on the efficacy and toxicity of carboplatin given in combination with vincristine in previously chemotherapeutically treated patients with SCLC. The latter drug was selected for its non-myelosuppressive character.

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Patients and methods

Between June 1986 and October 1988, 28 consecutive patients were entered in the study. Eligibility criteria included histological proof of SCLC and initial WBC of $>3.0\times10^9$/l, platelet count of $>100\times10^9$/l, a haemoglobin level of >6.8 mmol/l (unless lower values were caused by bone marrow involvement), a serum creatinine value of <120 μmol/l a bilirubin level of <25 μmol/l, and no sign of CNS metastasis. Informed consent was obtained from all patients according to local medical ethical committee regulations.

The patients' characteristics are shown in Table 1. Their median age was 62 years (range, 46–77 years). At the start of chemotherapy, 8 patients had LD (i.e., confined to one hemithorax and the supraclavicular nodes) and 20 had ED (i.e., beyond these borders). All patients had relapsed after chemotherapy. First-line treatment consisted of oral etoposide (E) alone for 10 patients, and for the 18 others it comprised i.v. cyclophosphamide (C), doxorubicin (D) and E combination chemotherapy. Responses to first-line treatment are also listed in Table 1. A total of 15 patients had shown a tumor relapse during induction treatment, i.e. within 1 month after the last course of induction chemotherapy; 7 patients had a treatment-free interval of 1–3 months, whereas in 6 cases it amounted to >3 months (Table 1).

In all 400 mg/m^2 carboplatin was dissolved in 250 ml 5% glucose and given as a 30-min i.v. infusion on day 1; 2 mg vincristine was given by bolus injection on days 1 and 8. Courses were repeated every 4 weeks until disease progression for a maximum of five cycles. Dose adjustments were made for myelosuppression (carboplatin) or neurotoxicity (vincristine).

Toxicity and response were measured according to WHO criteria [21] on day 21 after the start of every course. A complete response (CR) was defined as the disappearance of all measurable and evaluable lesions; a partial response (PR) was a reduction of >50% in the product of the greatest tumor diameter and its perpendicular for all measurable lesions. The term stable disease (SD) was applied if there was a decrease of <50% in measurable disease or an increase of <25% in tumor size. Progressive disease (PD) was defined as an increase of >25% in the

Table 1. Patient characteristics

	Patients (*n*)
Men : Women	26 : 2
Median age (range)	62 years (46–77)
LD : ED	8 : 20
ECOG performance status at start of therapy:	
0	2
1	7
2	8
3	10
4	1
Time off first-line treatment:	
<1 month	15
1–3 months	7
>3 months	6

product of perpendicular diameters of measurable lesions or the occurrence of any new lesions. Survival was measured from the start of second-line treatment. Patients were considered evaluable for survival if they completed at least one cycle of chemotherapy.

Results

Response and survival

No measurable or evaluable tumor localisations were found in 1 patient, leaving 27 cases evaluable for response. There were no CRs (Table 2). Ten patients had a PR (37%), including eight (36%) in the group that relapsed within 3 months after induction treatment. Ten patients had SD (37%), including two who had marked diminishment of pleural fluids and showed subjective improvement without fulfilling criteria for response. Of the seven patients who had PD, three died during the first cycle of chemotherapy due to tumor progression. The median survival (MS) for the whole group (25 evaluable patients) was 120 days (range, 39–503 days). The MS for the 22 patients who relapsed within 3 months after induction chemotherapy was 126 days (range, 53–503 days).

Table 2. Response to first-line treatment (FLT) and to carboplatin-vincristine (CV) combination

FLT (number of patients)	Response to FLT:			Response to CV:			
	CR	PR	SD	PR	SD	PD	NE
CDE (5)	1	4	–	2	1	2	–
CDE (13)[a]	1	11	1	4	5	4	–
E (1)	–	1	–	–	–	–	1
E (9)[a]	1	6	2	4	4	1	–

a Relapsed during treatment or within 3 months after off first-line chemotherapy C, cyclophosphamide; D, doxorubicin; E, etoposide

Toxicity

The total number of courses was 66 (median, 3). Thrombocytopenia and leucocytopenia of WHO grade 3/4 occured in 26% of courses. Reduction of the carboplatin dose was necessary in three patients. Peripheral neuropathy was seen in 13 patients, leading to a reduction of the vincristine dose in 8 cases. Symptomatic therapy for nausea and vomiting was given to all patients, usually with fair success, as grade 2 gastrointestinal toxicity was seen in only 16% of courses. None of the patients had a significant rise in serum creatinine levels, and none complained of hearing loss.

Discussion

Postmus et al. [14] have reported a total response rate of 62% with 13% CRs in a group of previously untreated patients given the same regimen used in the present study. In previous studies of carboplatin given as a single agent in pretreated patients, response rates varied between 0 and 19% [17, 22]. Our results show that the combination of carboplatin and vincristine is an active regimen in pretreated patients with SCLC.

Of particular interest is the 37% response rate in this group of pretreated patients. As Vincent et al. [20] have pointed out, disease progression after first-line chemotherapy does not necessarily indicate clinical drug resistance, as their patients responded to rechallenge with the same regimen that had been used as initial chemotherapy. The duration of a primary response might be of paramount importance for the results of second-line treatment; all patients reported by these authors had durations of response of at least 3 months (range, 3–30 months). After a treatment-free period of at least 14 weeks, Giaccone et al. [7] re-treated patients with the same regimen that had been used as induction chemotherapy; they reported 2 CRs and 4 PRs in a group of 13 selected patients.

Finally, Postmus et al. [13] found that patients whose first response lasted more than 34 weeks had a significantly higher probability of achieving a second response than did patients whose first response lasted <34 weeks. Also, the response duration after second-line treatment was clearly influenced by the time off treatment. From these data it therefore seems reasonable to consider patients who relapse within 3 months after treatment as being clinically resistant to the initial chemotherapy. Consequently, in this group of patients it is not necessary to demonstrate resistance to the initial chemotherapy before evaluating potentially non-cross-resistant regimens [20].

Because 22 of the patients in the present study relapsed during or within 3 months after induction chemotherapy, the responses seen in this group may be due to the absence of cross-resistance between the drugs given initially and those given at relapse. One might argue that responses seen after single-agent, first-line chemotherapy, i.e. E alone, are not surprising. However, the MS after second-line treatment with carboplatin and vincristine was only slightly worse for patients initially treated with combination chemotherapy, i.e. CDE, than for the first group. The MS for patients who received E alone as first-line treatment was 136 days (range, 60–503 days); for the group receiving CDE, it amounted to 116 days (range, 53–362 days).

A disappointing feature of the responses seen in this group of patients is that they were neither complete nor of long duration. This is common to almost all studies of second-line chemotherapeutic treatment of SCLC patients. The prognosis for patients with SCLC is probably denominated by the most resistant cell clones in a given tumor. Completely non-cross-resistant regimens are needed to eradicate these cell clones as well, e.g. regimens comparable with the alternating regimens MOPP/ABVD in Hodgkin's disease [15]. For SCLC, alternating chemotherapy has thus far been disappointing. However, most studies that have been reported used regimens that had not been sufficiently evaluated for their supposed non-cross-resistance [11]. From the present results, it is obvious that carboplatin is a good candidate for use in an alternating regimen with CDE. This is supported by the fact that CDE produces responses in patients who relapse on carboplatin-based regimens; the EORTC lung cancer study group reported 14 major responses in 29 patients previously treated with the latter regimens [5].

As anticipated, toxicity of the regimen predominantly involved myelosuppression, especially thrombocytopenia. However, there were no toxic deaths and only one patient had to be hospitalised due to bleeding episodes. None of the patients experienced aplasia-related sepsis. Dose reductions were undertaken only a few in patients. Nausea and vomiting were seen in the majority of patients and usually responded to simple anti-emetic regimens. No evidence of nephrotoxicity was seen as measured by serum creatinine levels. Neurotoxicity, probably due to vincristine, was encountered in 13 patients.

In summary, this study shows that the combination of carboplatin and vincristine is an active regimen in pretreated patients with SCLC and may be – partially – non-cross-resistant to CDE or E alone. The toxicity of this regimen is moderate.

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