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Carboplatin and etoposide in advanced lung cancer: – a phase I study

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Summary. This phase I study was carried out to determine the maximal tolerated dose of carboplatin (Car) together with a fixed dose of etoposide (E) and to recommend the optimal dose for a phase II study. The dose of E was 100 mg/m^2 given i.v. on days 1–3, and the starting dose of Car was 200 mg/m^2 given i.v. on day 1. The dose was escalated until WHO grade 4 toxicity developed after two treatment cycles in more than one-third of the patients. A total of 33 patients with advanced lung cancer entered the trial. The maximal tolerated toxicity of the combination was reached at a dose of 500 mg/m^2 Car. Myelosuppression was moderate, and hematological toxicity of WHO grade 4 was encountered in one of five patients at 475 mg/m^2 and in two out of five patients at 500 mg/m^2. The main toxic effects were leucopenia and thrombocytopenia. The frequency of treatment-related infections was low and no deaths were caused by treatment. There was a significant overall correlation between the platelet nadir and creatinine clearance. One complete response and three partial responses were achieved after two treatment cycles. Based on the results of the present study, the dose of carboplatin (combined with 100 mg/m^2 eposide given on days 1–3) recommended for phase II studies is 450 mg/m^2.

Introduction

Carboplatin (Car) is a new platinum compound that shows antitumor activity against lung cancer as a single agent [15] and in combinations [2, 11, 13, 14, 18] with acceptable toxicity. Etoposide (E), a semisynthetic derivative of podophyllotoxin, is one of the most active drugs against small-cell lung cancer [1, 16]; activity has also been demonstrated in non-small-cell lung cancer [4]. In lung cancer patients, some promising results have been obtained using a combination of carboplatin and etoposide [2, 7, 12, 14]. There is some evidence that this combination has a synergistic antitumor effect in experimental animal tumors [12]. Despite its high primary activity, only a short duration of response has been noted; its low toxicity indicates that the doses used may be too small and that the optimal Car dose in this combination has not been reached. The aim of this phase I study was to find the optimal dose of Car to be delivered in combination with 100 mg/m^2 E given i.v. on days 1–3.

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Patients and methods

Patients with histologically or cytologically proven extensive lung cancer were eligible for the study. No previous radiotherapy or cytotoxic chemotherapy was allowed; moreover, tumors had to be evaluable, patients were required to be <75 years of age, and their Karnofsky performance status had to be ≥60. Patients with active non-malignant diseases were excluded. The pretreatment peripheral blood leucocyte count required for eligibility was $\geq 4\times10^9$/l; the platelet count, $\geq 100\times10^9$/l; and the serum creatinine clearance, ≥0.9 ml s^{-1} 1.73 m^{-2}.

The trial was carried out in accordance with the principles of the Helsinki Declaration. The protocol was approved by the local ethical committee, and informed consent was obtained from all patients before their admission to the trial.

At the beginning of the study all patients underwent determinations of white blood cell (WBC) and platelet counts and hemoglobin levels, a whole blood examination, liver function tests (serum alkaline phosphatase, glutamyltransferase, bilirubin), determination of serum electrolyte (sodium, potassium, calcium, magnesium, chloride) and serum creatinine levels, bone marrow aspiration, a chest X-ray, bronchofiberoscopy, and an ultrasound examination of the upper abdomen. Computed tomography of the brain and bone scans were performed only if clinically indicated. The laboratory tests were repeated before each treatment cycle; WBC and platelet counts and hemoglobin measurements were done weekly during the treatment.

The dose of E was fixed at 100 mg/m^2 given i.v. on days 1–3 and the dose of Car was escalated, the starting dose being 200 mg/m^2 given i.v. on day 1. Each dose level included at least three patients, and the regimen was repeated every 28 days. The Car dose was increased until the maximal tolerated dose (MTD) was reached. The limit for maximal tolerated toxicity was grade 4 (WHO) for leukopenia ($<1\times10^9$ cells/l),

Table 1. Hematological toxicity after two chemotherapy cycles at different dose levels

Carboplatin dose (mg/m^2)	200		300		350		400		450		475		500	
WHO grade	3	4	3	4	3	4	3	4	3	4	3	4	3	4
Leucopenia	1	–	–	–	2	–	–	–	1	–	1	1[a]	3	–
Thrombocytopenia	–	–	–	–	–	–	1	–	1	–	1	1[a]	2	2
Anemia	1	–	–	–	–	–	–	–	–	–	1	–	–	1
Patients (n) at each dose level	4		3		5		4		7		5		5	

Data represent the number of patients developing WHO grades 3 or 4 hematological toxicity

[a] Occurred in the same patient

Table 2. Leucocyte and platelet counts and the median week at which nadir values occurred during two chemotherapy cycles at different dose levels

Carboplatin dose (mg/m^2)		200	300	350	400	450	475	500
Mean leucocyte nadir ($\times 10^9$/l)		4.0	4.4	3.1	3.2	3.6	3.2	3.4
Mean platelet nadir ($\times 10^9$/l)		231	192	188	112	151	60	94
Median week of nadir	Leucocytes	2	3	2	3	2	3	2
	Platelets	2	2	2	2	3	2	2
Patients (n) at each dose level		4	3	5	4	7	5	5

thrombocytopenia ($<25\times10^9$ platelets/l) and intractable vomiting, and that for creatinine clearance was <0.5 ml s^{-1} 1.73 m^{-2}. All patients for whom at least one hematological follow-up value could be obtained were evaluated for toxicity. If toxicity reached the above limits after two treatment cycles in more than one-third of the patients, this dose was considered to be the MTD. The optimal dose was defined to be 90% of the MTD [9]. Both drugs were infused in 500 ml 5% glucose over 1 h without previous hydration. Antiemetics were not used prophylactically but were given during subsequent courses if clinically indicated.

Tumor responses were evaluated according to WHO criteria [10]. Patients eligible for response were those who had received two cycles of chemotherapy; treatment was continued if no tumor progression was detected. Correlations between the nadir hematological values and the values for parameters of renal function were calculated using bivariate scatter plots. The deviation of values is expressed as the standard deviation.

Results

A total of 33 patients were admitted to the trial before the MTD of Car had been reached. They included 30 men and 3 women with a mean age of 61 years (range, 41–74 years) and a mean Karnofsky performance status of 80±11 (range, 60–100). In all, 23 had non-small-cell lung carcinoma and 10 had small-cell lung cancer.

Toxicity

Overall, 31 patients were evaluable for toxicity; 2 subjects were not evaluable since they died before the first weekly hematological control could be obtained. The cause of death was brain metastasis with cerebellar hemorrhage on day 4 in one patient and pericardial carcinomatosis and pulmonary embolism on day 3 in the other.

The frequency of myelosuppression increased with escalation of the Car dose, as expected. The main hematological toxic effects were leucopenia and thrombocytopenia, with similar frequencies. At the different dose levels myelosuppression remained moderate and WHO grade 4 toxicity was detected four times during the study. The number of patients developing grades 3 and 4 toxicity at various dose levels is given in Table 1.

At a dose of 500 mg/m^2, two of five patients experienced grade IV myelosuppression (two cases of thrombocytopenia, one of which was combined with anemia). In addition, the platelet nadir in a third patient was 28, which was near the limit of grade 4 toxicity. This dose level was thus considered to be the MTD and no more patients were entered the trial. According to our definition, the optimal dose of Car in this combination was 90% of 500 mg/m^2, i.e. 450 mg/m^2.

The median leucocyte nadirs most commonly occurred 2–3 weeks after administration of the drugs, and platelet nadirs were most commonly observed after 2 weeks (Table 2). However, at 1 week after drug administration the leucocyte nadir was detected in five patients; that of platelets, in seven subjects; and that of hemoglobin, in nine cases. In three cases the Car dose was reduced by 30% in the second cycle due to myelosuppression. Red blood cell transfusions were given if the hemoglobin value was <100 g/l; a platelet transfusion was given once due to grade 4 thrombocytopenia.

Altogether, four patients died before the start of the second treatment cycle. Two patients with adenocarcinoma died of cerebral metastases. A 71-year-old patient died of exacerbation of cardiac failure 3 weeks after the first drug administration; autopsy revealed no signs of possible drug-related toxicity in myocardial, hepatic or renal tissues. One patient with epidermoid carcinoma died 2 days after the first treatment; autopsy revealed pulmonary emboli and diffuse pericardial metastases of adenocarcinoma. The deaths were not considered to be treatment-related. Two patients were removed from the study after the first chemotherapy cycle: one, due to prolonged pneumonia and disease progression; the other, after a simultaneous decrease in leucocytes and thrombocytes (WHO grade 4) that lasted 7 days.

Treatment-related infections occurred in four patients. Two of these reactions were slight, involving one case of pneumonia (Car dose, 475 mg/m^2) and one of septicemia. Intravenous antibiotics were required in two patients.

The mean creatinine clearance did not change significantly during the treatments. The mean pretreatment value for all patients was 1.5 ml s^{-1} 1.73 m^{-2}. There was a significant ($P = 0.003$) correlation between the platelet nadir during any given treatment cycle and initial creatinine clearance (Fig. 1). Correspondingly, a significant ($P = 0.009$) negative correlation was found between platelet and

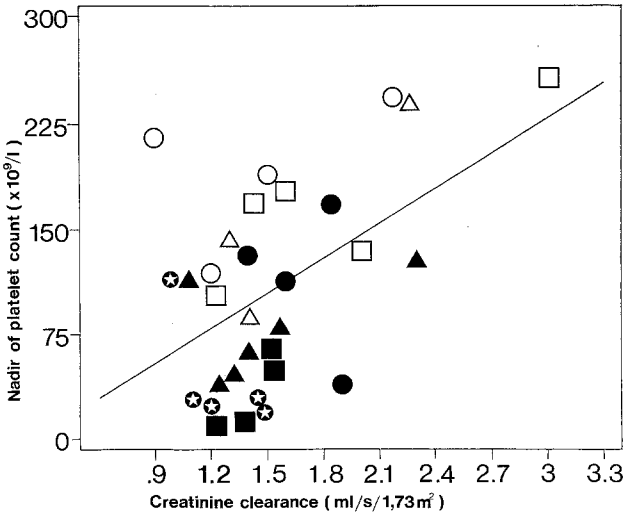

Fig. 1. The correlation ($r = 0.503$, $P = 0.003$) between creatinine clearance and platelet nadir. Values for all patients at various dose levels are included ($n = 32$): ○, 200 mg/m²; △, 300 mg/m²; □, 350 mg/m²; ●, 400 mg/m²; ▲, 450 mg/m²; ■, 475 mg/m²; ✪, 500 mg/m²

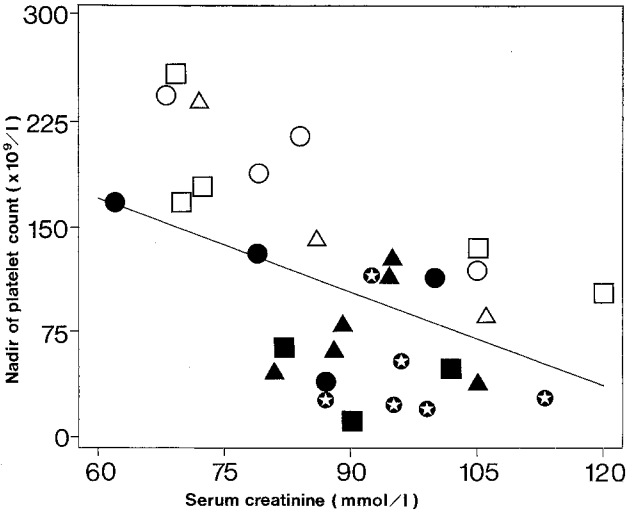

Fig. 2. The correlation ($r = -0.456$, $P = 0.009$) between serum creatinine and platelet nadirs. Values for all patients at various dose levels are included ($n = 32$): ○, 200 mg/m²; △, 300 mg/m²; □, 350 mg/m²; ●, 400 mg/m²; ▲, 450 mg/m²; ■, 475 mg/m²; ✪, 500 mg/m²

serum creatinine nadirs (Fig. 2). The correlation of nadir values for leukocytes vs creatinine clearance and serum creatinine were not significant ($P = 0.313$ and $P = 0.129$, respectively), and the same held true for hemoglobin ($P = 0.095$ and $P = 0.051$, respectively).

Grade 3 vomiting occurred in 15 of 32 patients (47%) but did not seem to be dose-related. No intractable vomiting was noted. Mild alopecia occurred frequently, and grade 3 or 4 hair loss was observed in 14 patients (44%).

Of the 20 patients who received >2 cycles of therapy, 8 completed ≥ 6 courses. During cycles subsequent to the first two, only one case of grade 4 thrombocytopenia occurred in third cycle at a dose of 475 mg/m². Otherwise, there were no marked changes in myelosuppression, and no cumulative toxicity could clearly be detected at any dose level. Moreover, no marked changes in electrolytes were observed, although one case of hypomagnesemia occurred at a dose of 475 mg/m².

Response

At total of 27 patients were eligible for the assessment of response. After two treatment cycles, one patient with small-cell lung carcinoma (SCLC) achieved a complete response and three subjects showed partial responses (two cases of SCLC and one of adenocarcinoma). In 18 cases (64%) there was no change in the primary tumor or in metastases, and 5 patients showed tumor progression.

Discussion

Car has proved to be one of the most effective agents for the treatment of SCLC. In comparison with cisplatin, Car is less nephro-, oto- and neurotoxic [6]. It does not require prior hydration and can thus be given on an out-patient basis. Car has been used as a single agent at doses of 250–400 mg/m² in the treatment of SCLC [13, 15]. The overall response rate is 50%–60% for previously untreated patients and 0–19% for previously treated subjects. The combination of Car and etoposide (E) has been used in several phase II trials for the treatment of SCLC [2, 7, 14]. We could find only one phase I trial report on this combination, in which the recommended dose of Car for phase II studies was 325 mg/m² on day 1, given with a dose of 100 mg/m² E on days 1–3 [17]. In phase II studies, some of which were carried out before any phase I results were published, the Car dose has been 300 mg/m² given on day 1 or, divided, on days 1–3 [2, 7, 14]; the dose of E has been 100–120 mg/m² given on days 1–3.

The responses have been around 80% for limited SCLC and 50%–80% in extensive disease; the duration of response has been rather short [14, 18].

The results of the present study demonstrate that Car combined with E can be given monthly as a 1-h infusion. Myelosuppression was the major toxicity. The optimal Car dose was 475 mg/m², which is substantially higher than that reported by other investigators. Myelosuppression was found to increase gradually with dose escalation from 200 mg/m² upwards. The maximal tolerated toxicity of the combination Car-E was reached at a dose of 500 mg/m² Car. After two chemotherapy cycles, the non-hematological toxicity was only mild or moderate and vomiting was acceptable, which is a marked clinical advantage for this combination as compared with cisplatin. According to our results, no cumulative toxicity occurred.

In the phase I trial by Tueni et al. [17], the criteria of unacceptable toxicity was grade 3–4 myelosupression, and these authors recommended that the optimal dose of Car be 325 mg/m². In the present trial, toxicity was considered to be unacceptable if it surpassed the limits of grade 4 toxicity. There were no cases of grade 4 myelosuppression at a dose of 450 mg/m². One reason for the differences in the results is that most of the patients investigated by Tueni al. [17] had previously been treated, whereas all patients in the

present study had not undergone prior treatment. In the phase II trial by Bishop et al. [2], at a dose of 100 mg/m^2 given on days 1–3, grade 4 thrombocytopenia occurred in 11% of patients; however, the inclusion criterion for creatinine clearance was 0.7 ml/min, lower than that in our study.

Renal clearance appears to be the main route of excretion of Car. It is unlikely that this involves tubular secretion, since total and renal clearance values correlate significantly with glomerular filtration rate (GFR) [8]. Egorin et al. [5] have shown that the percentage of reduction in platelet count correlates highly and linearly with the AUC for ultrafilterable platinum in plasma. These authors also provided a formula for estimating the Car dose required to obtain a desired percentage of reduction in platelet count.

Retrospectively, we also used the formula proposed by Calvert et al. [3] to calculate the optimal dose of Car for each patient, as follows: total dose (mg) = target AUC × (GFR +25), where GFR is the glomerular filtration rate and AUC is the target area under the free-carboplatin plasma concentration versus time curve. The target AUC was chosen to be 7 mg/ml as suggested by the authors for previously untreated patients. Creatinine clearance (ml/min) was used for GFR, and the surface area of each patient was taken into account in the calculations. Most of the patients who received $\leq$450 mg/m^2 Car in the present trial would have received more had the formula been used, and it logically follows that those who were given >450 mg/m^2 would have received less. This is in line with the dose-escalation approach used in our phase I study.

We examined the severe myelosuppression (grades 3 and 4) caused by Car. Two patients who had received 500 mg/m^2 experienced grade 4 myelosuppression (both had thrombocytopenia; one also had anemia and the other, leucopenia). Had the above formula been used, they would have received (24%) less drug. In these two patients, grade IV toxicity might have been avoided had the formula been available. The attainment of grade 4 toxicity was inevitable in our study design, in which the occurrence of grade 4 myelosuppression was actually the end point of the trial. On the other hand, three patients experienced grade 3 toxicity at doses of 400 mg/m^2 (thrombocytopenia), 200 and 350 mg/m^2 (leucopenia) and 200 mg/m^2 (anemia), which were markedly lower (by 15.1%, 50.9%, 28.5% and 31.6%, respectively) than they would have been if the formula had been used. Thus, had the latter condition been fulfilled, the toxicity observed in these patients could have crossed the borderline between grade 3 and grade 4 toxicity.

Carrying out phase I trials using the traditional dose-escalation approach naturally involves ethical questions. The inclusion of only a few patients at each dose level does not give statistically valid reliability for the toxicity values obtained at each dose. On the other hand, the assignment of an excessively high number of subjects to each dose level would lead to suboptimal treatment of too many patients. By definition, one must also achieve maximal toxicity in two of three patients, which requires utmost care in the monitoring of subjects. Again, when the so-called optimal dose level is reached, defined in our study as being 90% of the MTD, a valid picture of toxicity (and response) can be obtained only from a large patient population – usually in a phase II study.

If a formula such as that presented by Calvert et al. [3] works, it would be a very clinical useful tool for evaluation of the optimal individual Car dose. One should be careful, however, when estimating optimal doses to be given in various combinations that have not previously been tested. GFR should be evaluated after a few cycles of cytotoxic treatment, as renal function can be impaired by such therapy. The authors recommend the use of the [^{51}Cr]-EDTA method, which might not be available in all oncology centers.

In the present study there was a significant correlation between creatinine clearance and nadir platelet count, and a similar negative correlation was found between platelet nadirs and serum creatinine concentrations (Figs. 1, 2). The correlations were calculated using values for all patients obtained at various doses. An increase in the number of patients at each dose level could possibly provide a basis for the creation of a formula that could calculate a Car dose using a known serum creatinine (or creatinine clearance) value and the maximal acceptable platelet nadir. It may be that the measurement of serum creatinine concentration before the initiation of a Car-containing regimen would be sufficient and that measurement of creatinine clearance could be omitted.

The low response rate obtained in this study reflects the overall resistance of non-small-cell lung tumors to chemotherapy [3]. The majority of tumors in our study were epidermoid carcinomas. On the other hand, the present investigation was a phase I study in which most of the patients actually received less than the optimal Car dose due to the design of the trial. A phase II study using the optimal dose recommended in the present study will eventually reveal the efficacy of the phase I dose. The optimal dose of Car recommended for phase II studies of the combination Car-E is 450 mg/m^2.

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