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Cisplatin–Carboplatin Therapy in Extensive Non-small Cell Lung Cancer: a Cancer and Leukemia Group B Study

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The response to cisplatin in non-small cell lung cancer (NSCLC) is limited by the renal and neurological toxicities of this agent. Carboplatin has modest activity in NSCLC and when given in conventional doses has a different spectrum of toxicity. Both drugs were administered to 76 eligible patients with advanced NSCLC. No patient had been previously treated with chemotherapy. Cisplatin 50 mg/m^2 and carboplatin 350 mg/m^2 were administered every 28 days until disease progression occurred. There was 1 complete response and the overall response rate among the 68 evaluable for response patients was 13%. Neither histological subtype nor initial performance status was a significant factor influencing response. Median survival was 5.1 months with significant differences based on initial performance status but not on histological subtype. Severe or life-threatening leukopenia and thrombocytopenia occurred in 23% and 36% of the 76 patients, respectively. There were 2 toxic deaths, 1 each due to infection and haemorrhage. The efficacy of this combination is not different from that of carboplatin alone, and the combination may be of greater benefit in patients with more responsive tumours than NSCLC.
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INTRODUCTION

CISPLATIN IS a major component of combination chemotherapy for lung cancer. Although there is a dose–response effect with cisplatin, toxicity has often limited dose escalation or administration of multiple courses [1].

Carboplatin is less emetogenic and does not usually cause the renal and neurological toxicities seen with cisplatin [2]. Carboplatin's dose-limiting toxicity is myelosuppression. Carboplatin has considerable activity in small cell lung cancer and modest activity in non-small cell lung cancer (NSCLC) [3–6].

Cisplatin and carboplatin have different pharmacodynamics and dose-limiting toxicities. Some tumours may not be cross-resistant to both agents [7]. The combination of cisplatin and carboplatin may therefore have a superior therapeutic index than higher doses of either drug alone. Based on available phase I data [8], a phase II study of cisplatin–carboplatin in combination in patients with extensive NSCLC has been done. Our study is one of several phase II trials of the Cancer and Leukemia Group B (CALGB) designed to screen new single agents or chemotherapy combinations in advanced NSCLC [9].

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PATIENTS AND METHODS

Patients with advanced, histologically documented NSCLC were eligible. All were stage 4 (M1) or 3B by virtue of either a malignant pleural effusion (T4) and/or N3 adenopathy in supraclavicular nodes. Patients with recurrent tumour (regardless of stage) following surgery or radiation therapy were also eligible. Other entry criteria included the presence of measurable or evaluable disease (pleural effusion was neither measurable nor evaluable), CALGB performance status 0–2, no previous administration of chemotherapy and recovery from the toxicity of previous surgery or radiotherapy. Adequate haematological, hepatic and renal function (creatinine clearance over 60 ml/min and serum creatinine below 1.8 mg/dl) were required. Patients with previous or concomitant malignancy (other than *in situ* cervical or basal cell skin cancer), other serious medical or psychiatric problems that might interfere with treatment or an expected survival of less than 2 months were excluded. Written informed consent was obtained from all patients. Initial imaging included a chest radiograph, computed tomography of the thorax and upper abdomen to the level of the adrenals and a bone scan.

Each patient was hydrated with 1 litre of dextrose 5% in half-normal saline over 1–2 h. Carboplatin 350 mg/m^2 was then administered by intravenous bolus; then cisplatin 50 mg/m^2 was infused over 20–30 min and another 500 ml of fluid administered over 2 h. Chemotherapy was repeated every 28 days with dose reductions based on haematological, renal and neurological toxicities. There was no dose escalation.

Patients with brain metastases were given radiotherapy before registration on protocol. Those who subsequently developed brain metastases were not considered to have progressive disease. They were eligible to receive central nervous system radiotherapy and combination chemotherapy in which the dose of carboplatin was temporarily reduced to 250 mg/m^2.

Table 1. Patients' characteristics

No.	76
M/F	54/22
Median age (yr) (range)	62 (39–77)
Performance status	
0	28
1	27
2	21
Previous radiotherapy	35
Histology	
Squamous cell carcinoma	19
Adenocarcinoma	32
Large cell carcinoma	25

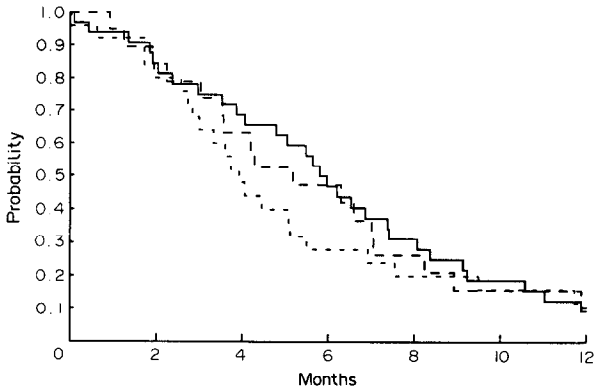

Fig. 1. Survival curves for patients with adenocarcinoma (——), squamous cell carcinoma (– – –) and large cell cancer (------). Overall median survival 5.1 months.

All patients received at least two courses of chemotherapy unless rapid progression occurred. Treatment was continued at the prescribed dose as long as progression did not occur. The need for radiotherapy to areas other than the central nervous system was regarded as evidence of disease progression.

The patients were evaluated for response and categorised as having complete response (CR), partial response (PR, measurable disease only), tumour regression (evaluable disease only) or stable/progressive disease (PD) with standard CALGB definitions. According to these definitions a CR or PR must last 4 weeks or more and tumour regression must last 8 weeks or more.

Patients who were ineligible or whose registration onto protocol was cancelled were excluded from analysis. The primary end-point of this study was response rate (CR, PR, tumour regression) within each of the histological subtypes (adenocarcinoma, squamous cell carcinoma and large cell carcinoma). The goal was to have 25 eligible patients with each subtype for evaluation of response. With this sample size, if the true response frequency was 15%, the probability of not seeing at least 1 response would be 0.0172.

The response frequencies were analysed by means of the Pearson χ^2 test for contingency tables. Survival was measured from the date of registration to the date of death from any cause or to the date of last follow-up. Survival and time to progression were estimated by the Kaplan–Meier method. The logrank test was used to evaluate differences in survival between groups.

RESULTS

80 patients were registered onto this study between April and September 1986. 3 patients were ineligible for the study (1 with stage 3A, another with performance status 4 and the third because of prior malignancy). A fourth patient was registered but subsequently cancelled due to rapid deterioration before any treatment was administered. The characteristics of the remaining 76 eligible patients are shown in Table 1. There were no significant differences in patients' characteristics between the three histological subtypes.

8 patients were considered unevaluable for response as they did not receive at least two cycles of therapy. 3 of the 8 were removed from treatment or refused therapy before any response/progression was documented; 2 others died of pneumonia, 1 had a cardiac arrest and 2 others died of pulmonary emboli. 1 of these 2 had a documented reduction of 50% or more in tumour size, but died before the 4 weeks required for designation as PR. The response rates of the 68 patients evaluable for response are shown in Table 2.

The overall response rate was 13%. 1 patient with squamous carcinoma had CR. There was no evidence for a difference in response rates among the three histological groups ($P=0.22$). Performance status within the range 0–2 (3 and 4 were ineligible) was not a significant factor for response since 4 (14%), 3 (11%) and 2 responders (10%) were performance status 0, 1 and 2, respectively ($P=0.61$).

Survival curves for all 76 eligible patients are shown in Fig. 1. The median survival was 5.1 months and the estimated 6 month survival was 41 (S.D. 6)%. There was no difference in survival among histological subtypes but there was a significant association between performance status and survival. Those with performance status of 2 survived a median of 3.6 months whereas those scored as 1 and 0 lived 6.3 and 6.6 months ($P=0.0009$).

The maximum toxicities experienced on treatment for all 76 patients are shown in Table 3. There were 2 treatment-related deaths, 1 due to haemorrhage and another because of infection.

Table 2. Response by histological subtype

Response	Adeno-carcinoma	Squamous cell	Large cell	Total
CR	0	1 (6%)	0	1 (1%)
PR/regression	4 (13%)	3 (18%)	1 (5%)	8 (12%)
Stable/PD	26 (87%)	13 (76%)	20 (95%)	59 (87%)
Total	30	17	21	68

*Table 3. Maximum toxicities (76 patients)**

	WHO Grade	
	III	IV
Leukopenia	19%	4%
Thrombocytopenia	25%	11%
Anaemia	28%	4%
Nausea/vomiting	9%	3%
Neurological	1%	0%
Renal	0%	0%

*1 patient had lethal infection and another died of haemorrhage.

Thrombocytopenia (platelets under 50 000/μl) occurred in 25% of patients whereas another 11% had counts below 25 000/μl. Severe or life-threatening leukopenia occurred in 23% of patients. There was a 28% frequency of mild renal toxicity (creatinine 1.3–1.8 mg/dl).

There was no instance of severe or life-threatening renal toxicity. 1 patient had moderate hearing loss; another had substantial worsening of pre-existing hearing loss and was removed from study. 1 patient, a 67-year-old non-insulin dependent diabetic, developed severe peripheral sensory neuropathy. Treatment was discontinued even though the patient had achieved PR.

DISCUSSION

Cisplatin 50 mg/m^2 plus carboplatin 350 mg/m^2 resulted in moderate but acceptable toxicity with platelets below 50 000/μl in 36% of patients. The greater myelotoxicity observed in our trial may reflect cumulative toxicity due to repeated courses of therapy in our patients compared with those of Trump *et al.* [8] who usually had only a single course of therapy. Although we did not observe significant nephrotoxicity or ototoxicity, these have been observed in a trial in which cisplatin 100 mg/m^2 plus carboplatin 300 mg/m^2 was administered each cycle [10]. Our response rate of 13% was disappointing but consistent with the 16% response rate in 6 patients with NSCLC studied by Trump *et al.* Unfortunately, the rate was similar to that (16%) for carboplatin 400 mg/m^2 alone in a previous CALGB study [3]. The combination may be of greater benefit in patients with more responsive neoplasms than NSCLC [10].

A phase I trial of cisplatin-carboplatin was tested by Trump *et al.* in 41 patients of whom 24 had received previous chemotherapy [8]. There was acceptable toxicity with cisplatin 50 mg/m^2 and carboplatin 350 mg/m^2. When the carboplatin dose was increased to 400 mg/m^2, the median platelet nadir was 44 000/μl. An increase of the cisplatin dose to 75 mg/m^2 (with carboplatin 280 mg/m^2) resulted in unexpected severe thrombocytopenia.

Cisplatin is active in patients with NSCLC in a dose-dependent manner—single-agent response rate of 35% at 200 mg/m^2 [4]. Unfortunately,the toxicity of cisplatin is prohibitive at this dose with disabling peripheral neuropathy and ototoxicity [1]. Nephrotoxicity also occurred in more than 30% of patients despite aggressive saline hydration [1]. Divided dose strategies designed to diminish these toxicities are being tested [11]. Carboplatin also has dose-dependent effect [12, 13]. In contrast to cisplatin, its primary dose-limiting toxicity is myelosuppression, with nephrotoxicity encountered at 800–1600 mg/m^2 and ototoxicity/neurotoxicity at doses over 1200 mg/m^2 [14]. Carboplatin was active in 9–16% of previously untreated patients with NSCLC in multicentre trials [3–6].

The pharmacokinetics, toxicities, efficacy and cross-sensitivity of carboplatin and cisplatin have been studied in detail. The pharmacology of these two agents is different [15]. Cisplatin is more avidly protein-bound and therefore, unlike carboplatin, it is not rapidly secreted in the urine. However, the two agents may have a final common pathway of chemical activation leading to formation of identical platinum–DNA adducts [16]. Theoretically, the combination of these agents might increase the total dose of platinum administered and enhance tumour cell kill, without producing the excessive toxicity encountered with higher doses of either drug alone.

There is conflicting evidence from studies on cell lines and human tumour xenografts in nude mice about cross-sensitivity and cross-resistance to cisplatin and carboplatin [17–20]. The combination has additive cytotoxicity on cell lines of small cell lung cancer, squamous cell carcinoma, and human T-cell lymphoblastic leukaemia [21–23]. Most patients with cisplatin-resistant ovarian carcinoma do not respond to carboplatin [13, 24]. Although the previous dose of cisplatin was often low, there are occasional responses to carboplatin in patients who did not respond to 100–120 mg/m^2 of cisplatin [24].

The combination of cisplatin and carboplatin produced a 13% response rate in patients with advanced NSCLC. The efficacy of this combination in NSCLC is no different from that of carboplatin alone. This combination may be of greater benefit in patients with more responsive neoplasma than NSCLC [10].

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Prediction of Superficial Bladder Cancer by Histoquantitative Methods

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A retrospective clinicopathological study was done of 136 T1 bladder cancer patients, mean follow-up 10 years. With interactive morphometry, mean nuclear area, mean standard deviation of nuclear area (SDNA) and the mean area of the 10 largest nuclei (NA10) were measured in biopsy specimens from primary tumours. Volume corrected mitotic index (M/V index) was estimated in the same sections. Histological grading was done according to WHO and clinical staging according to UICC. Progress in bladder cancer was observed in 26 cases. Progressing tumours had significantly higher M/V values ($P = 0.0038$) than tumours without progression. By χ^2 statistics NA10 ($P = 0.08$) and M/V index ($P = 0.0024$) were related to invasive potential. Tumours with high NA10 values ($P = 0.0065$) and high M/V index values ($P = 0.0104$) eventually metastasised. Nuclear area ($P = 0.0025$), NA10 ($P = 0.0053$), histological grade ($P = 0.0071$), NA ($P = 0.0563$) and M/V index ($P = 0.0979$) predicted bladder cancer-related survival, in that order. The recurrence rate or recurrence-free period were not related to histological indices. The results suggest the use of these morphometric features instead of histological grading in the prediction of T1 bladder tumours.
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INTRODUCTION

MOST DIAGNOSED bladder cancers are superficial and overall prognosis is good. However, bladder cancer has a high potential for recurrence and about one-sixth of initially superficial tumours develop into invasive recurrences [1]. The decision on treatment of superficial tumours is generally based on clinical stage [2] and histological grade [3, 4]. Subjective grading, however, is not reproducible [5, 6] and the prediction of recurrence and invasion in T1 bladder tumours is difficult and unsatisfactory with subjective grading [7]. Flow cytometry [8–12], mitotic activity [13], nuclear morphometry [8, 9, 14, 15], semiquantitatively assessed blood group antigens [12] and Lewis a antigen-related CA 50 [16] have been used to grade bladder cancer with promising results. Most of the studies with quantitative techniques have included all stage and grade categories and sub-

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