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Etoposide, carboplatin, cyclophosphamide and vincristine in previously untreated patients with small-cell lung cancer*

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Summary. The efficacy and toxicity of 120 mg/m^2 etoposide and 100 mg/m^2 carboplatin given i.v. daily $\times 3$ together with 750 mg/m^2 cyclophosphamide and 1.4 mg/m^2 vincristine given i.v. on day 1 (ECCO) in a regimen given every 28 days for 6 courses was assessed in 90 (40 limited stage, 50 extensive stage) previously untreated patients with small-cell lung cancer. Mediastinal irradiation using 50 Gy in 25 fractions was given to limited-stage patients without progression after 3 courses of chemotherapy. Cranial irradiation with 30 Gy in 10 fractions was given to all patients attaining a complete response (CR). Objective responses were seen in 83% [CR, 60%; partial response (PR), 23%] of patients with limited and 76% (CR, 22%; PR, 54%) of those with extensive disease. The median relapse-free survival for objective responders with limited disease was 13.4 months, with a median of 8.0 months for extensive-stage patients. The median relapse-free survival for patients achieving a CR was 13.4 months, with a median of 7.8 months for those undergoing a PR. The median survival was 13.3 months for patients with limited disease, with a median of 9.6 months for those with extensive disease. The median survival following a CR was 18.2 months, with a median survival of 9.9 months for those showing a PR. The combination was well tolerated, with either no nausea or nausea only (WHO grade 0 or 1) in 56% of patients and minimal mucositis, renal toxicity, neurotoxicity or ototoxicity. Neutropenia measuring $<1.0\times10^9$ WBC/l (WHO grade 3 or 4) was seen in 74% of patients, with two deaths due to infection occurring during neutropenia. Thrombocytopenia of $<50\times10^9$ platelets/l (WHO grade 3 or 4) occurred in 24% of patients. ECCO is a new, active, well-tolerated program for previously untreated patients with small-cell lung cancer.

Introduction

Combination chemotherapy in previously untreated patients with small-cell lung cancer has improved the median survival from 6 weeks to 7 months for extensive-stage patients and from 12 weeks to over 12 months for limited-stage patients [11, 14]. However, most patients relapse and die of their disease within 2 years of diagnosis. Thus, there is a need to identify more effective treatments that may improve response or survival or achieve current results with less toxicity.

Carboplatin (*cis*-diammine-1,1-cyclobutane dicarboxylate platinum(II), CBDCA, JM-8; NSC 241240) is a cisplatin analogue developed for its preclinical antitumour activity and the differences in its preclinical toxicology as compared with cisplatin [9, 10]. Phase I clinical trials [2, 16] revealed that myelosuppression, especially thrombocytopenia, was dose-limiting but that nephrotoxicity, neurotoxicity and ototoxicity were uncommon. Unlike cisplatin, carboplatin can be given in the presence of renal impairment, provided that modest dose adjustments are made [6].

Phase II trials [18] at the Royal Marsden Hospital, using a single i.v. bolus of carboplatin alone given every 4 weeks to patients with small-cell lung cancer, produced objective tumour response rates of 19% in pretreated patients and 60% in previously untreated patients. The two-drug combination of carboplatin and etoposide has produced high response rates in previously untreated patients with small-cell lung cancer [1, 19]. In the present phase II study, we built on our previous study of intensive carboplatin and etoposide by retaining those drugs at the full dose on the same schedule and adding cyclophosphamide and vincristine to develop a new, non-doxorubicin, four-drug combination.

Patients and methods

Patient eligibility. Patients with histologically or cytologically proven small-cell lung cancer who had received no prior chemotherapy or radiotherapy were eligible. Those presenting with central nervous system (CNS) disease or an Eastern Coperative Oncology Group performance status (ECOG PS) of 4 were excluded from the analysis. Eligible patients were required to have pretreatment peripheral blood neutrophil counts of $>1.5\times10^9$/l and platelet counts of $>100\times10^9$/l. Patients with renal impairment and a creatinine clearance of <0.8 ml/s were eligible but required carboplatin dose modification based on the method of Egorin et al. [6]. Patients with a creatinine clearance of 0.6–0.8 ml/s received 75% of the carboplatin dose, those with 0.4–0.59 ml/s were given 50% and patients with <0.4 ml/s were ineligible.

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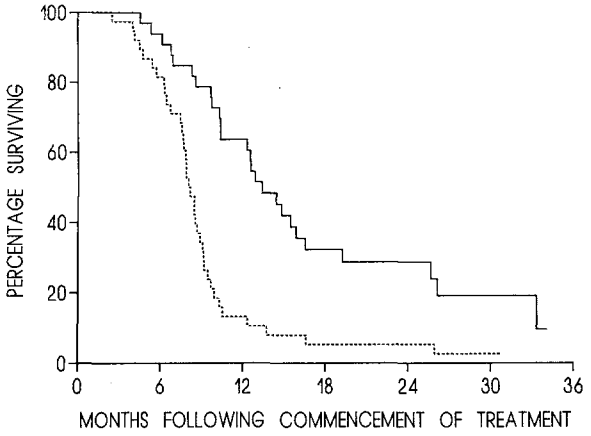

Fig. 1. Relapse-free survival by stage in (———) 33 cases of limited disease and (– – – – –) 38 cases of extensive disease. Log rank, $P = 0.0001$

Fig. 2. Survival by stage in (———) 40 cases of limited disease and (– – – – –) 50 cases of extensive disease. Log rank, $P = 0.0001$

Patient assessment. All patients underwent pretreatment full blood examinations, determinations of serum creatinine, urea and electrolytes, liver function tests, chest X-rays, computerised tomographic (CT) scans of the thorax and abdomen, electrocardiographs, bone marrow aspiration and trephine biopsies and bone scans. CT scan of the brain was carried out only if clinically indicated. Where possible, patients with limited disease had a simulator chest film for radiotherapy planning on study entry.

Limited disease was defined as tumour confined to one hemithorax with or without local extensions such as mediastinal nodes or any supraclavicular nodes but with disease that could be encompassed within a single radiation portal using modified VALG criteria [12, 15].

Assessments were done, with repeat of abnormal investigations, after three and six courses of chemotherapy; following the assessment after six courses, clinical assessments were carred out monthly until relapse. Standard World Health Organization (WHO) criteria were used to define objective response and toxicity [13]. All complete responses (CRs) were documented by CT scan and some, by additional bronchoscopy. Patients with persisting abnormalities in tumour volume on the chest X-ray or CT scan after treatment were not classified as complete responders even if these abnormalities were thought to be radiation-induced. Relapse-free survival (RFS) was calculated for patients with CRs or partial responses (PRs) only and was measured from commencement of the first treatment.

Treatment plan. Patients received three courses of chemotherapy including 120 mg/m^2 i. v. etoposide on days 1–3 (360 mg/m^2 per course), 100 mg/m^2 i. v. carboplatin on days 1–3 (300 mg/m^2 per course), 750 mg/m^2 i. v. cyclophosphamide on day 1 and 1.4 mg/m^2 vincristine on day 1 (maximum, 2 mg). Courses were repeated every 28 days because of the prolonged myelosuppression experienced in phase I studies and in accordance with the recommended schedule for carboplatin administration for phase II studies. Patients received minimal antiemetic cover usually consisting of only prochlorperazine every 6 h or as required. Following the assessment of disease status at 4 weeks after course 3, patients with limited disease who had not progressed received irradiation to the primary site and mediastinum up to a dose of 50 Gy in 25 fractions over 5 weeks. When possible, computer planning on CT images was used with corrections for tissue inhomogeneities. At 2 weeks after the completion of radiotherapy, patients with limited disease received a further three courses of chemotherapy and were then observed monthly without chemotherapy until relapse. Patients with extensive disease who had not progressed after three courses received a further three courses and were then observed monthly after the completion of therapy. Prophylactic whole-brain radiation using a 30-Gy mid-plane dose in 10 fractions over 2 weeks was given to patients achieving CRs after chemotherapy courses 3 or 6.

The overall aim was to deliver chemotherapeutic agents, particularly carboplatin, as intensively as possible and strictly according to the protocol dose and schedule. A reduction to 75% of the etoposide and cyclophosphamide doses was allowed for WHO grade 3 or 4 thrombocytopenia ($< 50 \times 10^9$ platelets/l) or for WHO grade 4 neutropenia ($< 0.5 \times 10^9$ WBC/l) only if these toxicities were complicated by an infection. Carboplatin was reduced to 75% of the initial dose only if cytopenia recurred as above following the first dose modification. Where possible, chemotherapy was delivered on time regardless of counts.

Statistical methods. All analyses were carried out using the BMDP statistical package [4]. The product-limit (Kaplan-Meier) method was used to obtain estimates of the survival distribution; percentages calculated in the survival context refer to those estimates. The log-rank test was used for the comparison of survival curves; the P values quoted are two-sided.

Ethics review. The protocol was written to comply with the National Health and Medical Research Council of Australia's Statement on Human Experimentation and was reviewed and approved by the Ethics Committee of each participating institution.

Results

A total of 90 previously untreated patients with small-cell lung cancer were assessed for response and toxicity. The sex ratio was 3:1 (M:F), the median age was 61 (range, 40–77) years and 40 patients (44%) had limited and 50 (56%), extensive disease. Overall, 40 patients had an ECOG PS of 0, 32 had PS 1, 13 Had PS 2 and 5 had PS 3. In all, 16 patients presented with superior vena caval obstruction. A total of 17 patients experienced a weight loss of $\geqslant 10\%$ in the 3 months preceding diagnosis.

Overall, a median of six courses of chemotherapy were given. More than 80% of the planned protocol dose of etoposide was delivered in 83% of the patients; that of carboplatin, in 94% of cases; that of cyclophosphamide, in 70% of patients; and that of vincristine, in 98% of cases. The median number of days between treatment was 28; however, there was a median of 35 days between courses 3 and 4 since chemotherapy was suspended for radiotherapy in patients with limited disease.

Three patients were inevaluable for response. Two early deaths occurred after one course of therapy, one due to sepsis during neutropenia and one due to acute myocardial infarction. A further patient received only two courses of therapy and was lost to follow-up after refusing further treatment. Overall, 87 patients were evaluable for response, with 40% achieving CRs and 41%, PRs. In limited disease, 62% achieved CRs and 23%, PRs; in extensive disease, 23% achieved CRs and 56%, PRs. Of 35 patients, 24 achieved CRs after 3 courses of treatment, with a further 11 doing so after 6 courses. All 36 patients who achieved PRs did so after $\leqslant 3$ courses. Seven limited-stage patients upgraded their responses to CRs after chest irradiation.

The overall median RFS was 9.4 months. There was a significant difference in RFS between limited- and extensive-stage patients ($P < 0.0001$; see Fig. 1). The median RFS for limited-stage patients was 13.4 months vs 8 months for patients with extensive disease. The median RFS was 13.4 months for patients attaining a CR and 7.8 months for those achieving a PR.

Of 26 limited-stage patients who relapsed, 8 relapsed in the chest alone; 3, in the chest and at distal sites simultaneously; 15, at distal sites only; and 9, within the thoracic radiation field. A total of 37 extensive-stage patients relapsed, with the relapse site documented in 36 cases. In all, 11 patients relapsed in the chest only; 7, in the chest and at distal sites; and 18, at distal sites only. There were 24 relapses in the CNS. Of the 20 patients who received prophylactic cranial irradiation, 3 relapsed in the CNS.

The median survival for all 90 patients was 11.1 months. Limited-stage patients survived significantly longer than those with extensive disease ($P < 0.0001$; see Fig. 2). The median survival for limited-stage patients was 13.3 months vs 9.6 months for extensive-stage patients. Patients achieving a CR had a median survival of 18.2 months vs 9.9 months for those attaining a PR. In all, 73 patients died of progressive disease and 2 of infection while neutropenic. There were four other deaths that were not specifically treatment-related, including one due to pneumonia without neutropenia, one because of acute myocardial infarction, one due to congestive heart failure and one suicide.

The major chemotherapy-related toxicity was neutropenia, with WHO grade 4 neutropenia [13] ($< 0.5 \times 10^9$ WBC/l) occurring in 66% of patients and grade 3 ($0.5 - 0.99 \times 10^9$ WBC/l), in 8% (Table 1). Grade 4 neutropenia was seen in 37% of all courses. Thrombocytopenia was less marked, with WHO grades 3 and 4 thrombocytopenia ($< 50 \times 10^9$ platelets/l) occurring in only 24% of all patients and 14% of all courses. Otherwise, the program was very well tolerated by patients, with either no nausea or nausea without vomiting (WHO grade 0 or 1) in 77% of all courses. Mucositis was seen in six patients, but this involved erythema and soreness only, without ulceration (WHO grade 1), in all six patients. Three patients had grade 1 renal toxicity. Neuropathy was documented in eight patients, with mild paresthesia (WHO grade 1) in three and severe paresthesia or mild weakness (WHO grade 2) in five. Clinical ototoxicity was identified in one patient, although audiometry was not routinely carried out.

Table 1. Toxicity of patients on ECCO (worst toxicity recorded for 90 patients)

	WHO grade (%)[a]				
	0	1	2	3	4
Hemoglobin	38	27	25	8	2
Neutrophils	19	1	6	8	66
Platelets	50	17	9	9	16
Nausea and vomiting	36	21	30	13	1
Alopecia	11	5	32	53	0
Renal	96	4	0	0	0
Infection	81	9	4	3	4

[a] According to Miller et al. [13]

Discussion

In contrast to its different spectrum of toxicity, carboplatin appears to have activity in tumour types usually responsive to cisplatin [2, 20]. Responses to cisplatin were seen in 11%–23% of previously treated patients with small-cell lung cancer, similar to the tumour response rates previously achieved with carboplatin [3, 5, 18]. However, the responses reported [18] in 18/30 previously untreated patients with small-cell lung cancer who were treated with carboplatin represent one of the highest single-agent responses achieved in small-cell lung cancer and warrant further study in this disease.

In patients with small-cell lung cancer, the combination of cisplatin and etoposide has been used successfully as initial therapy, as salvage treatment for relapse following CAV (cyclophosphamide, doxorubicin, vincristine) and as a regimen alternating with CAV [7, 8, 17]. We have previously shown [1] that the two-drug combination carboplatin-etoposide, when given intensively, was active and well tolerated and could produce prolonged remission duration and survival, especially in patients with limited disease or those achieving a CR.

Our previously reported two-drug combination (carboplatin and VP16) [1] and the present regimen were carried out in the same institutions, with the same investigators using the same criteria for assessing and reporting results [13]. In patients with limited disease ECCO may be

more effective, since 62% achieved a CR with ECCO and 40% did so with two drugs. The median RFS in limited-stage patients was 13.4 months with ECCO and 14.6 months with the two drugs. In addition to the larger numbers of patients achieving a CR with ECCO, the median survival for complete responders was 18.2 months vs the 16.5 months attained with two drugs alone in our previous study. Although these results are encouraging for ECCO, historical comparisons may well be misleading and a prospective, randomized comparison of the two regimens is required to define their relative efficacy.

Our policy of minimal dose reductions and punctual therapy was strictly observed, with the planned protocol doses delivered in a high percentage of courses. This policy resulted in neutropenia measuring $<1.0\times10^9$ WBC/l (WHO grade 3 and 4) in 74% of patients and in two deaths due to infection during neutropenia. It appears that ECCO is more myelosuppressive, with life-threatening neutropenia ($<0.5\times10^9$ WBC/l, WHO grade 4) occurring in 66% of ECCO patients vs 42% on our two-drug program. This may be expected because the same doses of etoposide and carboplatin were used in both programs, with additional cyclophosphamide given in the ECCO regimen. Thus, this program requires careful follow-up and the appropriate management of febrile episodes during neutropenia. As in our two-drug combinations, thrombocytopenia was not a major clinical problem with ECCO. Otherwise, patients tolerated the present regimen well, with either no nausea or nausea without vomiting in 77% of courses, minimal mucositis and without significant renal toxicity or clinical ototoxicity. More neurotoxicity was documented in patients on ECCO than in those receiving our two-drug combination, reflecting the addition of vincristine. ECCO was most useful in older patients in whom doxorubicin combinations were contraindicated by a significant pre-existing cardiac disease.

ECCO is a new, active combination with acceptable toxicity when given intensively in previously untreated patients with small-cell lung cancer.

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