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Acknowledgements—We express our appreciation to Dr J Mäenpää and Prof. M. Grönroos (Turku University Central Hospital, Department of Obstetrics and Gynecology, Turku, Finland) for their cooperation in the collection of normal controls for the TRH test, and to Dr R. Lammintausta for the constructive criticism of the manuscript. We thank Mrs F. Szeredás and Mrs Cs. Kazatsay for their expert technical assistance.

Pergamon

European Journal of Cancer Vol. 30A, No. 2, pp. 158–161, 1994

0959–8049/94 $6.00+0.00

Phase II Trial of Oral Etoposide Plus Cisplatin in Extensive Stage Small Cell Carcinoma of the Lung: an Eastern Cooperative Oncology Group Study

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Based upon the schedule specificity of etoposide and the *in vitro* and clinical synergy observed with cisplatin, the Eastern Cooperative Oncology Group conducted a phase II trial of oral etoposide and cisplatin in newly diagnosed, untreated patients with extensive stage small cell carcinoma of the lung. 35 patients received 100 mg/m² of cisplatin intravenously on day 1 and 50 mg/m² of etoposide orally for 21 consecutive days. Cycles were repeated every 28 days. The most common toxicity observed was myelosuppression. Sixty-seven per cent of patients had grade 3 or 4 leukopenia and 34% had grade 3 or 4 thrombocytopenia during cycle one. Of 26 evaluable patients, 4 had a complete response (15%) and 17 had a partial response (65%). The median survival for the group as a whole was 8.5 months. We conclude that this regimen was associated with significant myelosuppression, and offered no therapeutic advantage to other commonly administered chemotherapeutic regimens for small cell carcinoma of the lung.
Eur J Cancer, Vol. 30A, No. 2, pp. 158–161, 1994

INTRODUCTION

SMALL CELL lung cancer (SCLC) is a disease which is highly responsive to chemotherapy. Combination chemotherapy routinely produces response rates of 60–80% [1]. One such chemotherapy regimen, cisplatin and etoposide, prolongs survival in patients with limited stage SCLC and results in cure in 10–20% of cases [2]. However, despite this initial chemosensitivity, the majority of patients eventually relapse and die.

Etoposide, or VP-16, is a semisynthetic derivative of podophyllotoxin, a topoisomerase II inhibitor, which results in single strand breaks in DNA. It is one of the most active single agents in SCLC, with an overall response rate of approximately 45% [1]. Schedule-specific *in vitro* [3, 4] early studies have suggested that it may be schedule-specific *in vivo*, with prolonged schedules of administration more efficacious than single, high-dose administration [5–7]. With the recent availability of oral etoposide, trials examining the more prolonged administration of the drug have been conducted [8]. These studies suggest that oral etoposide is well tolerated and has significant therapeutic activity in patients with relapsed or refractory SCLC, including those who have received prior intravenous etoposide [9, 10].

Based upon the *in vitro* [11] and clinical synergistic activity observed with cisplatin, and the tolerability and efficacy of oral etoposide in refractory SCLC, we initiated a phase II trial to

determine the efficacy of cisplatin and oral etoposide in patients with untreated, extensive stage small cell carcinoma of the lung.

MATERIALS AND METHODS

All patients were required to have measurable or evaluable, previously untreated extensive stage small cell carcinoma of the lung. Patients had to have adequate bone marrow [white blood cells (WBC) $\geq 4000/mm^3$, platelet count $\geq 100\,000/mm^3$], hepatic (bilirubin ≤ 1.5 mg%) and renal function (creatinine ≤ 1.5 mg%) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2. Patients with brain metastasis, cardiac disease, a second primary cancer or active infection were excluded. All patients gave informed consent before enrolling on to the study.

Patients were treated with oral etoposide and intravenous (i.v.) cisplatin every 28 days for four cycles. Each cycle consisted of 50 mg/m^2 etoposide administered orally for 21 consecutive days, providing counts were adequate. Cisplatin was administered at a dose of 100 mg/m^2 i.v. in 1 l of normal saline over 2 h, following vigorous hydration. Maximal use of antiemetics was encouraged, but no specific regimen was defined. Patients achieving a complete response at any point were allowed prophylactic whole brain irradiation.

Etoposide was discontinued at any time during the cycle if the WBC fell below 2000/μl and/or the platelet count fell below 75 000/μl. On day 1 of a cycle, no therapy was given if the WBC was below 3000/μl and/or the platelet count was below 75 000/μl. Therapy was resumed 1 week later if the counts were adequate at 100% dose. If a 2-week delay was required, doses of cisplatin and etoposide were reduced by 25% each. Patients were taken off the study for delays greater than 14 days.

Cisplatin was reduced by 50% for a serum creatinine of > 1.5–2.5 mg, and was held for a serum creatinine > 2.5 mg%. Cisplatin was also modified by 50% for severe nausea, weakness or dysthesias, or moderate hearing loss.

Patients were evaluated for response following four cycles of therapy. A complete response to therapy was defined as the complete disappearance of all clinically detectable malignant disease for at least 4 weeks. Greater than or equal to 50% decrease in tumour size for at least 4 weeks, without an increase in size of any known malignant disease or appearance of new lesions, constituted a partial response. Stable disease was defined as no significant change in measurable or evaluable disease for at least 4 weeks, and progressive disease was defined as appearance of new lesions, or a greater than or equal to 25% increase in the area of tumour size.

Following four cycles of therapy, patients were taken off the study. No further treatment was given for complete or partial responders until relapse or progression was documented.

ECOG grades 1, 2, 3 and 4 leucopenia were defined as WBC counts of 3.0–3.9, 2.0–2.9, 1.0–1.9 and < 1.0 ($\times 10^9$/l), respectively. Grades 1, 2, 3 and 4 thrombocytopenia was defined as platelet counts of 75–150, 50–74.9, 25–49.9 and < 25 ($\times 10^9$/l), respectively. Grades 1, 2, 3 and 4 anaemia were defined as haemoglobin levels of 10.0–13.8, 8.0–10.0, 6.5–7.9 and less than 6.5 g/dl, respectively.

Table 1. Patients' characteristics

Number of patients	35
Ages (years)	
Median	61
Range	40–82
Sex	
Female	8
Male	27
Performance status	
0	8
1	18
2	9
Sites of metastatic disease	
Liver	15
Bone	8
Bone marrow	8
Other	11
Median number	3

RESULTS

35 patients were entered in the study (Table 1). 1 patient was ineligible at the time of the study due to the presence of brain metastases. Of the remaining 34 patients, 8 patients did not complete the first cycle of therapy and were considered evaluable for toxicity but not response. Of those 8 patients, 2 withdrew prior to completion of the first cycle of therapy for personal reasons and 1 patient withdrew due to severe toxicity (stroke). 5 patients died during treatment. Four deaths were due to neutropenic sepsis and one death was caused by a pulmonary embolism.

Therapeutic activity

26 patients were evaluable for response (Table 2). There were 4 complete responders (15%) and 17 partial responders (65%) for an overall response rate of 81%. 2 patients had no change in the size of their tumour during treatment, and 3 patients had progressive disease prior to completing four courses of therapy.

Table 2. Patient outcome

Number of eligible patients	34
Survival (days)	
Median	256
Range	3–569+
Number of evaluable patients	26
Disease outcome–number of patients (%)	
Responses	
Complete	4 (15%)
Partial	17 (65%)
Stable disease	2 (8%)
Progressive disease	3 (12%)
Duration of response (days)	
Median	121
Range	35–536+
Survival (days)	
Median	265
Range	37–569+

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Revised 14 June 1993; accepted 1 Sep. 1993.

The median duration of response was 121 days. The median survival was 8.5 months for all patients and 8.8 months for the 26 evaluable patients. 5 patients are still alive with a median duration of follow-up of 5 months; 1 patient is alive and disease-free for more than 18 months from entrance into the study.

Toxicity

20 of the 34 eligible patients completed all four cycles of therapy. Only 4 patients completed all four courses without any dose modifications.

The most common toxicity was myelosuppression. Of the 34 evaluable patients, 23 had grade 3 (44%) or grade 4 (24%) leucopenia during cycle 1, and 12 had grade 3 (29%) or 4 (6%) thrombocytopenia (Table 3). 27 patients had grade 3 or 4 leucopenia and 22 had grade 3 or 4 thrombocytopenia when all courses of chemotherapy are considered.

Because of myelosuppression, etoposide was stopped prematurely in 15 patients due to low neutrophil or platelet counts, 10 patients had their next cycle of etoposide delayed by 1 to 2 weeks, and 3 patients required a dose reduction of the etoposide. Treatment was stopped early in 4 patients due to leucopenia; in 11 patients, it was stopped early due to thrombocytopenia and in 1 patient it was stopped due to nausea and vomiting. 4 patients developed infectious complications while neutropenic and subsequently died of sepsis.

The other common toxicities included 6 patients with grade 3 or 4 nausea (no significant intake). No information was available as to whether these patients were unable to take their oral etoposide the first few days after cisplatin therapy. 3 patients had grade 3 or 4 hypotension (required therapy and hospitalisation) and 1 patient had grade 3 or 4 hypertension (required therapy), probably related to the anti-emetics or hydration for cisplatin. 1 patient developed grade 4 renal toxicity (creatinine $> 6 \times$ normal, blood urea nitrogen $> 10 \times$ normal). Only 2 patients experienced grade 3 or 4 mucositis (could not eat, required parenteral support), and 3 patients experienced grade 3 diarrhoea (seven to nine stools per day).

3 patients had grade 3 or 4 pulmonary toxicity (dyspnea at normal activity; dyspnea at rest). 1 patient expired due to pulmonary embolus, 1 had grade 3 dyspnea, and 1 patient developed adult respiratory distress syndrome. Other significant toxicities included grade 3 or 4 cardiac toxicities in 3 patients, which included myocardial infarction, and severe ischaemia and tachycardia requiring therapy. Grade 3 hepatic toxicity (serum glutamic oxalacetic transaminase $> 5 \times$ normal) was observed in 2 patients.

Table 3. Haematological toxicities

	Worst ECOG grade toxicity experienced per patient				
	0	1	2	3	4
Course one					
RBC	10	1	0	11	12
WBC	4	4	3	15	8
Platelets	21	0	1	10	2
All courses					
RBC	9	0	0	10	15
WBC	3	3	1	18	9
Platelets	11	1	0	14	8

DISCUSSION

The treatment of SCLC has been frustrating. Although newer chemotherapy regimens have increased the response rates, no major impact has been made in improving the median survival or cure rate of this disease. Due to the recognition that no significant improvement in survival can be made without first achieving a complete response, attempts at identifying more active drug regimens continue.

Since dose intensity of chemotherapy has not clearly correlated with outcome [12], recent strategies have focused on identifying new drugs [13] or more effectively utilising current drugs which are known to be active in this disease. Etoposide would appear to be an ideal drug to investigate in this latter category. When administered intravenously in a "standard" regimen over 3 days with cisplatin, it induces responses in about 60–80% of extensive stage SCLC patients and over 90% of limited-disease patients [14, 15]. Moreover, etoposide is clearly schedule-dependent. An early trial of etoposide scheduling was conducted in 60 patients with SCLC, 45 of whom were chemotherapy naive [5]. Patients were randomised to three schedules, in which they received 250 mg/m^2 i.v. weekly, 500 mg/m^2 orally over 3 days weekly, or 850 mg/m^2 orally over 5 days every 3 weeks. The response rates were 20, 65 and 42%, respectively, suggesting that more prolonged schedules of etoposide were capable of effecting higher response rates.

The superiority of a more prolonged administration of etoposide has been confirmed in two prospective trials in previously untreated SCLC [6, 7]. Slevin and co-workers randomised 39 patients with extensive disease to receive 500 mg/m^2 as a continuous infusion over 24 h or to receive five consecutive daily 2-h infusions each of 100 mg/m^2. The response rates were dramatically different, at 10 and 89%, respectively [6]. Abratt *et al.* randomised patients with limited stage disease to receive one of two combination regimens that differed only in the scheduling of etoposide [7]. Patients in one arm received 60 mg/m^2 i.v. on day 1 and 120 mg/m^2 orally on days 2–5 of each cycle, while patients in the other arm received 300 mg/m^2 of etoposide i.v. on day 1. The complete (53 vs. 26%) and overall (75 vs. 52%) response rates were significantly higher in the oral etoposide arm.

With the availability of oral etoposide, these studies were expanded to include even more prolonged administration of oral etoposide [8]. In a phase II trial of etoposide in patients with relapsed or refractory SCLC, 22 patients (18 of whom had received prior i.v. etoposide) received 50 mg/m^2/day for 21 days. 10 of 22 (46%) patients achieved a complete or partial response [10]. In elderly, untreated patients with SCLC, 800 mg/m^2 of etoposide orally over 5 days resulted in a 79% response rate and was very well tolerated, with minimal myelosuppression [16].

We decided to conduct a phase II trial of oral etoposide plus cisplatin because of the activity of cisplatin in SCLC, the synergistic activity that has been observed with etoposide *in vivo* and *in vitro*, and the high clinical response rate that has been observed with this i.v. combination in SCLC. Despite this rationale, however, we did not observe a significant improvement in patient outcome in this study. The response rate was similar to that observed in other randomised studies of cisplatin and i.v. etoposide [15, 16], and the overall medium duration of response and median survival was unchanged from historical controls [1].

We observed a significant degree of myelosuppression in this trial. Other phase II studies utilising oral etoposide as a single agent have reported a smaller incidence of grade 3 or 4 leucopenia (8–15%) and thrombocytopenia (0%) than we observed here

[6, 18]. The degree of myelosuppression also appeared to be somewhat higher than the degree of myelosuppression observed with cisplatin and i.v. etoposide. For example, in two recent randomised trials of cisplatin and i.v. etoposide, 46 and 41% of patients, respectively, developed grade 3 or 5 leucopenia, compared to 79% in our trial [15, 17]. Similarly, 21 and 13%, respectively, developed grade 3 or 4 thrombocytopenia, compared to our observed rate of 65%. 4 patients (12%) had toxic deaths.

Our results confirm a smaller study of oral etoposide plus cisplatin in extensive stage SCLC, in which a 13% complete response plus a 73% partial response rate was observed in 15 patients [19]. Although the combination was well tolerated, the median duration of response was only 7 months.

Therefore, we conclude that the combination of cisplatin and oral etoposide was similar in efficacy to other chemotherapeutic regimens for extensive stage small cell lung cancer. Given the limitations of retrospective comparisons, the regimen appears to be more myelosuppressive than the same regimen when etoposide is administered intravenously in a more standard 3–5-day schedule and, therefore, offers no advantage to more standard regimens. Continued efforts need to be made to identify more active cytotoxic agents for this disease.

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