Cancer Chemother Pharmacol (2005) 56: 521–528
DOI 10.1007/s00280-004-0994-8

ORIGINAL ARTICLE

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Phase I study of etoposide, cisplatin and irinotecan triplet in patients with advanced-stage small-cell lung cancer

Received: 6 July 2004 / Accepted: 25 November 2004 / Published online: 15 June 2005

Abstract *Aim*: The irinotecan–cisplatin combination has emerged as a new standard for the treatment of advanced-stage small-cell lung cancer (AS-SCLC). To move forward we developed a 3-day regimen of cisplatin, etoposide and irinotecan. *Methods*: Successive cohorts of AS-SCLC patients were treated with irinotecan administered as a single 1-h infusion in combination with fixed doses of cisplatin (20 mg/m^2) and etoposide (75 mg/m^2), both given for three consecutive days (ECI regimen). Irinotecan dose was escalated from 60 mg/m^2 by 40-mg/m^2 increments. At mid-step between the maximum tolerated dose (MTD) and the previous dose level, patients were randomized for the day of administration of irinotecan (day 1 vs day 3). *Results*: A total of 36 AS-SCLC patients received 166 courses of treatment at four dose levels. The MTD of irinotecan was 140 mg/m^2 (three dose-limiting toxicities, DLTs), and the recommended optimal dose (ROD) 120 mg/m^2 (two DLTs). DLTs were febrile neutropenia and grade 3 diarrhea. Other toxicities were mild. No difference in toxicity was seen between the two time schedules. A 77% (95% CI 63.25–90.75%) response rate was recorded among 31 evaluable patients and the median survival was 12 months. *Conclusions*: The ECI regimen was well tolerated and showed considerable activity in patients with AS-SCLC. Phase II/III evaluation is ongoing.

Keywords Etoposide · Cisplatin · Irinotecan · Small-cell lung cancer · Phase I

The results of this trial were presented at ECCO 12, Copenhagen, Denmark, September 2003.

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Introduction

Lung cancer remains the most lethal common cancer with an age-adjusted 5-year survival remaining below 10% for the approximately 200,000 men and women diagnosed with this malignancy each year in the European Union [1, 2]. The fact that small-cell lung cancer (SCLC) shares a similarly dismal prognosis with the non-small-cell type of lung cancer despite a higher sensitivity to cytotoxic chemotherapy underscores the need for continuous evaluation of new therapeutic regimens incorporating new active agents for this tumor type [3, 4].

The camptothecin derivative irinotecan (CPT-11) appears to be among the most promising new agents against bronchial carcinoma [5]. A phase III randomized trial has recently shown that irinotecan–cisplatin confers a survival benefit compared with the standard etoposide–cisplatin combination in patients with advanced-

stage SCLC (AS-SCLC) [6]. Following disclosure of those results, triple combinations of cisplatin, irinotecan and etoposide began to be evaluated in SCLC as the next rational step, but with rather inconvenient schedules of administration [7]. Still, more studies in progress will hopefully delineate a role for irinotecan in the management of lung cancer [8].

We developed a 3-day regimen of a combination of the three most active drugs against SCLC that achieves both scientific rationale and clinical convenience (ECI regimen). To address the existing debate and expand clinical information over potential schedule dependence of topo-I inhibitors in relation to both topo-II inhibitors and DNA-damaging compounds, we investigated two different time schedules of administration of irinotecan [9, 10]. This trial was conducted in chemotherapy-naive patients with the aim of obtaining a concise clinical evaluation of the study treatment. We adopted this approach because the study regimen incorporated acceptable doses of the cisplatin–etoposide combination which is considered standard therapy for patients with SCLC [11].

This trial (HE 1/01) was conducted from March 2001 until December 2002 by members of the Hellenic Cooperative Oncology Group (HeCOG, Athens, Greece). The protocol was approved by the HeCOG Protocol Review Committee and also by the local institutional review boards and ethics committees of participating institutions.

Methods

Study design and objectives

This was an open-label, uncontrolled, phase I trial with between-patient dose escalation. Seven HeCOG centers collaborated in this study.

The primary objectives were to determine the maximal tolerated dose (MTD) to define a recommended optimal dose (ROD) for phase II evaluation and to characterize the spectrum of toxicities and the dose-limiting toxicities (DLTs) of irinotecan given as a single 1-h infusion in combination with fixed doses of cisplatin and etoposide, both given for three consecutive days (ECI regimen). A secondary objective was to record evidence of the antitumor activity of this regimen as first-line chemotherapy for AS-SCLC.

Patients

Patients with histologically or cytologically proven AS-SCLC were considered eligible for this study if they fulfilled the following criteria: age greater than 17 years, performance status 0–2 on the World Health Organization (WHO) scale, no prior chemotherapy, life expectancy of at least 12 weeks, adequate bone marrow function (white blood cell count WBC $>3.5\times10^9$/l, absolute neutrophil count ANC $>1.5\times10^9$/l, platelet count $>100\times10^9$/l), renal function [serum creatinine 140 μmol/l (1.4 mg/dl)] and hepatic function (serum bilirubin less than 1.25 times the ULN, serum transaminases less then twice the ULN or less than five times the ULN in the presence of liver metastases), and absence of clinically relevant neuropathy, psychiatric illness, and pregnancy, lactation or inadequate contraception in female patients. Before the start of treatment, all patients had to sign written informed consent.

Treatment

The treatment scheme is outlined in Table 1. All treatment was delivered in the outpatient setting. Irinotecan was given at escalated doses on day 1, diluted in 500 ml normal saline (NS) and administered as a 1-h infusion following the administration of etoposide and cisplatin. Etoposide and cisplatin were given for three consecutive days doses at 75 and 20 mg/m^2, respectively, which are considered acceptable for the treatment of AS-SCLC [12]. They were both diluted in 250 ml NS each and administered as short 30-min infusions. Hydration with 500 ml intravenous fluid was given at the start of therapy and after cisplatin with 10 mg furosemide added in. Atropine (0.5–1.0 mg) was given as needed to patients developing abdominal cramps or diarrhea during infusion of irinotecan. Antiemetic medication consisting of $5HT_3$ antagonist (suggested granisetron 3 mg) was administered prior to administration of chemotherapy.

Therapy was repeated every 21 or 28 days depending on the occurrence of toxicity on the day of treatment. To administer chemotherapy, patients were required to maintain a WBC $>3.0\times10^9$/l, ANC $>1.5\times10^9$/l, platelet count 100×10^9/l, and serum creatinine <1.4 mg/dl.

Table 1 Treatment administration

Medication	Administration	Duration	Days
Granisetron 3 mg	Intravenously	Bolus	1, 2, 3
(hydration)	500 ml NS + 1 amp KCl	30 min	1, 2, 3
Etoposide 75 mg/m^2	In 250 ml NS	30 min	1, 2, 3
Cisplatin 20 mg/m^2	In 250 ml NS	30 min	1, 2, 3
(hydration)	500 ml NS + 1 amp Mg + 10 mg furosemide	30 min	1, 2, 3
Irinotecan escalating doses (baseline dose 60 mg/m^2)	In 500 ml NS	1 h	1 (at ROD randomized for day 1 vs day 3)

Dose escalation plan—definitions

The starting dose of irinotecan was 60 mg/m^2 of body surface area and escalation was planned to proceed in increments of 40 mg/m^2 in consecutive cohorts of at least three to six patients depending on the occurrence of toxicity. A minimum of three assessable patients (receiving at least one full course of treatment) were entered at nontoxic dose levels. In case of grade 2 or worse nonhematological toxicity (except alopecia or inadequately treated nausea and vomiting), or grade 3 or worse hematological toxicity at least three more patients (for a minimum total of six patients) were treated. At a given dose level, at least 2 weeks were to have passed between the entry of the first and the next two patients.

Whenever two DLTs occurred in a maximum of six patients, the assumption would be made that the MTD had been reached. Upon definition of the MTD, a mid-step between the MTD and the dose immediately below would be evaluated. At this level an expanded number of patients were randomly assigned to receive irinotecan on day 1 or day 3 to evaluate for variation in toxicity in regard to administration of irinotecan. Patients were allocated to each treatment group of irinotecan administration schedule alternately per registration sequence number (odd vs even numbers). Should this dosage level be found to be well tolerated, it would be characterized as the ROD.

Dose escalation decisions were made by assessing toxicity recorded during the first cycle of treatment in each patient. To make a decision, two prime investigators (the co-authors E.B. and E.S. of this study) regularly considered data which had accumulated at the Hellenic Cooperative Oncology Group data office.

Treatment delays and dose modification

Chemotherapy was given when appropriate hematological reserves were present (WBC $>3.0\times10^9$/l with ANC $>1.5\times10^9$/l, and platelet count $>100\times10^9$/l) and after recovery from significant nonhematological toxicity (grade 0–1). If this had not occurred, treatment was delayed until after hematological recovery, resolution of other organ toxicity or for a maximum of 2 weeks. In the case of occurrence of DLT or other clinically significant toxic effects, when further treatment was deemed to be beneficial for the patient, therapy was continued off-study at the dosage level immediately below, based on the clinical judgment of the investigator. Dose modifications were not allowed in this study. Administration of G-CSF was suggested in the presence of febrile neutropenia and as a 5-day prophylaxis around the recorded nadir day in patients who developed grade 3 or 4 neutropenia.

Patients who experienced an objective response or clinical benefit continued therapy to a maximum of eight courses, toxicity permitting. Patients with progressive disease or unacceptable toxicity discontinued treatment and were taken out of the study.

Safety assessment

All patients were seen clinically during their visits to the hospital. Hematology, biochemistry and urinalysis tests were performed at baseline and weekly intervals during the first cycle. Thereafter patients were assessed for toxicity prior to treatment administration. If treatment was discontinued due to adverse events, toxicity was assessed weekly until resolution of the abnormality. Adverse events were recorded throughout the period of treatment and until 4 weeks after the last treatment administration. Any abnormal outcomes were documented as adverse events and characterized by their relationship to the therapeutic regimen being studied. DLT was defined using National Cancer Institute Common Toxicity Criteria (version 2.0) [13].

DLTs were considered to be any grade 4 thrombocytopenia, grade 4 neutropenia lasting more than 5 days, febrile neutropenia (fever >38°C with neutrophils <1000/mm^3 lasting more than 4 days), the combination of grade 2 or higher diarrhea with grade 3 or higher neutropenia and grade 3 nonhematological toxicity (except alopecia, nausea and vomiting). These toxicities were considered as dose limiting if they occurred during the first cycle of treatment. A nonhematological toxicity could be considered as a DLT if it occurred during the first four cycles of treatment. Patients who did not complete one full course of treatment because of reasons not related to toxicity (withdrawal of consent, rapid disease progression, rapid decline of performance status) were replaced in the determination of DLT and MTD, but were included in overall toxicity analyses.

The MTD was defined as the dose level at which DLTs occurred in at least one-third of patients of a minimum six-patient cohort.

Response assessment

Patients with measurable target lesions completing at least two courses of treatment were considered evaluable for response. Tumor in all patients were assessed at baseline, after the second course of treatment, and thereafter every two treatment courses and every 2 months on follow-up until tumor progression was documented. Helical computerized tomographic (CT) scans were used for tumor measurements in all cases. Objective tumor response was assessed according the Response Evaluation Criteria in Solid Tumors [14]. When an objective response was observed, all assessments were to be repeated in 28 days for confirmation. The duration of objective responses were calculated from the time the response was first documented until the date of disease progression. The duration of stable

disease dated from the commencement of treatment to the date of disease progression.

Ethical considerations

The ethics committees at the centers involved approved the study protocol and the patient informed consent form. Informed written consent was obtained from each patient prior to enrollment. The trial was carried out in accordance with the principles of the Declaration of Helsinki, and the European Note for Guidance for Good Clinical Practice.

Monitoring

The study was monitored by the central data office of the Hellenic Cooperative Oncology Group (HeCOG) in Athens in collaboration with the HeCOG data office in Ioannina. Case report forms (CRFs) were specifically developed for this study by the data office of the Medical Oncology Department of the Ioannina University Hospital. Clinical investigators entered the information required by the protocol onto the CRFs and forwarded them to the central data office. Monitors visited the investigators regularly to verify the CRFs for correctness and completeness by visual data checking. The following items were regularly checked against source data: eligibility criteria, baseline physical examination results, drug administration, adverse events, laboratory outcomes, efficacy data and off-study data. Data quality assurance was performed by complete data check. On completion of the clean-up procedures, the database was locked.

Results

From March 2001 until January 2003, 36 patients (median age 58 years, males 33) received a total of 166 treatment courses at four different dose levels of irinotecan. One patient failed to start treatment for logistic reasons. The patient characteristics at baseline are shown in Table 2. All treated patients had histologically diagnosed extensive stage SCLC and had not received any other cytotoxic chemotherapy previously. The most common metastatic sites were liver (17 patients) and bone (10 patients) while seven patients were diagnosed with brain metastases at presentation. Most patients were symptomatic but maintained a good performance status.

Table 2 Demographics

		Number	%
Patients treated		36	100
Optimally dosed		17	47
Non-optimally dosed		19	53
Gender			
Female		3	8
Male		33	92
Age (years)			
Median	58		
Range	47–74		
PS			
0		15	22.6
1		18	50
2		3	8.4
Sites involved			
Lung		36	100
Distal metastases		36	100
Liver		17	47
Bone		10	28
Brain		7	19.5
Other		5	16.5
Treatment cycles administered, total	166		
Treatment cycles administered,per patient			
Median	5.5		
Range	1–9		

Treatment administered

Treatment details are presented in Table 3. Most patients received adequate treatment. Of the 36 treated patients, 21 completed six cycles of treatment and 15 discontinued treatment early because of toxicity (6 patients), disease progression (5 patients), doctors' decision or patient withdrawal (4 patients). The overall median number of treatments administered per patient was 5.5. In general, it was feasible to repeat treatment every 3 weeks in the first two cycles at all dosage levels. Only a limited number of treatments had to be given at 4-week

Table 3 Treatment administered

Level (irinotecan, mg/m^2)	Patients	Cycles administered		Cycle interval (median, weeks)		Cycles supported with G-CSF	
		Total	Median (range)	First two cycles	After third cycle	At event	Prophylactic
60	6	32	6 (4–6)	3	3.5	1	9
100	4	27	6.5 (6–9)	3	3	0	5
120 (day 1)	8	37	5 (1–6)	3	3	4	6
120 (day 3)	9	38	5 (1–6)	3	4	2	1
140	9	32	4 (1–6)	3	3	4	13
Total	36	166	5.5	3	3	11	34

intervals after the third cycle. G-CSF was administered in 11/166 treatment cycles for febrile neutropenia while 34 cycles were supported with G-CSF in patients who had developed grade 3 or 4 neutropenia.

Toxicity

The DLT with this regimen consisted of febrile neutropenia, grade III diarrhea and a combination of neutropenia plus diarrhea. Other toxicities recorded were mild asthenia, vomiting and neurotoxicity. There was no difference in toxicity between the two time schedules of administration of irinotecan.

Hematological toxicity was mild throughout the study up to the MTD. Grade 3 or 4 myelosuppression occurred rarely and without clinical sequelae. In the first two cohorts (irinotecan 60 and 100 mg/m^2) only three episodes of transient grade 3 and one episode of a grade 4 neutropenia were observed among ten treated patients. At the ROD level (irinotecan 120 mg/m^2) seven episodes of grade 3/4 neutropenia occurred with day-1 administration of irinotecan and five with day-3 administration. The median duration of grade 3/4 neutropenic episodes was 3 days. Detailed information on hematological toxic effects of treatment is shown in Table 4.

The most common nonhematological side effects in this study were diarrhea, nausea/vomiting, alopecia, fatigue and neurotoxicity. In the majority these toxicities were mild and manageable. There was only one episode of grade 2 neurotoxicity, four of grade 2 diarrhea that occurred at sub-MTD levels, and a peripheral arterial ischemia of grade 2 that occurred in a patient treated at the highest dose level of irinotecan (140 mg/m^2). Thrombosis was managed non-surgically without sequelae in that patient and he opted to complete therapy off-study at a lower dose. Detailed data on the nonhematological toxicity profile in each cohort are shown in Table 5.

Defined doses: MTD and ROD

The MTD of irinotecan in this triplet was 140 mg/m^2 and the ROD was 120 mg/m^2. At the MTD level three

Table 4 Hematological toxicity of CEI regimen reported as worst toxicity recorded per patient in cycle 1 and cycles 2–4 collectively

Irinotecan dose (mg/m^2)	Patients	ANC				Febrile neutropenia				Platelets			
		Cycle 1		Cycles 2–4		Cycle 1		Cycles 2–4		Cycle 1		Cycles 2–4	
		Grade 3	Grade 4	Grade 3	Grade 4	Grade 4	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
60	6	1		2		1							
100	4												
120 (day 1)	8	2	1	2	2	1			1		1		
120 (day 3)	9	1		3	1		1					1	
140	9	3	1	3		3					1		

Table 5 Non-hematological toxicity recorded as worst grade per patient, cycles 1–4

Irinotecan dose	Points	Diarrhea		Fatigue		Alopecia		N/V		Neurotoxicity	
		Gr2	Gr3	Gr1	Gr2	Gr1	Gr2	Gr1-2	Gr3	Gr1	Gr2
60	6			2	1	2	1	1	1	1	
100	4			2	1	2	1	1		1	1
120-D1	8	2			1	3	2	3		1	
120-D3	9	2		1		2	3	1	1	1	
140	9		1			3	3	2			

Gr = toxicity grade, N/V = nausea and vomiting.

Table 6 Dose-limiting toxicities

Irinotecan dose (mg/m^2)	Patients	DLT	Description
60	6	1	One febrile neutropenia
100	4		
120 (day 1)	8	2	One febrile neutropenia, one neutropenia grade 3 + diarrhea grade 2
120 (day 3)	9		
140	9	3	Two febrile neutropenia, one febrile neutropenia + diarrhea grade 3

Table 7 Documented confirmed activity in 27 evaluable patients (median time to progression 7 months)

Response	Patients	%
Objective response	21	77
Complete response	4	15
Partial response	17	62
Stable disease	3	11.5
Disease progression	3	11.5

out of nine patients developed febrile neutropenia and in one case this was also complicated with grade 3 diarrhea (Table 6). At the ROD level recorded toxicity was acceptable with only two DLTs. These were one febrile neutropenia and one grade 3 neutropenia combined with grade 2 diarrhea.

Activity

A total of 27 patients with measurable tumor lesions who received at least two treatment courses and had one confirmed tumor assessment after initiation of treatment were considered evaluable for tumor response. Four complete and 17 partial responses were documented among the evaluable patients giving a 77% response rate (95% confidence interval 63.25–90.75%; Table 7). Interestingly, four out of seven patients who had brain metastases achieved a complete remission of brain metastases (Fig. 1). The median survival of all patients was 12 months, while at 2 years the proportion of surviving patients was 18% (Fig. 2).

Discussion

Combination chemotherapy is the most effective treatment option for patients with SCLC [15]. However, the introduction of new anticancer agents has failed to improve the outcome in this tumor type during the last two decades. It seems that the therapeutic plateau that has been reached with the cisplatin plus etoposide combination and the equally effective cyclophosphamide–doxorubicin–vincristine combination has yet to be overcome [16]. A number of attempts such as hybrid regimens, dosage intensification and regimen alteration strategies have all failed to make any significant contribution to improve treatment outcome [16, 17]. Median survival remains 8–10 months for patients with extensive disease and 14–18 months for those with limited disease [18].

The unsatisfactory survival data in this chemosensitive tumor prompted clinical investigators to continue evaluating new agents and combination regimens in the treatment of this tumor. Among the new drugs, taxanes and the camptothecin derivatives topotecan and irinotecan have been shown as the most active [19, 20]. Both camptothecin derivatives topotecan and irinotecan demonstrate strong single-agent activity against SCLC [21, 22]. However, topotecan has not been adequately investigated in combination with cisplatin because the combination has a poor safety profile [23, 24]. In contrast, the competing camptothecin derivative irinotecan (CPT-11, Campto, Camptosar) has been studied more fully in combination with cisplatin in this tumor type [25–27]. Ultimately, this has led to the exciting results of a Japanese phase III study that favored the irinotecan plus cisplatin combination over etoposide and cisplatin marking a new standard of care for SCLC [6].

We considered that the development of a triplet that combines the three most active agents in SCLC would be the next most important step to improve therapy of patients diagnosed with this tumor. In the Japanese trial a weekly scheme for irinotecan was utilized and cisplatin was administered as a single infusion, but we developed a 3-day schedule for clinical convenience (the ECI regimen). In our regimen cisplatin and etoposide dosages were given fractionated over 3 days with the aim of reducing toxicity, and irinotecan was given as a single infusion on day 1 or day 3 to test potential schedule dependence. One could argue that weekly dosing of iri-

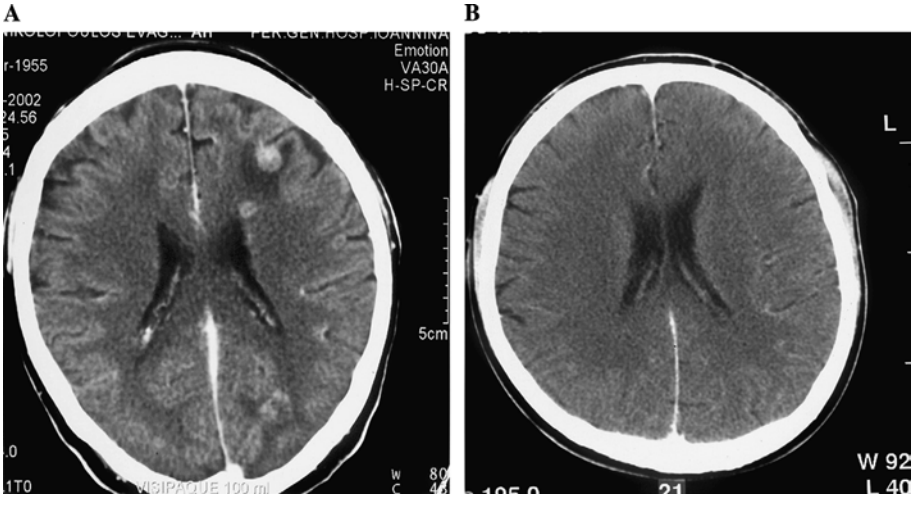

Fig. 1 Complete response of brain metastases following four cycles of ECI therapy in a patient treated at 120 mg/m^2 irinotecan dose level (**a** CT scan, pretreatment; **b** CT scan after fourth treatment course)

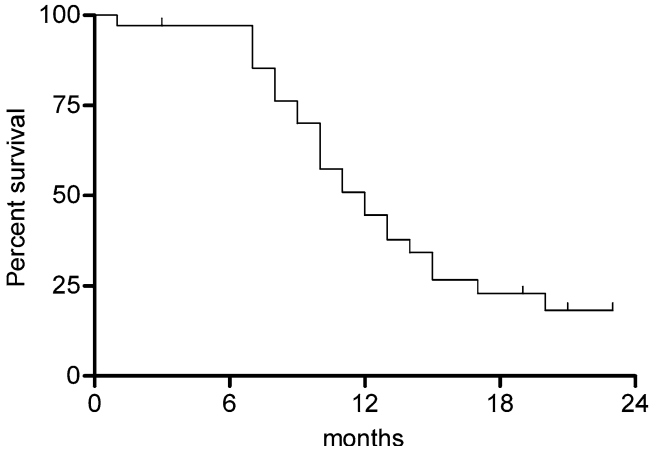

Fig. 2 Survival graph of 36 patients with AS-SCLC treated with the ECI regimen (median survival 12 months)

notecan, the regimen commonly used in the Japanese trials, could offer better therapeutic efficacy over a single-dosing schedule. However, while no direct comparison of these two schedules of administration of irinotecan has ever been done in SCLC, in colorectal cancer, single dosing every 3 weeks has been found to show activity equal to and toxicity less than that of a weekly administration schedule of irinotecan [28].

The ECI regimen proved feasible as most patients managed to receive adequate treatment and 58% completed six courses administered every 3 weeks. Moreover, a relatively small fraction of the treatment cycles were supported by G-CSF. Clinically relevant myelosuppression was acceptable at the ROD and diarrhea was minor and manageable. There was no significant variation in toxicity when irinotecan was given on day 1 or day 3.

Although assessment of efficacy was not a primary endpoint of this study, the ECI regimen produced efficacy data comparable to the Japanese doublet (12 months median survival, 18% of patients surviving at 2 years). One could argue that better efficacy results should be expected with a triplet. However, this was a phase I study with patients treated with a range of irinotecan dosages and there were also differences between the patient characteristics in our study and those in the Japanese trial. Most apparent was the extent of disease and the treatment administered. Characteristically, liver involvement was below 20% in the Japanese trial (16.8% in the etoposide arm and 18.2% in the irinotecan arm) while in our patient population 47% of the patients had liver metastases. Furthermore, only half of the patients in our study were given the optimal dosage.

The same group from Japan recently published a comparative phase II study of weekly irinotecan combined with cisplatin and etoposide given at two different schedules of administration in patients with AS-SCLC. In both arms, treatment was repeated every 4 weeks and irinotecan often needed to be skipped on day 15. Again the efficacy results were similar with those of our study [7].

In conclusion, we showed that irinotecan can be safely combined with cisplatin and etoposide in a convenient and simple schedule of administration over 3 days. The ROD of the combination is cisplatin 20 mg/m^2 plus etoposide 75 mg/m^2 both given on three consecutive days and irinotecan 120 mg/m^2 given as a single intravenous infusion. Efficacy obtained in this study compares favorably with historical data. Further clinical investigation of this regimen is under way by our group both in limited-stage (in combination with thoracic irradiation), and in extensive-stage SCLC.

Acknowledgements The authors would like to thank Ms Olga Siarabi for excellent work in data management of this study.

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