Triplet combination of carboplatin, irinotecan, and etoposide in the first-line treatment of extensive small-cell lung cancer: a single-institution phase II study

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Small-cell lung cancer is a rapidly progressive tumor and median survival is less than 10 months in patients with extensive stage of the disease. This study aims to evaluate the efficacy and tolerability of the carboplatin, etoposide, and irinotecan triplet as a first-line treatment in extensive small-cell lung cancer. Chemonaive patients with documented diagnosis of extensive small-cell lung cancer, performance status 0–2, and adequate organ function were eligible. Patients received triweekly carboplatin area under the curve 5 on day 1, irinotecan 150 mg/m^2 on day 2, and etoposide 75 mg/m^2 on days 1, 2, and 3 for up to six cycles. A total of 54 patients were enrolled. Forty-seven of 54 patients (87%) had a performance status of 0–1. The response rate was 75% and complete response was achieved in 10 of 54 patients (18%). The median time to progression was estimated at 8 months (95% confidence interval: 6.6–8.9) and median overall survival at 12 months (95% confidence interval: 10.3–13.9). Patients with one site of metastases had prolonged survival as compared with those with two or more sites. Normalization of lactate dehydrogenase values after treatment was not correlated to survival. Grade 3–4 neutropenia occurred in nine patients (16.7%) and grade 3 fetal thrombocytopenia in one patient (1.9%). Two toxic deaths (3.7%) were reported. The carboplatin, irinotecan, and etoposide triplet is a very effective and well-tolerated combination for the poor prognosis group of extensive-stage small-cell lung cancer patients. *Anti-Cancer Drugs* 21:651–655 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Lung cancer is the leading cause of cancer death worldwide. Approximately 12–15% of all lung cancer patients are classified as having small-cell lung cancer (SCLC) [1]. This histological type is distinguished from other forms of bronchogenic carcinomas by its aggressive clinical course with widespread metastases at the time of diagnosis, the frequent occurrence of paraneoplastic syndromes, and its sensitivity to both chemotherapy and radiation therapy. On account of its unique behavior, there is a separate staging system for SCLC, with tumors divided into limited or extensive stage (ED-SCLC) rather than the customary tumor-node-metastasis (TNM) classification. In patients with limited disease, chemotherapy combined with external thoracic radiotherapy and prophylactic cranial irradiation (PCI) yields a high response rate and survival prolongation. However, treatment of the extensive disease remains palliative with median survival time of less than 10 months [2,3]. Platinum-based combinations with etoposide have become the standard of care for SCLC since the 1980s [4]. Two randomized trials that substituted cisplatin with carboplatin in platinum-based combinations with etoposide or with tenoposide and vincristin did not show any significant differencies in the response rate or median survival [5,6]. Furthermore, the carboplatin–etoposide combination was found to be less toxic [5].

Most of the recent clinical trials in lung cancer have focused on non-small-cell lung cancer. There have been, however, some developments in the SCLC management. Among third-generation chemotherapeutics, paclitaxel and camptothecines seem to have the most promising antitumor activity in SCLC. The taxane paclitaxel has been found to be active as monotherapy in the first-line treatment of SCLC patients with a response rate of 34% [7]. Several trials have studied the addition of paclitaxel to platinum–etoposide (PE) regimens. Two randomized phase III trials have failed to show any survival benefit with the triple regimen, whereas significant increase in toxicity and mortality was also observed [8,9].

Irinotecan (CPT-11) is a semisynthetic derivative of the natural alkaloid camptothecan and acts as a topoisomerase I inhibitor. A randomized phase III trial conducted by the Japanese Clinical Oncology Group compared irinotecan and cisplatin (IP) with PE in ED-SCLC and found a statistically significant difference in the response rates (84.4 vs. 67.5%, $P = 0.02$) and median overall survival

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(OS) (21.8 vs. 9.2 months, $P = 0.002$) in favor of patients receiving IP [10]. A large North American phase III trial, designed and conducted by the Southwest Oncology Group, failed to confirm the earlier reported survival benefit observed with IP in Japanese patients [11].

We conducted a phase II trial to evaluate whether the addition of irinotecan to the standard carboplatin–etoposide combination leads to improved response rates in nonJapanese ED-SCLC patients without increasing toxicity.

Patients and methods

Inclusion criteria

Patients with histologically or cytologically confirmed diagnosis of SCLC staged as extensive disease (in terms of extension beyond one hemithorax or presence of pleural effusion [12]) were considered eligible for the study if they met the following criteria: (i) no earlier treatment for SCLC, (ii) performance status (PS) 0–2, according to the World Health Organization scale, (iii) estimated life expectancy of at least 12 weeks, (iv) adequate organ function including white blood count of more than 3.5×10^9/l, absolute neutrophil count of more than 1.5×10^9/l, platelet count of more than 100×10^9/l, serum bilirubin of less than 1.5 times the upper limit of normal (ULN), serum transaminases of less than $2 \times$ ULN (or $< 5 \times$ ULN if there were hepatic metastases), and serum creatinine of less than 1.4 mg/dl, (v) consent for implementation of adequate contraception measures, (vi) absence of history of bowel disease, (vii) willing to sign an informed consent form. This study was approved by the designated ethics review boards and was conducted according to the ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines. Written informed consent was obtained from each patient before treatment.

Exclusion criteria

Patients were not eligible for the study if they had (i) histological diagnosis of mixed SCLC/non-small-cell lung cancer type; (ii) serious concomitant systemic disorders, such as unstable angina and class III or IV heart disease, as defined by the New York Heart Association; (iii) history of other malignancies; (iv) untreated symptomatic central nervous system metastases (central nervous system metastatic disease was allowed if the patient had already been treated and was stable for more than 2 weeks after radiotherapy); and, finally, if they were (v) pregnant or breast feeding.

Baseline examinations consisted of initial assessment that included a detailed medical history and physical examination, complete blood cell, serum creatinine, electrolytes, and liver enzymes counts. No staging examinations were required except for those already performed for confirmation of ED-SCLC.

Treatment

All treatments were administered in a day-clinic setting. Patients received triweekly intravenous carboplatin area under the curve 5 by the Calvert formula on day 1, etoposide 75 mg/m^2 on days 1, 2, and 3 and irinotecan 150 mg/m^2 on day 2 for up to six cycles. Before each infusion of the carboplatin–etoposide–irinotecan triplet, the white blood count count had to be $\geq 3.0 \times 10^9$/l and platelets $\geq 100 \times 10^9$/l. Treatment could be delayed for up to 3 weeks until these cell counts had been restored. Dosage modifications were made according to protocol guidelines, generally resulting in a 75% reduction of the calculated doses in case of severe or prolonged hematological toxicity. Prophylactic granulocyte colony-stimulating factor administration was suggested on days 5–8 in patients who had already developed grade 3–4 neutropenia. Loperamide was used for the treatment of irinotecan-induced diarrhoea. Atropine (0.5 mg) was to be administered in patients who would develop abdominal cramps or diarrhoea during irinotecan infusion. Antiemetic treatment with 5HT3 antagonists was administered before chemotherapy at every cycle.

For patients with confirmed complete response (CR), the protocol recommended PCI. Chemotherapy was discontinued in case of unacceptable toxicity or disease progression. Further chemotherapy and palliative radiotherapy at relapse were permitted.

Response evaluation

Patients having completed at least one course of treatment were considered evaluable for response. Tumor in all patients was assessed with the aid of computed tomography at baseline, after the third and sixth course of treatment, and every 3 months thereafter until tumor progression was documented during follow-up. Objective tumor response and toxicity were assessed according to the Response Evaluation Criteria in Solid Tumors [13] and the Common Toxicity Criteria of the National Cancer Institute Grading System (version 3.0), respectively. No repeated bronchoscopy was planned to confirm CR.

Study endpoints/assessments during and after treatment

This study was designed as a single-institute phase II trial attempting to evaluate the efficacy and tolerability of the carboplatin–etoposide–irinotecan regimen in patients with ED-SCLC. The primary endpoint was the objective tumor response and the secondary endpoints were the safety and adverse event profile, time to progression (TTP), and OS.

Assuming that the expected overall response rate would be at least 50%, a sample of 24 patients was required in the first step. If a minimum of 12 responses was observed, we would move on to the next step of enrolling 54 patients into the study. OS and TTP were estimated using the Kaplan–Meier method. The Breslow (Generalized Wilcoxon) test was used to compare the survival

distribution according to clinical (sites and number of metastases) and laboratory [lactate dehydrogenase (LDH) levels] parameters. OS was measured from the date of registration to the protocol until death by any cause. Surviving patients were censored at the date of last contact. TTP was measured from the date of registration until relapse or death from the disease. For patients who responded to chemotherapy, duration of response was measured from the date of best response until relapse or death from the disease.

Results

Patient characteristics

From September 2004 to June 2006, a total of 54 patients were enrolled into this trial. The patient characteristics at baseline are shown in Table 1. The median age was 62.3 years (range 38–77 years), most patients (87.0%) were of good PS (0–1) and seven of 54 patients (12.9%) had a PS of 2. Thirty-three of 54 patients (61.1%) had metastases in more than one metastatic site. Six of 54 patients (11.1%) had brain metastases and in one of these patients the brain was the only site of documented extensiveness of the disease. Forty-three patients (79.6%) had elevated LDH levels (ULN 223 IU/l) at the time of registration, whereas for two patients LDH levels were unknown.

Table 1 Patient characteristics

Sex	
Male	46/54 (85.2%)
Female	8/54 (14.8%)
Performance status	
0	26/54 (48.1%)
1	21/54 (38.9%)
2	7/54 (13.0%)
Number of metastases	
1	21/54 (38.9%)
>1	33/54 (61.1%)
Sites of metastases	
Brain	6/54 (11.1%)
Liver	27/54 (50.0%)
Bones	26/54 (48.1%)
Pleural effusion	6/54 (11.1%)
Adrenals	8/54 (14.8%)

Treatment details

A total of 270 treatment cycles was administered. Thirty-six of 54 patients (66.7%) received all six cycles, as planned. Three of 54 patients (5.6%) received only one cycle because of the rapid deterioration of their condition, whereas one of them died as a result of toxicity.

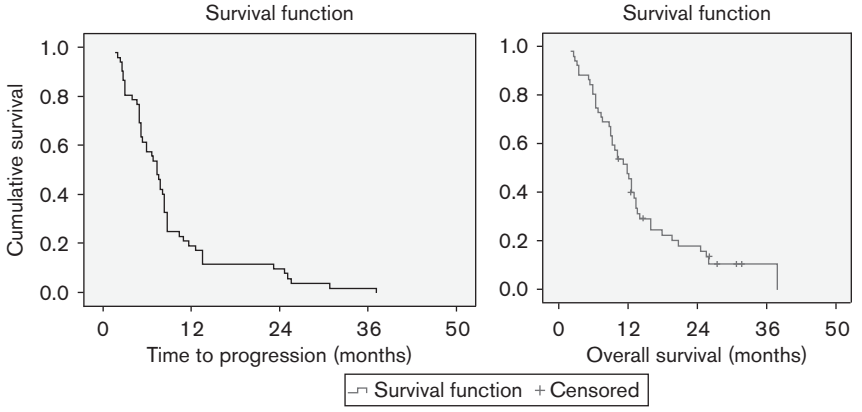
Treatment efficacy

CR, partial response, or stable disease were achieved in 40 of 54 patients (75% response rate). CR was observed in 10 patients (18%) after six cycles. Eight of them had disease remission after the first three cycles. In two of the patients with stable disease (3.7%), recurrence was observed right after the completion of therapy. The OS survival and TTP curves are presented in Fig. 1.

Median OS was estimated at 12 months [95% confidence interval (CI): 10.3–13.9], and 23 patients were still alive a year after their entry into the study. All the patients had disease progression at the time of the analysis and median TTP was 8 months (95% CI: 6.6–8.9). In four patients, there was no computed tomography confirmation of disease progression, but there was clinical progression based on performance status and laboratory results.

Forty-three of 54 patients (79.6%) had elevated LDH levels at baseline. In 14 of them (34.1%) the levels were normal after treatment, but no significant correlation was observed between these levels and OS ($P = 0.085$) or time to progression ($P = 0.680$). Survival was better in patients with only one site of metastases as compared with those with more than one site, and this difference

Fig. 1



Kaplan–Meier estimates of time to progression and overall survival for all patients.

was statistically significant ($P = 0.027$). The presence of brain metastases was also correlated to worse survival ($P = 0.041$), but this was based on only six patients.

Toxicity/safety

Hematological and nonhematological toxicities are summarized in Table 2. Two toxic deaths were reported. The first one occurred after the first cycle owing to fatal grade 3 thrombocytopenia. The second patient developed generalized peritonitis when he was being hospitalized for grade 4 neutropenia and grade 3 diarrhoea. The most common hematological toxicity was neutropenia. Abdominal cramps during irinotecan infusion were not reported. Hospitalization because of grade 3 diarrhoea was required in five of 54 (9.25%) patients.

Further treatment

Only five of the 10 patients with CR (50%) agreed to undergo PCI. Twenty-two patients received second-line therapy after recurrence. Two patients underwent palliative external thoracic radiotherapy and 20 were administered intravenous systematic chemotherapy. Eighteen of these 20 patients (90%) received topotecan as salvage treatment.

Discussion

Three decades ago, the sensitivity of SCLC to both chemotherapy and radiotherapy raised high hopes that this malignancy would be 'curable'. A quarter of a century later, the outlook is not much better concerning patients with this disease. Several therapeutic approaches, such as thoracic radiotherapy during chemotherapy and PCI [4], have improved the 5-year survival for limited SCLC but progress made in ED-SCLC has been minimal. Some third-generation antineoplastic drugs, such as taxanes and topoisomerase I inhibitors, had shown promising results [7,14–16]. However, it was only after Noda *et al.* [10] showed the superiority of the cisplatin and irinotecan doublet to the standard etoposide combination that the interest in new chemotherapy regiments for ED-SCLC was renewed. Unfortunately, these results, which had been observed in Japanese patients, were not reproduced in a phase III US trial in the Western population [17]. These differences in results may be attributed to different clinical trial designs and dosage schedules of the two studies. A Southwest Oncology Group trial further addressed the question of irinotecan superiority. Although patients receiving the cisplatin–irinotecan combination have a trend for better OS, progression-free survival, 1-year progression-free survival, and response as compared with patients receiving cisplatin and etoposide were not statistically significant [11]. In contrast, a Scandinavian study that compared the efficacy of irinotecan and carboplatin (IC) to that of oral etoposide and carboplatin has shown a statistically significant prolongation of survival in favor of the IC combination. The median survival time was 8.5 months for the IC doublet as compared with 7.1 months for etoposide and carboplatin ($P = 0.02$). Quality of life scores were also slightly better. No significant differences were observed in hematological toxicity [18].

Table 2 Incidence of toxicity

	Grade 1–4	Grade 3–4
	No. of patients (%)	No. of patients (%)
Neutropenia	18 (33.3)	9 (16.0)
Anaemia	9 (16.7)	0 (0.0)
Thrombocytopenia	14 (25.9)	1 (1.8)
Diarrhoea	12 (22.2)	5 (9.3)

In this study, we evaluated the addition of irinotecan to the standard carboplatin–etoposide combination (rather than replacing etoposide) in nonJapanese patients with ED-SCLC. The effort was to achieve response benefit without increase in toxicity. The triweekly schedule of irinotecan administration was based on phase II trials that show better results when irinotecan monotherapy and combinations are delivered every 3 or 4 weeks rather than on a weekly basis [19,20]. Triplet combinations have shown higher response rates than standard platinum doublets in the past, but there was greater toxicity without median survival improvement [8,9]. Our triplet regimen seems to be effective and well tolerated. The median OS of 12 months (95% CI: 10.3–13.9) and median TTP of 8 months (95% CI: 6.6–8.9) are better than results of the published studies so far (10 and 5.5 months, respectively) [2,10,11,17]. There were two toxic deaths (3.7%); the first one was because of fatal grade 3 thrombocytopenia whereas the second patient developed generalized peritonitis after grade 4 neutropenia and grade 3 diarrhoea. This percentage is much lower than the 7–8% death rate observed in other triplet regimen trials [8,21,22]. Pharmacogenomic analysis was not performed in our study, but a most recent trial showed that single nucleotide polymorphisms of ABCB1 and UGT1A1 genes can predict the occurrence of irinotecan-related toxicity [11]. The replacement of cisplatin with carboplatin makes this regimen an attractive solution to administer on a day-clinic setting. The above efficacy results, which were accompanied with limited toxicity, lead us to the conviction that this therapeutic approach is worthy of undergoing additional phase II and eventually phase III trials. It holds serious potential to become a preferable alternative to the standard therapy that is used to date.

In our study, no markers of efficacy were identified. Twenty-one of the enrolled patients had one site of metastases and a significantly better survival rate ($P = 0.027$) as compared with those with more than one site. The presence of only brain metastases was correlated to worse survival ($P = 0.041$) and this supports the proposal of the International Association for the Study

of Lung Cancer to extend the TNM descriptors to SCLC [23,24]. This will allow us to distinguish patients who should receive aggressive treatment despite their extensive disease.

Although comparing different clinical trials can lead to false conclusions, this phase II study suggests that the use of irinotecan combined with the standard platinum-based etoposide combination is superior to the standard first-line therapy. We recommend that more phase II trials be conducted to confirm these promising results to proceed to phase III trials in the future. Careful selection of patients according to their full TNM staging and genomic profile can lead to even more accurate results in future studies.

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