Cancer Chemother Pharmacol (2006) 58: 86–90
DOI 10.1007/s00280-005-0114-4

ORIGINAL ARTICLE

Kiyoshi Mori · Yukari Kamiyama · Tetsuro Kondo
Yasuhiko Kano · Tetsuro Kodama

Pilot phase II study of weekly chemotherapy with paclitaxel and carboplatin for refractory or relapsed small-cell lung cancer

Received: 24 May 2005 / Accepted: 15 August 2005 / Published online: 31 January 2006

Abstract *Purpose*: The safety and efficacy of weekly chemotherapy with paclitaxel and carboplatin for the treatment of patients with refractory or relapsed small-cell lung cancer (SCLC) were evaluated. *Patients and methods*: Paclitaxel (100 mg/m^2) and carboplatin (with a target area under the concentration versus time curve of 2 mg min/ml using the Calvert formula) were administered to patients with previously- treated SCLC on days 1 and 8 at every 3–4 weeks. *Results*: A total of 29 patients (pts) [male/female, 26/3 pts; median age 62.7 years (43–74); performance status 0/1/2, 9/10/10 pts] were enrolled between March 2000 and June 2002. The mean number of cycles administered per pt was 3 (1–7). The overall response rate was 69% (95% confidence interval 52–86%), and 83% (15/18) in sensitive pts and 45% (5/11) in refractory pts ($P < 0.01$). The overall median survival time was 29.6 weeks with a 1-year survival rate of 37% [34.1 weeks in sensitive pts and 23.1 weeks in refractory pts ($P = 0.085$), 46.9 weeks in PS 0–1 and 16.3 weeks in PS 2 ($P < 0.001$)]. The median time to progressive disease was 16.4 weeks [21.7 weeks in sensitive pts and 15.3 weeks in refractory pts ($P = 0.32$)]. Hematologic toxicities observed included grade ≥3 neutropenia in 55%, grade ≥3 anemia in 36%, and grade ≥3 thrombocytopenia in 3%. Non-hematologic toxicities were mild except for grade 3 diarrhea in three pts and grade 3 pneumonitis in one pt. *Conclusion*: Weekly chemotherapy with paclitaxel and carboplatin was well-tolerated and gave a high-response rate in pts with refractory or relapsed small-cell lung cancer.

K. Mori (✉) · Y. Kamiyama · T. Kondo · Y. Kano · T. Kodama
Department of Thoracic Diseases, Tochigi Cancer Center,
4-9-13 Yonan, Utsunomiya, 320-0834 Tochigi, Japan
E-mail: kmori@tcc.pref.tochigi.jp
E-mail: ykamiyam@ tcc.pref.tochigi.jp
E-mail: tkondo@tcc.pref.tochigi.jp
E-mail: ykano@tcc.pref.tochigi.jp
E-mail: tkodama@tcc.pref.tochigi.jp
Tel.: +81-28-6585151
Fax: +81-28-6585669

Keywords Small-cell lung cancer · Second line chemotherapy · Weekly chemotherapy · Carboplatin · Paclitaxel

Introduction

Small-cell lung cancer (SCLC) accounts for 15–20% of the total number of lung cancer patients. It grows more rapidly and shows a higher incidence of remote metastasis than non-small-cell lung cancer (NSCLC). It is apparently more sensitive to chemotherapy and radiotherapy than NSCLC, but is cured only in a small number of patients and recurs in a great majority of them. Recurrent SCLC is less responsive to chemotherapy, and the median survival time from recurrence to death is 2–3 months [3]. Chemotherapy has been reported to contribute to the improvement of symptoms and prolongation of the survival time in patients with recurrent SCLC [2, 6]. In general, first-line chemotherapy is conducted for sensitive disease (relapse ≥90 days after completion of first-line chemotherapy). For refractory disease (relapse during first-line chemotherapy or less than 90 days after completion of initial chemotherapy), however, salvage chemotherapy is undertaken due to the lack of a standard chemotherapy regimen. However, no standard chemotherapy has been established for recurrent SCLC [17].

In recent years, a number of institutions have undertaken weekly chemotherapy for lung cancer and reported the outcome [11, 14]. Weekly chemotherapy is being reported to be useful for recurrent SCLC as well [1, 4, 7, 10]. It is considered to be more suitable than the standard chemotherapy conducted every 3–4 weeks for recurrent cases with impaired bone marrow due to initial chemotherapy because it uses smaller doses of anti-cancer drugs in each administration cycle and it is possible to titrate their doses after starting the treatment depending on hemotoxicity and the patients' physical condition.

When used alone, paclitaxel was reported to produce good therapeutic results in patients with refractory SCLC with a response rate of 29% and a median survival time of 100 days [15]. When coadministered with carboplatin, paclitaxel showed even better results with a response rate of 73.5% and a median survival time of 31 weeks [5]. This report prompted us to conduct the present study to evaluate the efficacy and safety of weekly chemotherapy using carboplatin and paclitaxel in recurrent SCLC patients.

Patients and methods

Patient selection

All patients with histologically or cytologically confirmed SCLC with documented progression after chemotherapy were eligible for this phase II trial. Patients with either limited- or extensive-stage disease were allowed. The trial was initiated after a rest period of at least 4 weeks following previous chemotherapy (2 weeks in the case of radiotherapy). Patients were required to have recovered completely from prior therapy, with no ongoing toxicity greater than grade 1.

Other eligibility criteria included expected survival of 12 weeks, age $\leq$ 75 years, Eastern cooperative oncology group performance score of 0–2, measurable lesions, and adequate hematological function. Primary refractory disease was defined as relapse during first-line chemotherapy or less than 90 days after completing initial chemotherapy, and sensitive disease was defined as relapse ≥90 days after completion of first-line chemotherapy.

The ethical committee of the Tochigi cancer center approved the protocols. Written informed consent stating that the patient was aware of the investigational nature of this treatment regimen was obtained in every case.

Treatment

Paclitaxel was administered at a dose of 100 mg/m^2 intravenously during a 1-h infusion on days 1and 8 of the treatment cycle. Carboplatin was given at a dose designed to give an area under the curve (AUC) of 2 on days 1 and 8 with the use of the Calvert formula: 2 × (creatinine clearance + 25). Prior to each treatment, patients were given 50 mg diphenhydramine orally, and an H2 blocker intravenously along with 16 mg dexamethasone . Intrvenously administered antiemetics, 3 mg graniston, were used. The length of each chemotherapy cycle was 21 days. Patients who experienced grade 4 leukopenia or neutropenia that lasted for three days or more , or who experienced grade 4 thrombocytopenia, reversible grade 2 neurotoxicity, or liver dysfunction, received reduced doses of both paclitaxel and carboplatin (paclitaxel 80 mg/m^2, carboplatin AUC1.5) for the next cycle. If non-hematologic toxicities of grade 3 or more occurred, treatment was stopped. Subsequent courses of chemotherapy were started after 3–4 weeks when the leukocyte count was 3,000/mm^3 or more, the neutrophil count 1,500/mm^3 or more, the platelet count 75,000/mm^3 or more, serum creatinine less than 1.5 mg/dl, GOT and GPT less than twice the upper limit of the normal range, and neurotoxicity was grade 1 or less. If these variables did not return to adequate levels by the first day of the next course of chemotherapy, treatment was withheld until full recovery. If more than 6 weeks passed from the time of the last treatment before these criteria were satisfied, or if more than dose reduction were indicated, the patient was taken off the study at that time, but still included in the analysis.

Evaluation of response and toxicity

Pretreatment evaluation included medical history, physical examination, complete blood count, bone marrow examination, serum biochemical analyses, chest roentgenogram, electrocardiogram, and urinalysis. All patients underwent radionuclide bone scan, bone marrow aspiration or biopsy, magnetic resonance or computerized tomography (CT) of the brain, and CT of thorax and abdomen. Complete blood count, biochemical tests, serum electrolytes, urinalysis, and chest roentgenograms were obtained weekly during this phase II trial.

Response and toxicity were evaluated on the basis of tumor images obtained by CT and other techniques, laboratory data and subjective/objective symptoms before, during, and after administration of the study drugs and during the period from completion of treatment to final analysis. Measurable disease parameters were determined every 4 weeks by various means such as CT. Evaluation was made in compliance with response evaluation criteria in solid tumors (RECIST) guidelines [16] for anti-tumor activity, and with NCI common toxicity criteria Version 2 for safety. Patients were withdrawn from the study if evidence of tumor progression was observed. The Institutional Ethical Review Committee approved the study.

Statistical analyses

Time to progression was measured as a period from the start of this treatment to the identifiable time for progression. Survival time was measured from the start of the present treatment until death or last follow-up. The Kaplan–Meier method was used to calculate survival curves. Survival differences between subgroups were compared using the log-rank test. The chi-square test was used to compare the percentage of patients in each group.

Primary endpoints were response rate and toxicity; secondary endpoints were survival and time to pro-

gression. We chose a 50% response rate as a desirable target level and a 25% response rate as an undesirable target. Our design had a power in excess of 95% and less than 20% type I error, requiring 26 patients. Considering the percentage of probable dropout cases, 29 patients were required.

Results

Patient characteristics

Twenty-nine patients were enrolled in this study from March 2000 to June 2002. All patients were assessed for toxicity, response and survival. Characteristics of the 29 patients are listed in Table 1. There were 11 refractory cases and 18 sensitive cases against the first-line chemotherapy.

Efficacy of treatment

The mean number of cycles administered per patient was three, and ranged from one to seven. There were no cycles of dose reduction. One patient achieved a complete response (CR) and 19 patients showed partial response (PR). Overall response rate was 69% (20/29) [95% confidence interval (CI) 52–86%]. The response rate was 83% (15/18, 95% CI: 66–100%) in sensitive cases and 45% (5/11, 95% CI: 16–75%) in refractory cases, with significant differences between the two groups ($P < 0.01$). The median time to progressive disease was 16.4 weeks [21.7 weeks in sensitive pts and 15.3 weeks in refractory pts ($P = 0.32$)]. The overall median survival time was 29.6 weeks (Fig. 1) with no significant differences between sensitive cases (34.1 weeks) and refractory cases (23.1 weeks) ($P = 0.085$). The median survival time differed significantly between PS 0 or 1 patients (46.9 weeks) and PS 2 patients (16.3 weeks) ($P < 0.001$). The 1-year survival rate was 38% (11/29).

Toxicities

Table 2 lists the toxicities observed during this study. Hematological and blood biochemical reactions included a high incidence of leukopenia and neutropenia, leukopenia, and neutropenia of grade 3 or higher occurred in 55 and 55%, respectively. All neutropenia patients recovered upon treatment with G-CSF. Anemia and thrombocytopenia of grade 3 or higher occurred in 27 and 3%, respectively. Subjective and objective symptoms observed included grade 3 diarrhea in three patients who all showed improvement after administration of anti-cholinergic drugs, and grade 3 pneumonitis in one, who showed rapid recovery following administration of steroids. Other subjective and objective symptoms observed were of grade 2 or less and included nausea in 34%, vomiting in 10%, alopecia in 59%, neuropathy in 28%, and flushing in 17%. All of these toxicities disappeared or improved by symptomatic treatment. There were no toxic deaths.

Discussion

No standard chemotherapy for recurrent SCLC has been established since only two Phase III clinical studies have been reported to date on chemotherapy for this disease [13, 17]. In contrast, many studies have been undertaken on salvage chemotherapy for recurrent SCLC, with monotherapy with new third-generation anti-cancer agents and platinum-based multi-drug chemotherapy being the mainstay in recent years [1, 4, 5, 8–10, 14, 15]. Some institutions administer anti-cancer drugs on a weekly basis (weekly chemotherapy) [1, 4, 7, 10]. This treatment regimen makes it possible to titrate the dose of anti-cancer drugs depending on adverse reactions and the patients' physical condition after starting the treatment by dividing the dose into some installments.

The results reported with weekly chemotherapy are summarized in Table 3 [1, 4, 7, 10]. While the study by Goto et al. [4] included only sensitive cases, all other studies included 35–64% of refractory cases. The overall response rate ranged between 31% and 88%: 37–91% in sensitive cases and 23–83% in refractory cases. No study, apart from ours, reported any significant difference between sensitive and refractory cases. The overall median survival time was 6.1–11.8 months with no significant differences between sensitive and refractory cases [10]. In our study, the median survival time was 46.9 weeks in PS 0 or 1 patients and 16.3 weeks in PS 2 patients ($P < 0.001$). Naka et al. [10] reported significant differences between PS 0 or 1 patients (6.9 months) and PS 2 patients (3.8 months) [10]. Hemotoxicity was the main adverse reaction in all studies. Thrombocytopenia was milder in our study than in other studies. Diarrhea also showed a high incidence in regimens including CPT-11.

Groen et al. [5] reported therapeutic results similar to ours with carboplatin and paclitaxel therapy: overall response rate of 73.5% and overall median survival time of 31 weeks. They administered carboplatin and paclitaxel at AUC 7 and 175 mg/m^2, respectively at an interval of 3 weeks. These doses were 1.7 and 0.88 times that obtained by us. . The main adverse reaction was hemotoxicity in both studies, but thrombocytopenia was milder in our study. In the study by Groen et al., 22 and 4 of 34 patients received RBC transfusions and platelet transfusions, respectively [5].

In a phase III trial, which compared topotecan versus cyclophosphamide, doxorubicin and vincristine (CAV) in patients with recurrent SCLC [17], the response rate was 24.3 and 18.3%, respectively; time to progression 13.3 and 12.3 weeks; median survival time 25.0 and 24.7 weeks; 1-year survival rate 14.2 and 14.4%. In our study, the response rate was 69%, time to progression 16.4 weeks,

Table 1 Patient characteristics

Eligible patients	29
Gender	
Male	26
Female	3
Age (years)	
Median	63
Range	43–74
Performance status	
0	9
1	10
2	10
Disease extent at relapse	
Limited disease	7
Extensive disease	22
Relapse type	
Refractory case	11
Sensitive relapse case	18
Prior therapy	
Chemotherapy alone	21
Chemotherapy and irradiation	8
Prior chemotherapy regime	
CBDCA + ETOP	3
CDDP + ETOP(PE)	11
CODE + PE	1
CDDP + CPT-11(PI)	9
CDDP + ETOP + CPT-11	3
PE + PI	2
Response to prior chemotherapy	
Complete response	4
Partial response	21
Stable disease	3
Progressive disease	1

CBDCA carboplatin, *ETOP* etoposide, *CDDP* cisplatin, *CODE* cisplatin/vincristine/doxorubicin/etoposide, *CPT-11* irinotecan

median survival time 29.6 weeks, and 1-year survival rate 37%, and our study showed better therapeutic performance in terms of all four parameters although ours was a pilot study and direct comparisons cannot be made.

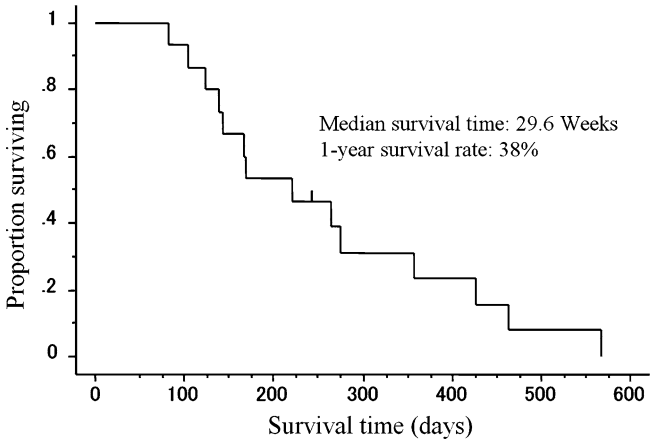

Fig. 1 Kaplan–Meier estimated overall survival curves. Median survival time, 29.6 weeks; 1-year survival rate, 38%

In Japan, cisplatin and irinotecan chemotherapy is the standard therapy for untreated patients in extensive SCLC. Only 8 of 40 patients in the study by Goto et al. [4] and 14 of 29 in our study received irinotecan-based regimens in initial therapy, and no other weekly chemotherapy studies included in Table 3 used such regimens. Carboplatin and paclitaxel combination chemotherapy appears rational in patients with recurrence following initial therapy with cisplatin and irinotecan because the two regimens are not cross resistant.

Conclusion

Weekly chemotherapy with paclitaxel and carboplatin is tolerable and an active regimen for patients with refractory or relapsed SCLC. It is to be recommended as a candidate regimen in planning a phase III clinical study in refractory or relapsed SCLC, and this regimen will ultimately be evaluated in a phase III clinical study.

Table 2 Toxicities ($n = 29$)

	Grade (common toxicity criteria)				Grade ≤ 3 (%)
	1	2	3	4	
Leukopenia	1	7	14	2	16 (55%)
Neutropenia	1	5	9	7	16 (55%)
Anemia	5	8	6	2	8 (27%)
Thrombocytopenia	8	3	1	0	1 (3%)
Diarrhea	7	0	3	0	3 (10%)
Pneumonitis	0	0	1	0	1 (3%)
Nausea	9	1	0	–	
Vomiting	3	0	0	–	
Fatigue	3	3	0	0	
Alopecia	17	0	–	–	
Neuropathy	8	0	0	0	
Flushing	5	–	–	–	
Edema	4	0	0	0	
Arthralgia	3	0	0	0	
Rash	3	0	0	0	
Arrythmia	2	0	0	0	

Table 3 Weekly chemotherapy studies for relapsed small-cell lung cancer

References	Regimen	No. of pts	% of ref pts (%)	RR	RR in sen pts (%)	RR in ref pts (%)	MST (months)
7	CODE	17	35	88	91	83	8.2
10	CPT-11/CBDCA	28	46	31	37	23	6.1
1	CPT-11/CDDP	25	64	80	78	81	7.9
4	CPT-11/CDDP/ETOP	40	0	78	78	–	11.8
Present study	CBDCA/PTX	29	38	69	83	45	7.4

pts patients, *ref* refractory, *sen* sensitive, *RR* response rate, *MST* median survival time, *CODE* cisplatin/vincristine/doxorubicin/etoposide, *CPT-11* irinotecan, *ETOP* etoposide, *CDDP* cisplatin, *PTX* paclitaxel, *CBDCA* carboplatin

Acknowledgements This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare (Tokyo, Japan), and by a second term comprehensive 10-year strategy for cancer control.

References

1. Ando M, Kobayashi K, Yoshimura A, Kurimoto F, Seike M, Nara M, et al (2004) Weekly administration of irinotecan (CPT-11) plus cisplatin for refractory or relapsed small cell lung cancer. Lung Cancer 44:121–127
2. Einhorn LH, Pennington K, McClean J (1990) Phase II trial of daily oral VP-16 in refractory small cell lung cancer: a Hoosier Oncology Group study. Semin Oncol 17:32
3. Glisson BS (2003) Recurrent small cell lung cancer. Update. Semin Oncol 30:72
4. Goto K, Sekine I, Nishiwaki Y, Kakinuma R, Kubota K, Matsumoto T, et al (2004) Multi-institutional phase II trial of irinotecan, cisplatin, and etoposide for sensitive relapsed small-cell lung cancer. Br J Cancer 91:659–665
5. Groen HJ, Fokkema E, Biesma B, Kwa B, van Putten JW, Postmus PE, et al (1999) Paclitaxel and carboplatin in the treatment of small-cell lung cancer patients resistant to cyclophosphamide, doxorubicin, and etoposide: a non-cross-resistant schedule. J Clin Oncol 17:927–932
6. Johnson DH, Greco FA, Strupp J, Hande KR, Hainsworth JD (1990) Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. J Clin Oncol 8:1613
7. Kubota K, Nishiwaki Y, Kakinuma R, Hojo F, Matsumoto T, Ohmatsu H, et al (1997) Dose-intensive weekly chemotherapy for treatment of relapsed small-cell lung cancer. J Clin Oncol 15:292–296
8. Masters GA, Declerck L, Blanke C, Sandler A, DeVore R, Miller K, et al (2003) Phase II trial of gemcitabine in refractory or relapsed small-cell lung cancer: eastern cooperative oncology group trial 1597. J Clin Oncol 21:1550–1555
9. Masuda N, Fukuoka M, Kusunoki Y, Matsui K, Takifuji N, Kudoh S, et al (1992) CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol 10:1225–1229
10. Naka N, Kawahara M, Okishio S, Hosoe S, Ogawara M, Atagi S, et al (2002) Phase II study of weekly irinotecan and carboplatin for refractory or relapsed small-cell lung cancer. Lung Cancer 37:319–323
11. Neubauer M, Schwartz J, Caracandas J, Conkling P, Ilegbodu D, Tuttle T, et al (2004) Results of a phase II study of weekly paclitaxel plus carboplatin in patients with extensive small-cell lung cancer with Eastern cooperative oncology group performance status of 2, or age? 70 years. J Clin Oncol 22:1872–1877
12. Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, et al (2002) Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 346:85–91
13. Schiller JH, Adak S, Cella D, DeVore RF III, Johnson DH (2001) Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593-A phase III trial of the Eastern cooperative oncology group. J Clin Oncol 19:2114–2122
14. Sekine I, Nishiwaki Y, Kakinuma R, Kubota K, Hojo F, Matsumoto T, et al (2003) Phase I/II trial of weekly cisplatin, etoposide, and irinotecan chemotherapy for metastatic lung cancer. JCOG 9507. Br J Cancer 88:808–813
15. Smit EF, Fokkema E, Biesma B, Groen HJ, Snoek W, Postmus PE (1998) A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. Br J Cancer 77:347–351
16. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
17. von Pawel J, Schiller JH, Shepherd FA, Fields SZ, Kleisbauer JP, Chrysson NG, et al (1999) Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 17:658