

A weekly regimen of cisplatin, paclitaxel and topotecan with granulocyte-colony stimulating factor support for patients with extensive disease small cell lung cancer: a phase II study

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Summary The present study was aimed at defining the antitumour activity of the cisplatin-paclitaxel-topotecan (CPT) weekly administration with G-CSF support in chemo-naïve SCLC patients with extensive disease (ED-SCLC). Chemo-naïve ED-SCLC patients received cisplatin 40 mg/m², paclitaxel 85 mg/m², and topotecan 2.25 mg/m² weekly, with G-CSF (5 µg/kg days 3–5) support, for a maximum of 12 weeks. 37 patients were treated, for a total of 348 cycles delivered. 8 complete responses (22%) and 22 partial responses (59%) were recorded, giving an 81% [95% CI = 65–92%] ORR. At a 13-month (range, 4–26) median follow-up, median progression-free and overall survival were 8 months and 12.5 months, with 1-year and 2-year projected survivals of 55% and 21%, respectively. No toxic deaths occurred. Grade 4 neutropenia and thrombocytopenia occurred in 6 and 3 patients, respectively. Only one case of neutropenic sepsis was recorded, while haemorrhagic thrombocytopenia was never observed. Diarrhoea, paraesthesias and fatigue were the main nonhaematologic toxicities being severe in 6, 2 and 10 patients, respectively. The weekly CPT combination with G-CSF support represents a well tolerated therapeutic approach in chemo-naïve ED-SCLC patients. The activity rate seems at least similar to that achievable with the standard front-line approaches. © 2001 Cancer Research Campaign <http://www.bjcancer.com>

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Lung cancer still represents one of the most relevant health problems in Western countries, being the most common cause of cancer-related death. Small cell lung cancer (SCLC) accounts for 25% of all lung cancers (Landis et al, 1998). The majority of SCLC patients already have extensive disease at diagnosis.

In spite of more than two decades of intensive investigation with various chemotherapy combinations, the prognosis of these patients remains very poor, the median survival time still being shorter than one year, and the probability of remaining alive after 5 years being remote (Johnson et al, 1990).

Recently, several new agents have demonstrated activity against SCLC.

Topotecan is a semisynthetic hydrophilic analogue of camptothecin, an alkaloid derived from the oriental tree *Camptotheca acuminata*. It exerts its cytotoxic effects through the inhibition of the nuclear enzyme topoisomerase I (Chen and Liu, 1994). Single-agent topotecan, administered as a short-term infusion daily × 5 days every 3 weeks, has produced remarkable results in either chemo-naïve or pretreated SCLC patients (Schiller et al, 1996; Ardizzoni et al, 1997). Although this schedule has been the most commonly used in phase II trials, other schedules like the 24-hour infusion weekly administration, the 21-day low-dose continuous

infusion etc. have been testing in the last few years, giving interesting results (Slichenmeyer et al, 1993; Burris et al, 1994; Haas et al, 1994; Hochster et al, 1994).

Paclitaxel has also been tested as single agent in SCLC patients. In two phase II studies it produced an ORR of 34% and 41% in untreated patients with extensive disease (Kirshling et al, 1994; Ettinger et al, 1995). It has also been tested in combination with cisplatin (or carboplatin) and etoposide with promising preliminary results (Levitan et al, 1995; Kelly et al, 1996; Hainsworth et al, 1997; Glisson et al, 1999).

It has recently been reported that the weekly short-term (1- or 3-hour) administration of paclitaxel may result in a dramatic increase of the dose-density, at a price of a moderate toxicity (Fennelly et al, 1997; Akerley et al, 1998; Sikov et al, 1998).

The combination of topotecan and paclitaxel was tested in chemo-naïve SCLC patients, showing a very promising ORR and median survival. However, haematologic toxicity proved to be relevant, and prolonged G-CSF support was required (Jett et al., 1997).

In view of the relevant myelotoxicity associated with both the topotecan-cisplatin (Rowinsky et al, 1997) and topotecan-paclitaxel combinations (O'Reilly et al, 1997) when the standard 5-day topotecan administration is used, we previously conducted a phase I study testing the simultaneous weekly administration of cisplatin, paclitaxel and topotecan (CPT). In the presence of G-CSF support from days 3 to 5 of each week, doses of cisplatin 40 mg/m², paclitaxel 85 mg/m² and topotecan 2.25 mg/m² were given weekly at a price of mild haematologic and nonhaematologic toxicity (Frasci et al, 1999).

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In view of the promising therapeutic activity observed in the phase I study in both chemo-naïve and pretreated SCLC patients, we have undertaken this phase II study aimed at better defining the efficacy of this new regimen as a front-line approach in patients with extensive-disease small cell lung cancer.

METHODS

Eligibility criteria

Candidates for this study were patients with histologically/cytologically proven SCLC who had not received prior chemotherapy or radiotherapy. Disease had to extend beyond the hemithorax of origin and regional lymph-nodes. Other eligibility criteria included clinically or radiologically measurable or evaluable disease, age between 18 and 75 years, Zubrod performance status of 0 to 2, life expectancy of at least 12 weeks, no previous or concurrent malignancy, except for inactive non-melanoma skin cancer, and *in situ* carcinoma of the cervix.

Adequate bone marrow (absolute neutrophil count $>2 \times 10^9/l$, platelet count $>100 \times 10^9/l$, and haemoglobin level $>10 \text{ g l}^{-1}$), liver (bilirubin level <2 times the upper normal limit, AST and/or ALT <3 times the upper normal limit, prothrombin time <1.5 times control), and renal function (creatinine clearance $>60 \text{ ml min}^{-1}$) were also required. The presence of severe cardiac arrhythmia or heart failure, second- or third-degree heart block or acute myocardial infarction within 4 months prior to study entry were considered as exclusion criteria. CNS metastases were not considered an exclusion criterion, provided that a good symptomatic control could be achieved with steroids. All patients gave their witnessed written informed consent, and the protocol was approved by the Ethical Committee for the Biologic Research of the National Tumor Institute of Naples.

Pretreatment workup

Pretreatment evaluation included a complete history and physical examination, determination of haematology, chemistry, and tumour marker levels (CEA, TPA, NSE), ECG, chest X-ray, brain, chest and abdomen CT, radionuclide scan of bone and bronchoscopy. Additional radiologic examinations were also performed as necessary to document the extent of disease.

Treatment

All eligible patients received paclitaxel 85 mg/m^2 (as a 1-hour infusion) followed by cisplatin 40 mg/m^2 and topotecan 2.25 mg/m^2 as a 30-min i.v. infusion, weekly. Prophylaxis for hypersensitivity reactions consisted of dexamethasone 8 mg i.v. 1 hour and promethazine $50 \text{ mg i.v. plus ranitidine } 50 \text{ mg i.v. 30 minutes}$ before paclitaxel administration. G-CSF was given at the dose of $5 \mu\text{g/kg}^{-1} \text{ day}^{-1}$ days 3–5 of each week. A minimum of 6 treatment administrations were delivered. Patients showing a clinical complete or partial response received additional 6 administrations. In absence of a major tumour regression patients were shifted to a cyclophosphamide-doxorubicin-etoposide treatment. This regimen was also used for patients relapsing after initial response.

Patients with brain metastasis who developed progressive disease at any time, or did not have a major response in the brain after 6 administrations, received whole brain radiotherapy. In patients who

had a major response in the brain after 6 administrations, whole brain radiotherapy was deferred until after the 12th administration.

Adjustments according to toxicity

Chemotherapy was given at full doses if neutrophil count was $\geq 1500/\text{mm}^3$, and platelet count $\geq 100\,000/\text{mm}^3$. For neutrophil count $>1000/\text{mm}^3$, or platelet count $>75\,000/\text{mm}^3$, it was delivered at 50% of the planned dose. For neutrophil count $<1000/\text{mm}^3$, or platelet count $<75\,000/\text{mm}^3$ chemotherapy was always omitted on that day. In presence of grade 4 neutropenia lasting more than 7 days, febrile neutropenia ($>38.5^\circ\text{C}$ with ANC <500), grade 4 thrombocytopenia (lasting longer than 4 days), grade 4 anaemia, grade 3–4 nonhaematologic toxicity (except for nausea/vomiting and alopecia) the weekly chemotherapy dose was reduced to 75% in the subsequent administrations. Dose reduction was not performed for shorter than 4 days severe myelosuppression.

Toxicity and response assessment

Toxicities and response were graded according to the WHO criteria (Miller et al, 1981).

Haematologic toxicity was assessed by performing weekly blood cell count and differential. In cases of grade 4 haematological toxicity occurrence these tests were performed every other day.

For each patient, the worst toxicity encountered during the treatment was reported.

The clinical restaging was performed after 6- and 12-weekly administrations. It consisted of physical examination, routine laboratory tests, serum tumour markers, and repetition of all initially abnormal diagnostic procedures. For bone metastases, the standard WHO response criteria were applied: CR was considered as the complete disappearance of all lesions on X-ray or scan for at least 4 weeks; PR was defined as a greater than 50% reduction in the number of the areas of uptake from the pretreatment radionuclide scan, or partial decrease ($>50\%$) in size of lytic lesions, recalcification of lytic lesions, or decreased density of blastic lesions for at least 4 weeks.

All eligible patients were included in the response and survival analysis, on an 'intent to treat' basis. Duration of complete response was calculated from the date of the first documentation of CR until date of disease progression; duration of partial response, and time to treatment failure were both calculated from the day of initial treatment until PD was firstly noted. Overall survival (OS) was calculated from the beginning of treatment to death by any cause.

For time-to-event data, the cumulative proportion of patients who had not yet experienced the event was plotted as function of time by means of the Kaplan–Meier product-limit approach (Kaplan and Meier, 1958).

Study design

Since we believe that the achievement of a complete response often translates in a prolongation of survival in SCLC patients, we have chosen the cCR rate as the main end-point of this study.

We aimed at obtaining a 30% cCR rate with this new combination, and set a cCR rate of 10% as the lowest level of interest. According to the Simon two-stage minimax design (Simon, 1989), at least 7 complete responses were required among 33 patients to

consider this combination worth of further evaluation ($\alpha = 0.05$; $1-\beta = 90\%$). A first analysis was planned after 22 patients had been enrolled. The accrual would have been stopped if fewer than 3 complete responses had been observed.

RESULTS

Demographics

Between August 1997 and July 1999 3 patients entered the study.

Table 1 outlines the main patient characteristics. 29 patients were male. Median age was 51 (range, 38–76) years, and 14 patients (38%) had a Zubrod performance status of 2. Clinically asymptomatic brain involvement was present in 10 (27%) patients, and 23 (62%) patients had increased LDH serum levels. 22 (59%) patients had 3 or more sites of involvement.

Response

All the 37 enrolled patients were evaluated for response on an 'intent to treat' basis.

33 patients completed at least 6 administrations and were assessed for response. 4 patients did not complete the first 6 administrations due to disease progression (2 cases), protracted thrombocytopenia (1 case), or refusal (1 case). All of them were considered as failures.

An overall, 8 complete (22%) and 22 partial responses (59%) were recorded, for a 81% [95% CI = 65–92%] overall response rate (Table 2). All the 8 complete responses occurred in the first 33 enrolled patients. 6 complete responses were achieved after 6 administrations. In another 2 patients residual tumour persisted in lung and liver after 6 cycles, but disappeared by the 12th administration. Liver was the main site of disease involvement in 5/8

Table 2 Responses (37 assessable patients)

	No. of patients
Complete responses (%)	8 (22)
Partial responses (%)	22 (59)
Stable disease (%)	2 (5.5)
Progressions (%) or treatment failures	5 (13.5)
Overall responses (%)	30 (81)

complete responders, the tumour being localized in bone (2) and adrenal (1) in the remaining 3 cases.

26 out of 30 responder patients received the planned 12 administrations of chemotherapy. In 3 patients chemotherapy was suspended because of the occurrence of severe fatigue (2), or peripheral neuropathy (1), while another patient refused treatment after 8 administrations.

7 of the 10 patients with brain metastasis achieved a major response after 6 cycles. In 5 of these cases a major tumour regression was also observed in the brain, but it was never complete.

Of the 14 patients with poor performance status, overall 6 major responses (43%) were recorded, only one being complete.

Survival

At the time of the present analysis 5 patients were still progression-free and 11 were still alive, with a median follow-up time of 13 (range, 4–26) months in the survivors. Actuarial estimation of median failure-free and overall survival for the entire population was 8 months [95% CI = 6–9] and 12.5 months [95% CI = 8–14], the 1- and 2-year survival rates were 55% and 21%, respectively (Figures 1 and 2). The one-year survival probability was 68%, 61% and 29% in complete responders, partial responders, and nonresponders, respectively. Among the 8 patients still alive at a >18-month follow-up, 4 had achieved a complete response, and 3 a partial response, while the last one had failed to respond either to first-line or second-line treatment. The 14 patients with Zubrod performance status 2 experienced a substantially shorter median survival time (8 months) than those with better performance status (14 months). A worse survival outcome was also seen in the 23 patients with increased LDH serum levels at diagnosis. Indeed, median survival was 7.5 months in this group, as compared to 14 months in the others. The median survival time was slightly shorter in the 10 patients with brain metastasis (10 months) as compared to the others (13 months).

Table 1 Patient characteristics

Characteristic	No. of patients
Age, years	
Median	51
Range	38–76
Sex	
Male	29
Female	8
ECOG performance status	
0	6
1	17
2	14
Site of metastasis	
Contralateral lung	21
Extrathoracic lymph-nodes	4
Liver	26
Brain	10
Bone	24
Adrenal	8
No. of disease sites	
1–2	15
≥3	22
LDH serum levels	
Normal	14
Increased	23
Total	37

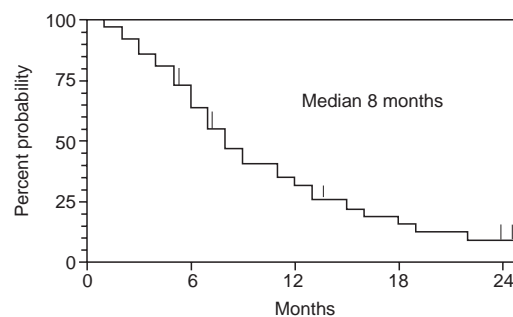


Figure 1 Progression-free survival. Total patients = 37; progression-free = 5

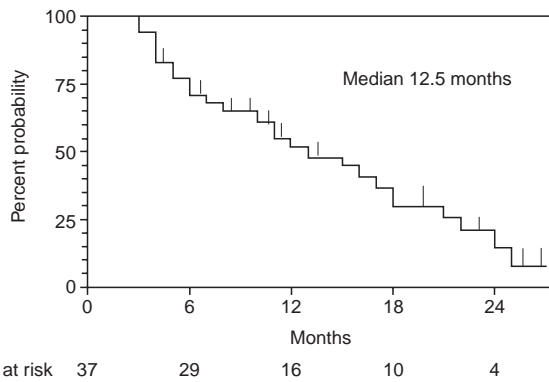


Figure 2 Overall survival. Total patients = 37; alive = 11

Toxicity

Table 3 summarizes the myelotoxicity data on the overall 348 administrations.

No toxic deaths were observed. Only one case of neutropenic fever was recorded, after 9 chemotherapy administrations, in a patient with massive liver and bone involvement. Overall, grade 3 and 4 neutropenia occurred in 10 (27%) and 6 (16%) patients, respectively. Thrombocytopenia was less relevant, being of grade 3 in 7 patients (19%), while grade 4 never occurred. However, in one patient (with a concomitant chronic hepatitis) a persistent grade 3 thrombocytopenia occurred after 2 administrations, which caused the definitive suspension of chemotherapy. Anaemia was quite frequent especially in patients who received more than 6 administrations. Haemoglobin levels fell below 11 g l^{-1} in all patients, and in 7 patients (19%) a packed red blood cell transfusion was required.

Alopecia was very frequent, occurring in 33 of the 37 enrolled patients. Other nonhaematologic toxicities were generally mild/moderate. Severe hypersensitivity reactions to paclitaxel were not observed. Gastrointestinal toxicity was moderate in the majority of patients and never led to definitive treatment discontinuation. Grade 3 vomiting and diarrhoea occurred in 4 patients (11%) and 7 patients (19%), respectively.

A 25% reduction of all 3 drug doses was performed in patients showing severe diarrhoea and this prevented a further occurrence of this side effect.

Severe constipation was observed in 6 patients, and an additional 3 patients had moderate transient elevation of hepatic enzymes. Severe fatigue occurred in 10 patients, and in 2 cases it led to the definitive suspension of the treatment (both patients

Table 3 Worst acute toxicity (37 patients)

Toxicity	WHO grade			
	1	2	3	4
Haemoglobin	13	17	6	1
ANC	6	15	10	6
Platelets	15	12	7	0
Vomiting	20	11	4	0
Diarrhoea	8	9	6	0
Neuropathy	12	4	2	0
Mucositis	9	5	0	0
Fatigue	15	9	10	0
Alopecia	11	15	7	0

were responsive after the first 6 chemotherapy cycles). Neurologic toxicity was not a problem in the majority of patients. Mild peripheral paraesthesia occurred in 12 patients (32%) and in an additional 4 patients (11%) a grade 2 neurotoxicity was observed. Only 2 patients showed grade 3 peripheral neuropathy: in one case it occurred after 8 cycles, causing the discontinuation of chemotherapy, the other patient showed a worsening of peripheral neuropathy after the completion of treatment. In both cases neurotoxicity persisted for several months.

Musculoskeletal symptoms like transient arthralgia and myalgia were quite frequent, occurring in an overall 19 patients (51%) but they were never severe, and responded well to anti-inflammatory drugs.

Nephrotoxicity was almost non-existent: only 4 cycles were associated with a mild and transient elevation of creatinine serum level.

Mucositis was not uncommon, but it was never severe. One or more episodes of rhinorrhagia occurred in 13 patients.

DISCUSSION

The haematologic data of the present study confirms the findings of our previous phase I trial testing this new weekly combination (Frasci et al, 1999). Indeed, the occurrence of severe neutropenia or thrombocytopenia was negligible with this combination, while anaemia, although more frequent, actually cannot be considered as a life-threatening toxicity. Severe nonhaematologic toxicity was also uncommon. Gastrointestinal and neurologic side effects were frequent, but rarely compromised the continuation of the treatment.

In view of the high chemosensitivity of SCLC, we did not consider the rate of objective responses as a reliable parameter to evaluate the capability of this new regimen to improve the prognosis of SCLC patients. Indeed, ORRs higher than 80% have also been reported in the past with the use of standard combinations not including new agents (Johnson et al, 1990).

In order to ascertain whether our new combination could be a real step ahead in the treatment of SCLC patients, we set a quite restrictive criterion to pursue in future phase III trials. Indeed, we set a 30% complete response rate as the target activity rate, and considered a complete response rate with a 95% confidence interval which fell below 10% as uninteresting.

A high proportion of patients has shown a major regression of the tumour in the present trial, and the number of complete responses observed (8), although not very impressive, exceeded the minimum required by the study design. Moreover, it deserves to be remarked that all patients showed disseminated disease at beginning of chemotherapy.

The short duration of the treatment could have had a role in determining this unimpressive complete response rate.

The presence of poor prognostic features at beginning of treatment like poor performance status, brain metastases, and elevated LDH serum levels could also have had a substantial role in underestimating the CR rate. Indeed, about 30% of patients treated by us had brain metastasis, and none obtained a complete regression of the tumour in the brain. The relevant number of patients with poor performance status could also have contributed to reducing the ORR and the CR rate of the whole population, since they were 43% and 7% in this group.

The survival outcome of our patients deserves some additional comments. Of course the absence of a randomization makes it

difficult to draw definite conclusions on this issue; however, we think that the median survival time observed in our study population is interesting. Indeed, if we look at the previous experiences conducted either with 'old' or with 'new' combinations, the achievement of a longer than 1-year median survival time was very uncommon in extensive-disease patients. Moreover, as previously remarked, our study population was not at all a 'good-prognosis' one. In fact, the survival outcome looks much better in our study if patients with poor performance status or with elevated LDH serum levels are excluded from the analysis, in these cases the median survival times are 14 months and 15 months, respectively.

Although it is impossible, on the basis of our results, to conclude that the addition of cisplatin of paclitaxel and topotecan can substantially modify the life expectancy of ED-SCLC patients, it must be remarked that also in other trials which tested the topotecan-paclitaxel regimen a good median survival was seen, even when an unimpressive ORR and CR rate were obtained (Jacobs et al, 1999; Lynch et al, 1999; Tweedy et al, 1999). However, the results of the recent CALGB 9430 phase II trial testing the paclitaxel-topotecan combination do not suggest an advantage to this regimen compared to standard etoposide and platinum (Lynch et al, 2000).

The use of weekly rather than daily times 5 every 3 weeks topotecan was a peculiarity of the present study. It is interesting to remark that the cumulative 3-week dose of topotecan in our study (6.75 mg/m²) was much higher than those reported in other trials testing the topotecan in two- or three-drug regimens (O'Reilly et al, 1997; Rowinsky et al, 1997; Dunphy et al, 1998; Ten Bokkel Huinink et al, 1998; Raefsky et al, 1999). Other phase II trials testing the cisplatin-paclitaxel-topotecan regimen in SCLC patients have not been conducted. However, in a phase I study from the Netherlands the cisplatin-paclitaxel-topotecan triple combination was also tested, by using the standard every 3-week schedule for all 3 drugs. In presence of G-CSF support doses of cisplatin and paclitaxel of 75 mg/m² and 110 mg/m² (24-hour) were given, and the dose of TPT did not exceed 0.4 mg/m² d 1-5 every 3 weeks (Ten Bokkel Huinink et al, 1998). Preliminary phase I experiences in refractory solid tumours with the carboplatin-paclitaxel-topotecan combination have also been reported. A standard daily times 3 or 5 every 3 weeks schedule had always been performed. The recommended dose of TPT was 0.5 mg/m²/d × 5 days, or 0.75 mg/m²/d × 3 days, in both cases giving a cumulative over 3-week dose less than half of that delivered by us (Raefsky et al, 1999; Dunphy et al, 1998). Preliminary phase II results of this regimen in small cell lung cancer have also been recently reported. An 88% overall response rate was obtained in patients with extensive disease, although patients with poor performance status tolerated treatment poorly (Gray et al, 2000).

The very good tolerance of weekly topotecan given in a short-term infusion as single agent has been recently confirmed by the preliminary data of a phase I study, although activity data were not reported (Clark et al, 1999). Therefore, further confirmations of the efficacy of this schedule are required.

In conclusion, the results of the present phase II study suggest that 2 new drugs like paclitaxel and topotecan can be safely combined at full doses with cisplatin, by using a weekly schedule with G-CSF support. This combination results in both a good ORR and promising median survival time. Only a large phase III trial will establish whether this dose-dense chemotherapy approach can produce a substantial prognostic improvement in extensive-stage SCLC patients.

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