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ORIGINAL ARTICLE

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Second-line chemotherapy in small cell lung cancer in a modified administration of topotecan combined with paclitaxel: a phase II study

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Abstract *Purpose*: Our main objective was to investigate the response rate in pretreated patients with small cell lung cancer (SCLC) who received a weekly administration of topotecan and paclitaxel; our secondary objectives were to assess toxicity and survival. *Methods*: Topotecan 1.75 mg/m^2 was combined with paclitaxel 70 mg/m^2; these cytotoxic agents were administered once every week (day 1) for 3 consecutive weeks (one cycle), and repeated every 28 days (three infusions per cycle) for a minimum of three cycles. *Results*: Forty-five patients were enrolled, 41 of whom were evaluable for response and toxicity. The median number of cycles was two (range 1–6). Eleven/forty-one (26.83%) patients responded: one complete response and ten partial responses; the median duration of response was 4 months (range 2–8 months); the median overall survival was 7 months (95% CI: 4.2–9.8). Myelotoxicity was the most common adverse reaction (grade 3 neutropenia in 19.5% of the patients and grade 4 in 7.32%). Non-hematologic toxicities varied from 2.44% to 9.76%. No patient had to stop treatment due to toxicity. *Conclusion*: Topotecan combined with paclitaxel, given on day 1 on a weekly basis, produced a response rate of 26.83% in pretreated patients with SCLC. Myelotoxicity, particularly neutropenia, was the main adverse reaction, but in a minority of patients.

Keywords Topotecan · Paclitaxel · Weekly administration · SCLC

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Introduction

Topotecan is one of the new cytotoxic agents [1] shown to have efficacy as second-line treatment in both ovarian [2, 3] and small cell lung cancer (SCLC) [4, 5]. The toxicity of a 5-day administration of topotecan has resulted in a modification of this treatment modality and a weekly administration has been promoted [6]. Weekly administration combined with paclitaxel was tested in a Phase I study and the dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) were defined [6]. According to the preliminary report, the advantage of this modality is myelotoxicity reduction without diminishing efficacy. Five-day topotecan administration [2] and the once-every-3-week administration of paclitaxel [7] have been reported and both the agents have also been tested as single agents once every week. The combination with an adjusted dosage has been tested as well [6]. In the present study we administered the new modality to patients with SCLC as second-line treatment with the objectives to investigate response rate, time to tumor progression (TTP), toxicity, and survival.

Patients and methods

Eligibility criteria

Patients > 18 years of age with a histologically or cytologically confirmed diagnosis of SCLC and with bidimensionally measurable disease, pretreated by

chemotherapy and radiotherapy of the primary site, were enrolled in the study. Other eligibility criteria included a World Health Organisation (WHO) performance status (PS) of 0–2, life expectancy of at least 3 months, adequate bone marrow reserves (granulocyte count^3 1.500 dl, platelet count ^{3} 120.00/dl), normal renal (serum creatinine concentration < 1.2 mg/dl) and liver function tests (total serum bilirubin concentration < 3 mg/dl, provided that serum transaminases and serum proteins were normal), normal cardiac function with no history of clinically unstable angina pectoris or myocardial infarction, or congestive heart failure within the previous 6 months. Patients with central nervous system involvement were eligible if they were in remission after radiation therapy. Patients with active infection, malnutrition or a second primary tumor (except for a non-melanoma skin epithelioma or in situ cervix carcinoma) were excluded from the study. The study was approved by our institutional review boards and all the patients gave their written informed consent to participate.

Treatment

All the patients were treated on an outpatient basis. The chemotherapy agents used were paclitaxel and topotecan on a weekly basis for 3 consecutive weeks every 28 days. The plan was to give three courses (each course included three once-every week infusions). The doses were based on the MTD defined by a previous phase I study [6]. Topotecan (Hycamtin; Glaxo SmithKline, Brentford, UK) was supplied in vials of 4 mg lyophilized formulation and was reconstituted with 2 ml sterile water, then diluted with 5% dextrose solution, and administered as a 30-min intravenous infusion. Paclitaxel (Bristol-Myers Squibb, New York, NY, USA) was infused after topotecan and after premedication with dexamethasone 8 mg and both H1 and H2 receptor antagonists to prevent hypersensitivity reactions. Both treatments were given on day 1.

The dose of topotecan was 1.75 mg/m^2 and paclitaxel 70 mg/m^2. Dose adjustment criteria were based on hematological parameters. In cases of grade 3 or 4 febrile or afebrile neutropenia, we reduced both drug doses by 25% in subsequent cycles and rhG-CSF was administered and the next scheduled treatment was postponed for 1 week; this applied to 11 patients (26.83%). Toxicities were graded according to WHO guidelines [8].

Patient evaluation

Pretreatment evaluation included complete medical history and physical examination, full blood count including differential leukocyte and platelet counts, a standard biochemical profile (and creatinine clearance when necessary), electrocardiogram, chest X-rays, ultrasound of the upper abdomen, and computed tomography (CT) scans of the chest, upper and lower abdomen. Additional imaging studies were performed upon clinical indication. Full blood counts with differential were performed weekly; in case of grade 3 or 4 neutropenia or thrombocytopenia, full blood counts were evaluated daily. A detailed medical and physical examination was completed before each course of treatment (three infusions once weekly for 3 consecutive weeks) in order to document symptoms of the disease and treatment toxicities. Biochemical tests, ECG, and chest X-rays were performed every 3 weeks and CT scans at the end of the third cycle (nine infusions).

Definition of response

Complete response (CR) was defined as the disappearance of all measurable or evaluable disease, signs and symptoms and biochemical changes related to the tumor for at least 4 weeks, during which time no new lesions may appear. Partial response (PR) was defined as > 50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions compared with pretreatment measurements, lasting for at least 4 weeks, during which time no new lesions may appear and no existing lesions may enlarge. For hepatic lesions, a reduction of > 30% of the sum of the measured distances from the costal margin at the midclavicular line and at the xiphoid process to the edge of the liver was required. Stable disease (SD) was defined as < 50% reduction or a < 25% increase in the sum of the products of the two perpendicular diameters of all measured lesions and the appearance of no new lesions for 8 weeks. Progressive disease (PD) was defined as an increase in the product of the two perpendicular diameters of any measurable lesion by > 25% over the size present at entry into the study, or, for patients who responded, the size at the time of maximum regression and the appearance of new areas of malignant disease. A two-step deterioration in PS, a > 10% loss of pretreatment weight or increasing symptoms did not by themselves constitute progression of the disease; however, the appearance of these complaints was followed by a new evaluation of the extent of the disease. All responses had to be maintained for at least 4 weeks and be confirmed by an independent panel of radiologists.

Statistical design

This was an expected two-step Phase II study. According to the trial design, 30 patients were to be enrolled during the first part of the study and if an objective response rate of less than 15% was achieved, the treatment would have been abandoned; otherwise, 15–20 additional patients were to be enrolled. The primary endpoint of the study was to determine the efficacy of the regimen and the secondary endpoints, tolerance and survival. The duration of response was calculated from

the day of the first demonstration of response until PD. TTP was calculated from the day of entry into the study until documented PD. Overall survival (OS) was calculated from the day of enrollment until death. The estimation of survival distribution was done by the Kaplan-Meier method.

Results

Patients' demographics

From September 2003 till December 2004, 45 patients were enrolled in this multicenter trial. Forty-one patients were evaluable for response and toxicity and four patients were excluded as they had received one or two infusions which was not a complete cycle; either they refused to continue treatment or there was a rapid deterioration in their condition. The patients' characteristics are shown in Table 1. There were 35 males and six females with a median age of 63 years (range 35–78). Six patients had stage III SCLC and 35 stage IV. Twenty-nine patients had previously undergone radiation therapy (primary site and brain metastasis). All patients had been pretreated: 30 with the combination of cisplatin and etoposide (VP-16) and 11 with cisplatin-paclitaxel. At the time of entry into the present trial all patients had disease recurrence or new metastasis 3–9 months after the end of first-line treatment. The sites of metastases at enrollment were: lungs 20 patients, liver 15, brain eight, bones eight, adrenal gland two and spleen one. Of the 41 evaluable patients, 32 (78%) had responded (PR + CR) after first-line treatment; the remaining patients had SD or DP. There was no difference in the response rate in the two different first-line chemotherapy schedules.

Table 1 Patients' characteristics

		No.	Percentage
Patients evaluable		41	100
Gender			
Male		35	85.37
Female		6	14.63
Age (year)			
Median	63		
Range	35–78		
Disease stage			
III		6	14.63
IV		35	85.37
Histology, primary site			
SCLC		41	100
Performance status (PS) (WHO)			
0		2	4.88
1		28	68.29
2		11	26.83
Prior chemotherapy			
Cisplatin-etoposide		30	73.17
Cisplatin-paclitaxel		11	26.83
Radiation			
On primary site, brain		29	70.73

Compliance with treatment

A total number of 82 chemotherapy cycles with a median of two cycles (three infusions per cycle) per patient were given. Analytically, the number of weekly drug infusions was 378, median 4.6, range 3–12. In five patients, there was a 1-week delay, due to hematological toxicity: four due to neutropenia and one to thrombocytopenia. Dose reduction of topotecan and paclitaxel by 25% was considered necessary in three patients. The aforementioned eight patients were given hematopoietic growth factor and continued treatment until completion of the planned number of courses or until PD. At the time of analysis, nine patients (21.95%) were still alive and 32 dead. The cause of death was disease progression.

Response to treatment and survival

Responses were analyzed on an intention-to-treat basis. There was one complete remission (2.44%) out of the 41 evaluable patients; this patient had only liver metastasis and the evaluation was based on a CT-scan. The duration of response was 4 months. Of the remaining 40 patients, 10 showed PR (24.39%). Total CR and PR was 26.83%. The sites of the responses were in the liver and in the lung. Nineteen (46.34%) patients had SD and 11 (26.83%) disease progression. Median duration of response (11 patients) was 4 months (range 2–8 months) and median TTP was 4 months (range 1–9 months). Five (12.20%) patients reached 1-year survival, counting from the beginning of the present trial. The median OS was 7 months (95% CI: 4.2–9.8) (Fig. 1). No amelioration in PS was observed, while in patients with PD, PS deteriorated: 11 (26.83%) patients went from PS 1 to PS 2, or 3. Of the 11 responders, there were three patients who had undergone prior chemotherapy which included paclitaxel; all the three patients had also responded to first-line therapy which was administered 6–8 months before second-line treatment. Responses are shown in Table 2.

Toxicity

Forty-one patients were evaluable for toxicity. The main adverse reactions were myelotoxicity, diarrhea, asthenia, and alopecia. The number/percentage of patients who suffered from these side effects was rather low, taking into account the fact that all patients had been pretreated within the same year and some had been heavily pretreated. Grade 3 neutropenia was observed in 19.5% of the patients and grade 4 in 7.32%. Grade 3 thrombocytopenia was seen in 2.44% of the patients and diarrhea as well as asthenia in 9.76%. Only patients with grade 4 neutropenia required hospitalization. Toxicity is shown in Table 3.

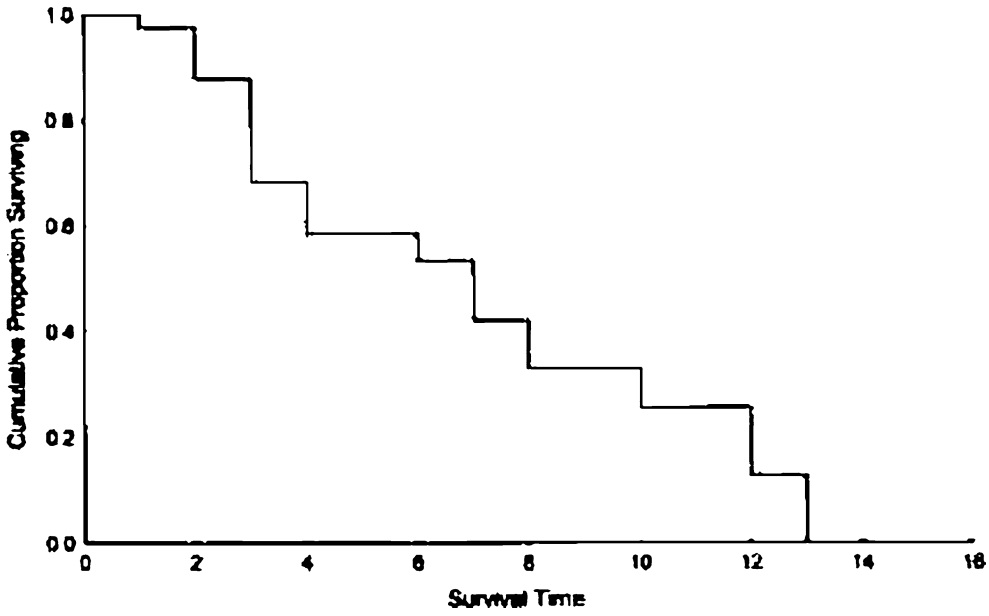

Fig. 1 Kaplan-Meier overall survival (OS)

Table 2 Response rate

	n	Percentage
Complete	1	2.44
Partial	10	24.39
Total response	11	26.83
Stable disease (SD)	19	46.34
Disease progression	11	26.83

Table 3 Serious hematological and non-hematological toxicity: all patients, all cycles

	Grade 3		Grade 4	
	n	Percentage	*n*	Percentage
Neutropenia	8	19.5	3	7.32
Anemia	–	–	–	–
Thrombocytopenia	1	2.44	–	–
Nausea/vomiting	2	4.88	–	–
Diarrhea	4	9.76	–	–
Neurosensory	4	9.76	–	–
Muscular pain	2	4.88	–	–
Asthenia	4	9.76	–	–
Allergy	–	–	–	–
Alopecia	10	24.39	–	–
Cardiac	–	–	–	–
Nephrotoxicity	–	–	–	–

Discussion

Small cell lung cancer is a biologically aggressive tumor with a tendency to metastasize within a short period of time; the percentages of metastases in other organs varies from 28–87%. The most common metastatic sites are the mediastinal lymph nodes, liver, bones, adrenals, and brain [9]. Standard first-line chemotherapy agents, cisplatin or its analogue carboplatin and etoposide, have been established during the last decade [10–14]. Although the partial and CR rate is very high, there is a recurrence within 6–12 months in the great majority of patients. Several attempts have been made in order to optimize chemotherapy response. One attempt was the alternating cyclic combination [14, 15] or dose intensification [16–18]. Since dose intensity is defined both by the dose and the time interval required to deliver the dose, [19] weekly regimens also became incorporated into clinical practice. Several weekly treatments have been tested and the weekly schedule has been compared with the 3-weekly schedule in randomized studies. CRs varying from 15%–40% have been reported in chemotherapy-naive patients [20–22]. In general, the prognosis in advanced SCLC has been affected very little. In order to improve the effectiveness of chemotherapy and the prognosis of SCLC, there has been a tendency to incorporate new cytotoxic agents in the optimization and intensification of the treatment. The present study attempts to contribute to a better prognosis in advanced SCLC chemotherapy by choosing a weekly treatment with a new combination of agents used very little for this particular tumor. Paclitaxel has often been tested on a weekly basis either as a single agent or in combination [23–25]. Topotecan has not been tested a great deal on a weekly basis [6, 26, 27], but has instead been used on a 5-day administration which has been shown to be very toxic [2, 3]. The actual effectiveness of topotecan and paclitaxel in pretreated and recurrent SCLC patients is promising as indicated by the 26.83% CR and PR in our study. This is, however, similar to responses produced by other second-line treatments [20–22]. It is worth mentioning that the toxicities reported in our study were observed in a lower percentage of patients than that observed in other treatments for SCLC [20–22]. In one study where topotecan was given as second-line treatment, there was 46% myelotoxicity (grade 3 neutropenia) and 12%,

grade 4. Topotecan 1.5 mg/m^2 was administered as a single agent and the high percentage of neutropenia may have been due to the 5-day daily administration of this agent [28]. Weekly administration of cisplatin 50 mg/m^2 (day 1) and etoposide 75 mg/m^2 (days 1 and 2), alternating with ifosfamide 2 g/m^2 IV and doxorubicin 25 mg/m^2 IV, resulted in 76.9% cycle reduction due to hematologic toxicity by 67.4%, renal toxicity by 7.2%, and other toxicities by 23.5% [20] Similar findings with respect to toxicity were observed in another combined trial which included topotecan and where G-CSF support was given prophylactically [23]

One has to take into account that many of our patients had been quite heavily pretreated and 11 out of 41 had received paclitaxel as first-line treatment. The combination of topotecan and paclitaxel has well-tolerated toxicity with only a low percentage of patients with grade 3 or 4 myelotoxicity and a very small number of patients who had treatment delay and dose reduction.

To conclude, the combination of topotecan and paclitaxel administered weekly as second-line chemotherapy in SCLC was effective in at least 25% of our patients. Toxicity was well-tolerated since only 11/41 (26.83%) patients had dose reduction or treatment postponement. The weekly administration of these agents decreases toxicity and maintains efficacy.

References

1. Burris HA III, Hanauske AR, Jahnson RK et al. (1992) Activity of topotecan, a new topoisomerase I inhibitor, against human tumor colony-forming units in vitro. J Natl Cancer Inst 84:1816–1821
2. Ardizzoni A, Hansen H, Dombernowsky P, et al. (1997) Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: a phase II study in patients with refractory and sensitive disease. J Clin Oncol 15:2090–2096
3. Markman M (1997) Topotecan: an important new drug in the management of ovarian cancer. Semin Oncol 4 (suppl 5):55–58
4. Bokkel Huinick WT, Gore M, Carmichael J. et al. (1997) Topotecan vs paclitaxel for the treatment or recurrent epithelial ovarian cancer. J Clin Oncol 15:2183–2187
5. Giaccone G (1989) Second line chemotherapy in small-cell lung cancer. Lung Cancer 5:207–213
6. Stathopoulos GP, Rigatos SK, Christodoulou Ch. et al. (2004) Weekly administration of topotecan and paclitaxel in pretreated advanced cancer patients: a phase I/II study. Cancer Chemother Pharmacol 54:259–264
7. Nabholtz JM, Gelmon K, Bontenbal M, et al. (1996) Multicenter randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. J Clin Oncol 14:1858–1867
8. Miller AB, Hoogstraten B, Staqnet M (1981) Reporting results of cancer treatment. 47:207–214
9. Murren J, Glatstein E, Pass PI (2001) Small cell lung cancer. In: De Vita VT, Hellman S, Rosenberg SA (eds) Cancer of the lung. Cancer principles and practice of oncology, 6th edn. Lippincott Williams and Wilkins, Philadelphia, pp 983–1018
10. Clark PI, Slevin ML, Joel SP, et al. (1994) A randomized trial of two etoposide schedules in small-cell lung cancer: the influence of pharmacokinetics on efficacy and toxicity. J Clin Oncol 12:1427–1432
11. Smith IE, Harland SJ, Robinson BA et al. (1985) Carboplatin: a very active new cisplatin analog in the treatment of small cell lung cancer. Cancer Treat Rep 69:43–47
12. Evans WK, Feld R, Osoba D, et al. (1984) VP-16 alone and in combination with cisplatin in previously treated patients with small cell lung cancer. Cancer 53:1461–1465
13. Evans WK, Shepherd FA, Feld R, et al. (1985) VP-16 and cisplatin as a first-line therapy for small-cell lung cancer. J Clin Oncol 3:1471–1475
14. Roth BJ, Johnson DH, Einhorn LH et al. (1992) Randomized study of cyclophosphamide, doxorubicin and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 10:282–291
15. Ettinger DS, Finkelstein DM, Abeloff MD, et al. (1990) A randomized comparison of standard chemotherapy versus alternating chemotherapy and maintenance versus no maintenance therapy for extensive-stage small-cell lung cancer: a phase III study of the Eastern Cooperative Oncology Group. J Clin Oncol 8:230–235
16. Arriagada R, Le Chevallier T, Pignon JP et al (1993) Initial chemotherapeutic doses and survival in patients with limited small-cell lung cancer. N Engl J Med 329:1848–1853
17. Pujol JL, Donillard JY, Riviere A, et al. (1997) Dose-intensity of a four-drug chemotherapy regimen with or without recombinant human granulocyte-macrophage colony-stimulating factor in extensive-stage small-cell lung cancer: a multicenter randomized phase III study. J Clin Oncol 15:2082–2089
18. Thatcher N, Girling DJ, Hopwood P, et al. (2000) Improving survival without reducing quality of life in small- cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support: results of a British Medical Research Council Multicenter Randomized Trial. Medical Research Council Lung Cancer Working Party. J Clin Oncol 18:395–404
19. Hryniuk W, Bush H. (1984) The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 2: 281–285
20. Souhami RL, Rudd R, Ruiz de Elvira MC, et al. (1994) Randomized trial comparing weekly versus 3-week chemotherapy in small-cell lung cancer: a Cancer Research Campaign trial. J Clin Oncol 12:1806–1813
21. Murray N, Shah A, Osoba D, et al. (1991) Intensive weekly chemotherapy for the treatment of extensive-stage small-cell lung cancer. J Clin Oncol 9:1632–1637
22. Murray N, Livingston R, Shepherd F, et al. (1997) Randomized study of CODE versus alternating CAV/EP for extensive-stage small-cell lung cancer: an intergroup study of the National Cancer Institute of Canada Clinical Trials Group and the Southwest Oncology Group. J Clin Oncol 17: 2300–2308
23. Frasci G, Nicollela G, Comella P, et al. (2001) 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. Br J Cancer 84:1166–1171
24. Klaassen V, Wilke H, Strumberg D, et al. (1996). Phase I study with a weekly 1-h infusion of paclitaxel in heavily pretreated patients with metastatic breast and ovarian cancer. Eur J Cancer 32A:547–552
25. Seidman AD, Hudis CA, Albanel J. et al. (1998). Dose-dense therapy with weekly 1-h paclitaxel infusions in the treatment of metastatic breast cancer. J Clin Oncol 16:353–361
26. Chank RS, Fracasso PM, Picus J. (1999). A phase I study of weekly topotecan as a bolus infusion [abstract]. Proc Am Soc Clin Oncol 18:207a
27. Rowinsky EK. (2002) Weekly topotecan: an alternative to topotecan's standard daily×5 schedule? Oncologist 7:324–329
28. Schiller JH, Adak S, Cella D, et al. (2001) Topotecan vs observation after cisplatin plus etoposide in extensive stage SCLC: E7593—a phase III trial of the Eastern Cooperative Group. J Clin Oncol 19:2114–2122