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ORIGINAL ARTICLE

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Front-line paclitaxel and topotecan chemotherapy in advanced or metastatic non-small-cell lung cancer: a phase II trial

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Abstract *Purpose*: Based on previous experience, we combined topotecan with paclitaxel (weekly administration) in patients with non-small-cell lung cancer (NSCLC). Our primary objective was to determine the response rate and survival and our secondary objective, the safety of the regimen. *Methods*: From October 2003, until March 2005, 45 patients all with histologically or cytologically confirmed NSCLC were enrolled. All patients were chemotherapy and radiotherapy naive. Both agents were infused on day 1 of every week once for three consecutive weeks, every 28 days. Three infusions were considered as one course. The treatment plan was to give three courses (nine infusions) and then to evaluate the response. Topotecan (1.75 mg/m^2) was infused for 30 min and paclitaxel (70 mg/m^2) for 90 min; these doses had been established as the maximum tolerated dose in a previous phase I–II trial. *Results*: Eighteen/45 (40%) patients responded, 2 (4.4%) complete responses and 16 (35.6%) partial responses. Twenty-one (46.7%) patients had stable disease, and 6 (13.3%) disease progression. The median duration of response was 8 months and median time to tumor progression 9 months. Grade 3 and 4 neutropenia was observed in two patients (in these two patients, the dose of both drugs was reduced by 25% and G-CSF was given), grade 4 thrombocytopenia in one patient and grade 4 anemia in one patient. *Conclusion*: This novel combination of topotecan–paclitaxel in a weekly administration rendered a 40% response rate, with very low toxicity in stages IIIA, IIIB and IV NSCLC patients.

Keywords Topotecan · Paclitaxel · Non-small-cell lung cancer

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Introduction

There has been a gradual tendency over the last 10 years to avoid cisplatin in the chemotherapy treatment of patients with non-small-cell lung cancer (NSCLC). Several other newer cytotoxic agents have been used in combinations based on carboplatin or taxanes (paclitaxel or docetaxel) [1–6], in attempts to achieve lower toxicities and higher responsiveness. Gemcitabine, vinorelbine and irinotecan are some of the newer agents also used in combination [7–12]. The results have shown a similar responsiveness to that observed with cisplatin-based combinations but the adverse reactions, although different, still exist. Even though renal or gastrointestinal (GI) tract toxicities may have been reduced, myelotoxicity was increased [13]. Of the newer class of cytotoxic agents, camptothecines were introduced for other tumors; irinotecan mainly, is one of the most used agents for GI tract malignancies [14–16]. Topotecan is a drug which has been administered mainly as second-line treatment in small-cell lung cancer (SCLC) and ovarian cancer [17–19]. This agent has not been adequately tested in other malignant tumors but by reducing its myelotoxicity (by substituting the 5-day administration with a weekly administration) there might be more opportunities for it to be tested and to show its activity in other solid tumors such as NSCLC. In a previous trial [20] the mode of topotecan administration was modified and instead of a 5-day consecutive infusion, it was administered once weekly. The 5-day treatment produced neutropenia which was often not acceptable [17–19]. Weekly administration did greatly diminish

neutropenia without reducing the efficacy [20, 21]. In this weekly mode of administration, topotecan can be safely combined with other cytotoxic agents and tested in other malignancies.

The aim of the present phase II trial was to combine topotecan with paclitaxel in untreated, advanced, inoperable NSCLC patients. The choice of paclitaxel was based on the fact that it is an acceptable first-line agent for NSCLC [3, 22–24] and it has also been administered effectively on a weekly basis [25, 26].

Patients and methods

Eligibility criteria

Patients >18 years of age with a histologically or cytologically confirmed diagnosis of NSCLC, stage III (IIIA and IIIB) and IV with bidimensionally measurable disease, who were chemotherapy and radiotherapy naive were enrolled in the study. Other eligibility criteria included a World Health Organization (WHO) performance status (PS) of 0–2, life expectancy of at least 3 months, adequate bone marrow reserve (granulocyte count_1,500 μl^{-1}, platelet count_120,000/μl^{-1}), normal renal function (serum creatinine concentration <1.2 mg/dl), and liver function tests (total serum bilirubin <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 prior 6 months. Patients with central nervous system involvement were eligible if they were asymptomatic. 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 patients gave their written informed consent to participate.

Treatment plan

All patients were treated on an outpatient basis. Topotecan and paclitaxel were administered on a weekly basis for three consecutive weeks on days 1, 8 and 15, every 28 days. The plan was to give three courses (each course included three once-weekly infusions) and the doses were based on the maximum tolerated dose defined by a previous phase I–II study [20]. Topotecan (Hycamptin; Glaxo SmithKline, Brentford, UK) was supplied in vials of a 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 (90 min) after topotecan and after premedication with dexamethasone (8 mg) and both H_1 and H_2 receptor antagonists to prevent hypersensitivity reactions. Both agents were given on day 1.

The dose of topotecan was 1.75 mg/m^2 and of 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 the subsequent cycles, rhG-CSF was administered and the next scheduled treatment was postponed for 1 week: this applied to 4 patients (8.9%). Toxicities were graded according to the WHO guidelines [27].

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 cases 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 three consecutive weeks), in order to document the 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

For the assessment of response, we used imaging-based evaluation. Complete response (CR) was considered to be the disappearance of all measurable disease confirmed at 4 weeks at the earliest; partial response (PR), a 30% decrease, also confirmed at 4 weeks at the earliest. In stable disease (SD), neither the PR nor the progressive disease (PD) criteria were met; PD, a 20% increase of tumor burden and no CR, PR or SD documented before increased disease. Response data were based on the response evaluation criteria in solid tumors (RECIST) [28]. A two-step deterioration in PS, a >10% loss in 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

Simon's two-stage minimax design was used for the calculation of the sample size. The significance level was set to be 5% and the power 90%. Low response prob-

ability was set to be 20% and the level of useful activity 40%. In the first stage, 24 patients enrolled in the study. If five or fewer responses were observed then the study was terminated. Otherwise, if more than five responses are observed then another 21 patients are recruited for a maximum sample size of 45 patients.

The primary endpoints of the study were to determine efficacy and survival and the secondary endpoint, the safety of the regimen. The duration of response was calculated from the day of the first demonstration of response until PD. Time to tumor progression (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, or to the end of the study. The estimation of survival distribution was done by the Kaplan–Meier method.

Results

From October 2003 until March 2005, 46 patients were enrolled in this multicenter trial. Based on the planned statistical design, among the first 24 patients, the objective response rate was 33% and 21 additional patients were recruited for the study. Forty-five patients were evaluable for response and toxicity and one patient was excluded as he refused to continue after the first infusion. The patients' characteristics are shown in Table 1. There were 36 males and 9 females with a median age of 64 years (range 45–81 years). One patient was of stage IIIA N_2 inoperable, 17 stage IIIB and 27 stage IV. No patient had had prior chemotherapy or radiotherapy treatment. The majority of the patients (68.9%) were of WHO PS 1.

Table 1 Patients' characteristics

		No.	%
Patients enrolled		46	100
Patients evaluable		45	97.8
Gender			
Male		36	80.0
Female		9	20
Age (year)			
Median	64		
Range	45–81		
Disease stage			
IIIA		1	2.2
IIIB		17	37.8
IV		27	60.0
Histology			
Adenocarcinoma		18	40.0
Squamous cell		14	31.1
Undifferentiated		13	29.9
Performance status (WHO)			
0		12	26.7
1		31	68.9
2		2	4.4
Metastatic site (Stage IV) $n = 27$			
Skeleton		10	37.0
Liver		5	18.5
Bone–liver		5	18.5
Adrenal		2	7.4
Other lung		1	3.7
Brain		1	3.7
Bone–brain		1	3.7
Liver–brain		1	3.7
Bone–adrenal–brain		1	3.7

Compliance with treatment

One hundred and forty-seven chemotherapy cycles (441 infusions) with a median of three cycles (9 infusions) and range 1–6 (3–18 infusions) were given. In five patients there was a 1-week treatment delay (in four due to hematological toxicity: three due to neutropenia and/or thrombocytopenia, one to anemia) and in one due to grade 3 diarrhea. The doses of paclitaxel and topotecan were reduced by 25% in two patients. Two patients were given growth factor and they continued treatment until completion of the planned doses. At the time of analysis, 26 patients (57.8%) were still alive and 19 were dead. The cause of death was due to the disease progression in 18 patients and due to pulmonary insufficiency and heart failure in 1.

Response to treatment and survival

Survival was evaluated on an intention-to-treat basis. There were two CRs (4.4%) out of the 45 evaluable patients, both stage IIIB and the evaluation was based on a CT scan. The duration of the response was 6+ months and 10 months for these two patients. Sixteen patients out of 45 had a PR (35.6%). The total CR and PR was 40%. Lung and visceral (liver) were mainly the sites of disease of the responders. Twenty-one/45 patients had SD (46.7%) and 6/45 PD (13.3%). The median duration of response (18 patients) was 8 months (range 3–12 months, 95% CI: 6.62–9.38) and the median TTP was 9 months (range 5–14 months, 95% CI: 6.36–11.64). Fourteen patients (31.1%) survived over 1 year and another 10 patients were still alive and well 9–10 months after treatment. The median OS according to the Kaplan–Meier calculation was 15 months (range 2–20 months, 95% CI: 10.75–19.25) (Table 2). Figure 1 shows the Kaplan–Meier survival curve.

Toxicity

Forty-five patients were evaluable for toxicity. The most common adverse reactions were alopecia and asthenia;

Table 2 Results

	No.	Median	95% CI
Survival time (months)	44	15	10.75–19.25
Duration of response (months)	18	8	6.62–9.38
Time to tumor progression (months)	31	9	6.36–11.64

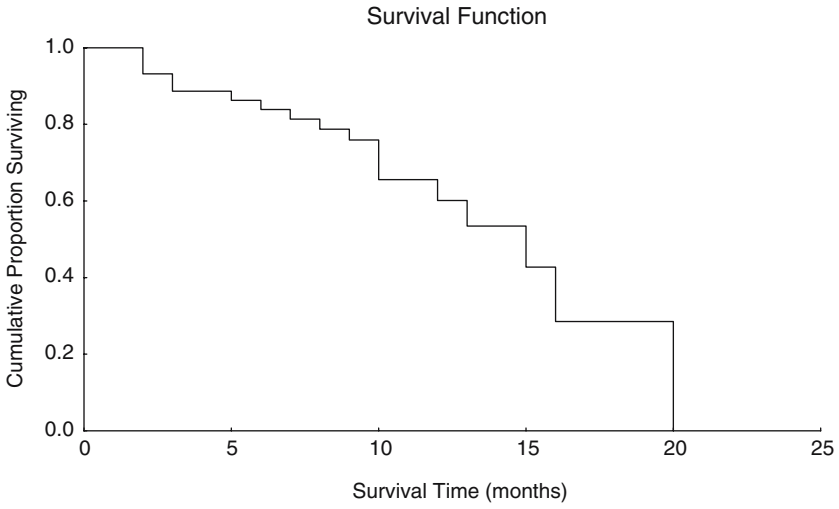

Fig. 1 Kaplan–Meier survival distribution

grade 1 myelotoxicity was often observed, whereas advanced grading was quite uncommon. Grade 3 and 4 neutropenia was seen in 2 patients (4.4%), grade 4 thrombocytopenia in 1 (2.2%) and grade 4 anemia in 1 (2.2%) patient. Four (8.9%) patients required hospitalization because of myelotoxicity and 1 patient (2.2%) because of diarrhea. There were no toxicity-related deaths. Toxicity is shown in Table 3.

Second-line treatment

Radiation was administered to seven patients with bone metastasis and to four patients with brain metastasis. Second-line chemotherapy was administered to ten patients, six with PD and four with disease recurrence. Eight patients received cisplatin (80 mg/m^2) with gemcitabine (1 g/m^2) once every 3 weeks and two patients received paclitaxel and vinorelbine (175 and 25 mg/m^2, respectively) once every 3 weeks. Three courses on average were given. No patient showed CR or PR. Eight out of ten patients showed SD (including minor responses).

Discussion

Topotecan has not, as yet, been tested in NSCLC in combination with paclitaxel as front-line chemotherapy. The effectiveness of this agent in other malignant tumors such as SCLC and ovarian cancer even as a second-line treatment could justify the combination in the present trial. The modification of the five consecutive days to the once-weekly administration significantly reduces the myelotoxicity without decreasing the efficacy [20, 21]. Paclitaxel is a well tested agent in NSCLC and also in the modality of a weekly administration. Non-cisplatin combinations have been thoroughly tested in NSCLC and studies have shown that the effectiveness and median and 1-year survival have not improved [13, 29]. Combinations with newer cytotoxic agents may be required. The present trial achieved quite a long median survival (15 months) and a very low percentage of adverse reactions. Serious myelotoxicity was not higher than 4.4%. The response rate was not lower than that of other trials with or without cisplatin [13]. Toxicity, which influences the

Table 3 Hematologic and non-hematologic toxicity in all patients, all cycles

	Grade			
	1*n* (%)	2*n* (%)	3*n* (%)	4*n* (%)
Neutropenia	14 (31.1)	4 (8.9)	1 (2.2)	1 (2.2)
Thrombocytopenia	3 (6.7)	–	–	1 (2.2)
Anemia	17 (37.8)	4 (8.9)	–	1 (2.2)
Nausea/vomiting	11 (24.4)	–	–	–
Diarrhea	16 (35.6)	–	1 (2.2)	–
Constipation	–	1 (2.2)	–	–
Asthenia	29 (64.4)	2 (4.4)	–	–
Alopecia	33 (73.3)	3 (6.7)	6 (13.3)	–
Neuropathy	13 (28.9)	2 (4.4)	–	–
Myalgia	16 (35.6)	–	–	–
Allergy	6 (13.3)	–	–	–
Renal toxicity	2 (4.4)	–	–	–
Thrombosis	2 (4.4)	–	–	–

Table 4 Results of chemotherapy trials in NSCLC

Authors	Patients No.	Response rate %	Median survival months	1-year survival %	Toxicity (%) Neutropenia Grade 3–4	Drugs
Oshita et al. [11]	61	21.3	10.0	36.1	39	Etoposide Irinotecan
Kouroussis et al. [30]	46	36.6	5.0	24.0	36.6	Vinorelbine Docetaxel
Pectasides et al. [8]	45	46.6	13.5	51.1	46.6	Carboplatin Docetaxel Gemcitabine
Iaffaioli et al. [7]	26	50.0	16.0	> 50	30.0	Carboplatin Gemcitabine
Georgoulias et al. [2]	51	37.5	13.0	50.7	8.0	Docetaxel Gemcitabine
Miller et al. [31]	35	51	14.0	60.0	54.0	Docetaxel Vinorelbine
Frasci et al. [32]	120	22	7.1	30.0	38.0	Gemcitabine Vinorelbine
Lorusso et al. [12]	52	39	12.5	64.0	30.0	Vinorelbine Gemcitabine
Present trial	45	40	15.0	> 50	4.4	Paclitaxel Topotecan

patient's quality of life, could be considered as an important parameter during the chemotherapy administration phase. The combination of topotecan with paclitaxel in a weekly administration showed prolongation of the patients' median and OS, a 40% response rate, 31% 1-year survival and only 4.4% serious myelotoxicity. Reviewing the data of other trials concerning the effectiveness and adverse reactions of non-cisplatin combinations, there are varied results with regard to response rate, median survival and toxicity. Carboplatin combined with paclitaxel showed a response rate of 40%, median survival of 8 months and 1-year survival of 42%. This combination with its acceptable low toxicity is one of the established first-line treatments in NSCLC [22]. Another trial using the same combination reported a 50% response rate but quite a high percentage of myelosuppression; this was mainly due to the escalating paclitaxel dosage from 175 to 225 mg/m^2 [6]. Higher dosage increased the leukopenia. Etoposide combined with irinotecan was reported to have a low response rate of 21.3% and a high percentage (39%) of grade 3–4 neutropenia [11]. Docetaxel has often been tested with other agents (vinorelbine, carboplatin or gemcitabine) as first-line chemotherapy with responses varying from 37.5 to 51% [2, 8, 30, 31], median survival ranging from 5 to 13 months, and in 3 trials neutropenia ranged from 30 to 54%, and in the fourth trial, 8%. One other trial reported a 50% response rate, quite a long median survival of 16 months and neutropenia as high as 30% [7]. Two trials of vinorelbine and gemcitabine given on days 1 and 8 documented a low response rate of 22% in the first and 39% in the second, with a median survival of 7.1 and 12.5 months, respectively; neutropenia was 38 and 30%, respectively [26, 12]. These non-cisplatin combinations are quite effective with respect to response rate but the main adverse reaction, with rare exceptions, was the toxicity with neutropenia > 30%, (Table 4). The response and median survival in our study was comparable to the aforementioned trials, but with the main advantage of low myelotoxicity which could be attributed to the weekly low-dose drug administration. These results need further confirmation as this combination may prove to be eligible for advanced NSCLC treatment. Second-line chemotherapy does not seem to have affected survival since it was given to only ten patients and produced no response.

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