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ORIGINAL ARTICLE

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Combination of topotecan and cisplatin in relapsed patients with small cell lung cancer: a phase II study of the hellenic cooperative oncology group (HeCOG)

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Abstract *Purpose*: To assess the safety and efficacy of a 3-day schedule of cisplatin and topotecan in patients with recurrent small-cell lung cancer (SCLC). *Methods*: Thirty-four relapsed patients were treated with cisplatin 20 mg/m^2 and topotecan 0.9 mg/m^2, both given on days 1–3 every 3 weeks, in a phase II study. *Results*: Complete response (CR) was achieved in two patients (6%), partial response (PR) in 4 (12%), stable disease in 6 (18%) and progressive disease in 14 (41%). Eight patients (23%) were non-evaluable for response. Among 21 sensitive patients, 2 (9.5%) achieved CR and 3 (14%) PR. Among 13 refractory patients, none achieved CR and only 1 (8%) PR. Median survival was 6.5 months for all patients, 7.8 for sensitive and 6.2 for refractory. Median time to progression (TTP) was 4.4 months for all patients, 5.9 for sensitive and 3.2 for refractory. Grade 3–4 toxicities included anemia (15%), thrombocytopenia (15%), neutropenia (42%), nausea/vomiting (3%), and alopecia (6%). No toxic death occurred. *Conclusions*: This 3-day schedule was well tolerated, produced modest response rates but good survival and TTP both in sensitive and refractory patients with relapsed SCLC.

Keywords Small cell lung cancer · Relapse · Topotecan · Cisplatin

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Introduction

Small cell lung cancer (SCLC) is a highly chemosensitive tumor to initial chemotherapy, however, the vast majority of patients will relapse within 6–12 months after the completion of first-line chemotherapy [15]. Cisplatin and etoposide (EP) combination chemotherapy is the standard of care for first-line therapy. Its status was confirmed in a study by Sundstrom et al. [18] comparing EP to a combination of cyclophosphamide, epirubicin and vincristine (CEV). A significant survival advantage was demonstrated for EP, however, this advantage was restricted to limited stage patients. In extensive stage SCLC, both EP and CEV had equivalent efficacy. Carboplatin and etoposide combination has been shown to be equally effective with EP but significantly less toxic [17].

Chemotherapy options for recurrent SCLC are dependent upon several clinical factors-performance status, treatment free interval, prior treatment, best response and toxicities. Based on their different probability of responding to second-line chemotherapy, patients with SCLC are categorized as refractory, who have never responded to first-line chemotherapy or progressed within 3 months from the end of induction treatment, and sensitive, who have responded to first-line chemotherapy and relapsed after a treatment-free interval of ≥3 months [8]. The median survival for patients with recurrent disease is approximately 5–7 months [8]. The

most active single agents yield response rates in the range of 10–30% [9] and response rates with combination chemotherapy are usually below 40% [7–9].

Camptothecin analogues are the most promising new agents in the treatment of SCLC. Irinotecan combined with cisplatin has been shown to be an effective treatment for extensive stage SCLC [4]. Topotecan, a semisynthetic water-soluble analogue of camptothecin, with specific targeting to topoisomerase-1, has been tested in patients with relapsed SCLC in several phase II studies. Response rates 2–11% in refractory SCLC patients and 14–38% in sensitive patients have been reported [1, 4, 5, 14, 19]. Intravenous topotecan has demonstrated equivalent activity and outcome to cyclophosphamide-doxorubicin-vincristine (CAV) in patients with recurrent sensitive disease, but with improved symptom control [19]. Oral topotecan has the same activity, outcome and quality of life in sensitive relapsed SCLC when compared to intravenous topotecan [6].

Cisplatin, commonly used in combination regimens for the initial treatment of SCLC, has been also given as salvage treatment with single agent activity 5–22% in relapsed patients [9]. In preclinical models, cisplatin has been shown to be synergistic with topotecan [10]. Briasoulis et al. [3] performed a phase I trial of a 3-day schedule of cisplatin plus topotecan in various solid tumors, including eight pretreated patients with SCLC. They concluded that it is well tolerated with mainly hematological toxicity. The maximum tolerated doses of the combination were 25 mg/m^2 daily dose for cisplatin and 1.15 mg/m^2 daily dose for topotecan. The recommended doses for further trials were 20 mg/m^2 $d_{1\text{-}3}$ for cisplatin and 0.9 mg/m^2 $d_{1\text{-}3}$ for topotecan [3].

We conducted a phase II study with the above 3-day schedule, in order to assess the safety and efficacy of the combination in patients with recurrent SCLC.

Patients and methods

Eligibility

Patients meeting the following criteria were eligible for enrollment in our study: (1) histologically confirmed SCLC (2) at least one bidimensionally measurable target lesion, outside of prior radiotherapy field (3) one prior chemotherapy regimen for limited or extensive disease (4) WHO performance status 0–2, (5) life expectancy over 3 months, (6) adequate bone marrow function with platelets ≥100,000/mm^3, hemoglobin >9 gr/dL, neutrophils 1.5×10^3/mm^3, (7) adequate renal function with serum creatinine <1.5 times the upper limit of normal, (8) adequate liver function with bilirubin <2 times the upper limit of normal. Patients with CNS metastases were included in the study, unless they were symptomatic. Prior chemotherapy with cisplatin was allowed but not with camptothecin analogue.

Patients with pre-existing uncontrolled cardiac disease, uncontrolled bacterial, viral or fungal infection and history of other primary tumor except basal or squamous cell carcinoma of the skin and carcinoma in situ of the cervix were excluded from the study.

An informed consent was obtained from all patients. The study was approved by the HeCOG Protocol Review Committee.

Pretreatment and follow-up evaluation

Within 4 weeks of the start of chemotherapy patients underwent a complete medical history, physical examination, assessment of performance status, weight, ECG, chest-X-rays, CT or MRI scan of brain, CTs of chest and abdomen, full blood count, blood biochemistry and urine analysis.

Blood counts were repeated weekly and blood chemistry, physical examination, assessment of performance status and weight before each course. Imaging studies (CT and MRI) were repeated every other cycle using the same method as baseline. Additional imaging studies were performed if clinically indicated.

Treatment plan

Both agents were administered intravenously on a daily basis for three consecutive days: cisplatin 20 mg/m^2 followed by topotecan 0.9 mg/m^2 (30 min). Adequate pre- and post-hydration was applied, according to the policy of each participation center. Treatment cycles were repeated every 3 weeks if ANC≥1.5×10^3/mm^3, platelets≥100,000/mm^3 hemoglobin ≥9.0 gr/dL, creatinine ≤ 1.5 mg/dl and drug-related nonhematological toxicity was no longer clinically significant. Otherwise treatment was delayed for a maximum of 2 weeks. If ANC grade 3 or 4 toxicity was observed on nadir, granulocyte colony stimulator factor (GCSF) was given prophylactically in the following cycles. A dose reduction for topotecan (0.75 mg/m^2) was recommended for patients developing grade 3–4 neutropenia despite the use GCSF or in case of grade 3 or 4 thrombocytopenia.

The treatment was continued until disease progression or unacceptable toxicity for a maximum of eight cycles. A minimum of two courses was required before response evaluation.

Evaluation of response, survival and toxicity

Response and toxicity were evaluated according to WHO criteria [20]. All responses were confirmed by two observations made not less than 4 weeks apart. Overall survival was measured from the date of registration to the day of the death, regardless of the cause of death. Patients still alive at the time of the analysis were cen-

sored at the last date known to be alive. TTP was measured from the date of registration to the date of documented progression or death. Patients without documented progression were censored at the date of death or last date known to be alive.

Study design and statistical considerations

This study was a phase II study. The primary end point was response and toxicity of the combination cisplatin/topotecan in relapsed patients with SCLC. Secondary end points were TTP and survival.

The sample size was based on overall response rate. Regimens with old drugs produce responses less than 30% in relapsed SCLC patients. Exception to this rule are the patients, who received CAV as first line and are treated with EP in second line setting, with response rate over 50% [8]. Based on retrospective analysis of the activity of effective chemotherapy drugs in different populations, response rates ≥10% in patients with refractory disease and ≥20% in patients in sensitive relapse have been proposed as the appropriate targets to declare novel compounds active in SCLC [12]. According to Simon's two stage minimax design [16], assuming that the expected overall response rate would be at least 30% and the minimum acceptable response rate 10%, a sample of 22 patients was required in the first step. If a minimum of three responses was observed, a total of 33 patients would be accrued. Thereby, if at least seven responses occurred the probability of accepting a treatment with real response rate of less than 10%, would be 5%. On the other hand the risk of rejection at the second stage, a treatment with a response rate of more than 30% would be 10%. The assumptions for both minimum and expected overall response rate were made after considering that in the study both sensitive and refractory patients would be included.

The overall survival and TTP were estimated using the Kaplan–Meier technique [11]. Exact binomial intervals (CI) were used to determine the 95% upper and lower confidence limits of the response rates.

Results

Patient characteristics

From October 1999 to October 2001, 34 patients with relapsed SCLC were recruited from six centers and registered in the central office of the HeCOG. Among them, 21 were sensitive and 13 refractory, 31 had received platinum-based chemotherapy as first-line treatment for SCLC and 22 had prior radiotherapy. Most patients (28) were men. The median age was 62 years. Selected patient characteristic are included in Table 1.

Table 1 Selected patient characteristics

N	34	
Age		
Median	62	
Range	44–76	
	N	%
Sex		
Men	28	82
Female	6	18
Category		
Sensitive	21	62
Refractory	13	38
Performance status		
0	16	47
1	12	35
2	6	18
Superior vena cava syndrome		
Yes	4	12
No	30	88
Hemoptysis		
Yes	9	26.5
No	25	73.5
Weight loss (>10%)		
Yes	4	12
No	30	88
History of smoking		
Yes	33	97
No	1	3
Laterality		
Right lung	19	56
Left lung	14	41
Unknown	1	3
Stage		
Limited	18	53
Extensive	15	44
Unknown	1	3
Site of metastasis		
Lung	23	68
Nodes	18	53
Liver	10	29
Brain	4	12
Bones	4	12
Adrenal	9	26
Pleura	7	21
Other	4	12
Number of metastatic sites		
1	11	32
2	11	32
≥3	12	35
Previous RT	22	65
Thoracic	15	44
Brain	1	3
Thoracic + Brain	4	12
Other	2	6
First-line chemo		
Cisplatin-based	1	3
Carboplatin-based	30	88
Other	2	6
Unknown	1	3

Treatment characteristics

Thirty-three patients received 140 cycles of chemotherapy. Four patients received one cycle, two patients two cycles, seven patients three cycles, six patients four cycles, twelve patients six cycles, one patient seven cycles

and one patient eight cycles. One patient was registered but we could not retrieve his medical files. One hundred and twenty cycles were given at full dose. Median duration between cycles was 21 days. Median dose intensity for cisplatin was 17.6 mg/m^2/week (range 6.7–19.8) and for topotecan 0.79 mg/m^2/week (range 0.3–0.9). Median relative dose intensity for cisplatin was 0.89 (range 0.3–1.0) and for topotecan 0.88 (range 0.3–1.0).

Efficacy

Complete response was achieved in two patients (6%, 95% CI 0.7–19.7), PR in four patients (12%, 95% CI 3.3–27.4), SD in six patients (18%, 95% CI 6.8–34.5), PD in fourteen patients (41%, 95% CI 24.6–59.3). Eight patients (23%, 95% CI 10.7–41.2) were nonevaluable for response. Three patients had early tumor death: two of them died after the first cycle and one patient after the second cycle. One patient died after the third cycle without first been evaluated. Moreover, three patients refused to undergo re-evaluation and discontinued treatment; two of them after the third cycle and one after the fourth cycle. Finally for one patient, we had not any information since we could not retrieve his medical files.

Among 21 sensitive patients, 2 (9.5%, 95% CI 1.2–30.4) achieved CR, 3 (14%, 95% CI 3.0–36.3) PR, for an ORR 24% (95% CI 8.2–47.2). SD was observed in three patients (14%, 95% CI 3.0–36.3), PD in nine patients (43%, 95% CI 21.8–66.0) and four patients (19%, 95% CI 5.4–41.9) were nonevaluable for response. Among 13 refractory patients, none achieved CR only 1(8%, 95% CI 0.2–36.0) achieved PR for an ORR of 8% (95% CI 0.2–36.0). SD was observed in three patients (23%, 95% CI 5.0–53.8), PD in five patients (38%, 95% CI 13.9–68.4) and four patients (31%, 95% 9.1–61.4) were nonevaluable.

One patient is still alive after 38.3 months. Another patient, alive after 7.8 months, was lost to follow-up. All the other patients died from their disease. Median survival was 6.5 months (95% CI 4.3–8.7) and median TTP 4.4 months (95% CI 2.6–6.1) (Fig. 1). Median survival and median TTP for sensitive patients was 7.8 months (95% CI 4.9–10.7) and 5.9 months (95% CI 3.5–8.3), respectively, while median survival and median TTP for refractory patients was 6.2 months (95% CI 3.5–8.9) and 3.2 months (95% CI 1.4–5.0), respectively (Figs. 2, 3).

Toxicity

No toxic death was reported. The most frequent and severe toxicity was myelosuppression. Grade 3 anemia was observed in five patients (15%), grade 3–4 neutropenia in 14 patients (42%) and grade 3–4 thrombocytopenia in five patients (15%). Nonhematological toxicity was generally mild. Twenty-four patients (73%) received growth factors, six patients (18%) underwent blood transfusion, two patients (6%) underwent platelet transfusion and antibiotics were administered in six patients (18%). All toxicities reported are described in Table 2.

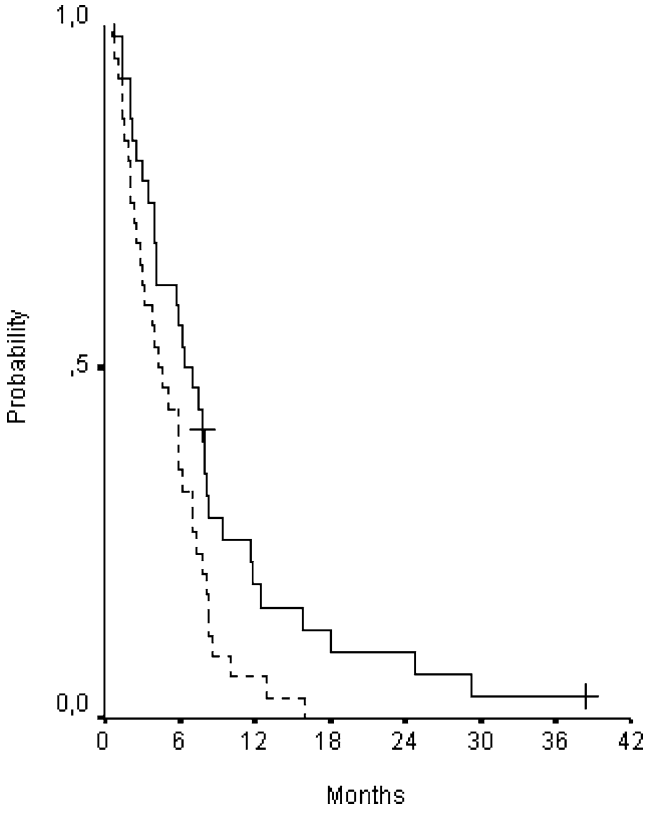

Fig. 1 Time to progression (*broken line*) and overall survival (*solid line*)

Discussion

Topotecan is the only single-agent therapy approved by the US Food and Drug Administration for the treatment of patients with recurrent SLCC. A large phase III randomized trial comparing intravenous topotecan to CAV in chemosensitive patients demonstrated equivalent tumor effect but improved symptom control with intravenous topotecan. Response rate was 18% for CAV compared to 24% for topotecan and median survival was 25 weeks for both groups [19]. Hematological toxicities were the main complications, with febrile neutropenia rates of 26–28% seen in both groups [19].

The 3-day schedule of cisplatin and topotecan tested in our study has a modest activity in relapsed SCLC. Despite the relatively low ORR (18%) the median survival of 6.5 months for the whole group, as well as the median survival of 7.8 months for sensitive patients and 6.2 months for refractory patients are encouraging. Eight patients were nonevaluable in our study, but the analysis was performed in all patients, including the nonevaluable, on an intent to treat basis. This is a

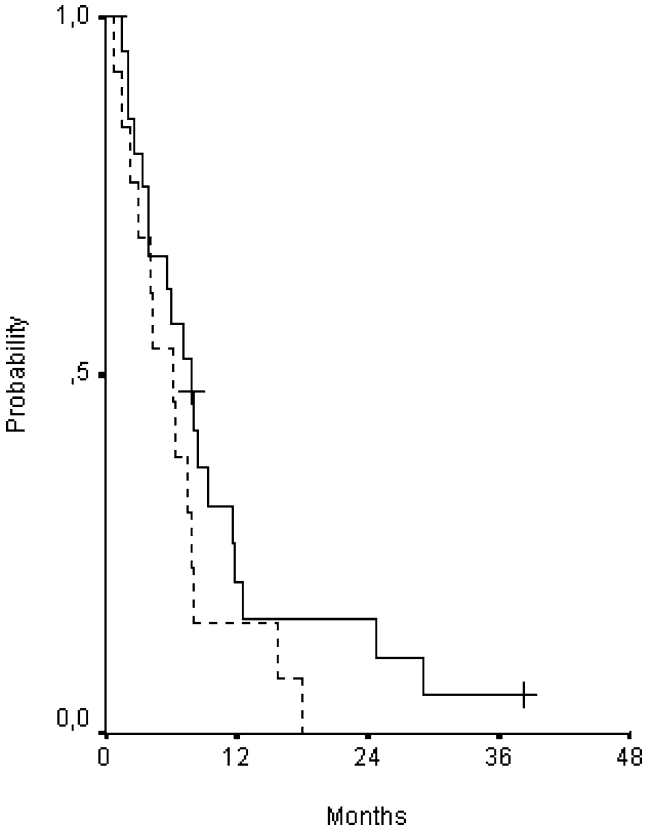

Fig. 2 Overall survival for refractory (*broken line*) and sensitive (*solid line*)

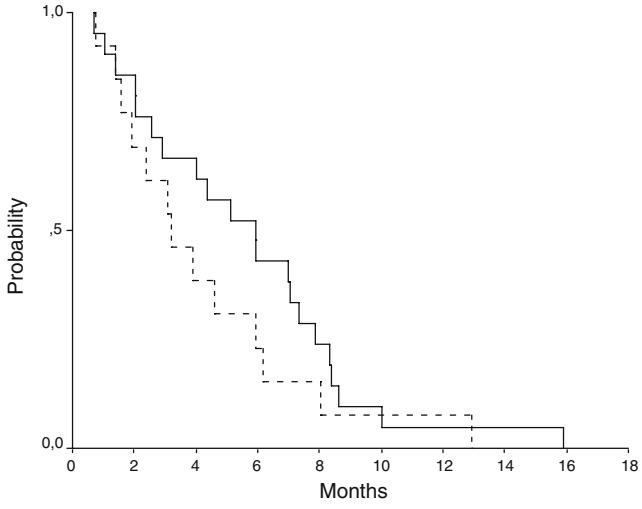

Fig. 3 TTP for refractory (*broken line*) and sensitive (*solid line*)

conservative approach that ends up in a lower response rate than if all patients were evaluable. For example in our study, excluding the eight nonevaluable patients, the overall response rate would have been 23% (6/26). Taking into consideration that single-agent topotecan produced response rates of 2–31% [1, 4, 5, 14, 19] and cisplatin 5–22% [9] in relapsed SCLC and that the two compounds have shown to be synergistic in preclinical models [10], a higher response rate would be expected.

European Organization for Research and Treatment of cancer (EORTC) has performed two parallel studies of cisplatin 60 mg/m^2 on day 1, combined with topotecan, administered at the dose of 0.75 mg/m^2/day for five consecutive days, in patients with sensitive and in patients with refractory relapsed SCLC [2].

Response rates were 29.4% in sensitive patients, which is close to ours, but surprisingly, 23.8% in refractory patients, which is higher to ours and higher to what the investigators themselves expected.

More surprising perhaps, was the observation of the similar survival outcome in the two groups of patients (6.4 versus 6.1 months in sensitive and refractory patients, respectively). These survival rates are not superior to the survival rates observed in our study. We should also mention that in the EORTC 08957 study, only 46% of sensitive and 40% of refractory patients had platinum-based first-line treatment and prior cisplatin was allowed only in case of response and if chemotherapy treatment had been completed at least 6 months before.

Table 2 Toxicities N (%)

	N = 33			
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Anemia	8(24)	12(36)	5(15)	–
Thrombocytopenia	7(21)	5(15)	4(12)	1(3)
Leukopenia	5(15)	10(30)	9(27)	–
Neutropenia	4(12)	6(18)	9(27)	5(15)
Nausea/Vomiting	6(18)	2(6)	1(3)	–
Diarrhea	1(3)	–	–	–
Alopecia	4(12)	3(9)	2(6)	–
Fever	1(3)	4(12)	–	–
Infection	1(3)	2(6)	–	–
Constipation	6(18)	–	–	–
Fatigue	9(27)	6(18)	–	–
Neurotoxicity	5(15)	–	–	–
Drawziness	1(3)	–	–	–
Rash-edema	–	1(3)	–	–

In our study, among 34 patients, 31 had received platinum-based first-line chemotherapy.

But the main difference between our study and the EORTC 08957 study was the severity and frequency of myelotoxicity.

In the EORTC 08957 study, grade IV neutropenia occurred in 62% of sensitive and 49% of refractory patients, grade IV thrombocytopenia in 54 and 44%, febrile neutropenia in 19 and 15% respectively and five toxic deaths occurred among sensitive patients only. Myelosuppression occurred most frequently during the first cycle of therapy and required dose reductions in 41% of sensitive and in 21% of refractory patients as well as treatment delays in 62% of sensitive and 57% of refractory patients. Overall 46.1% of cycles given in sensitive patients and 36.9% of cycles given in refractory patients required a dose reduction and/or delay because of toxicity. In 72.1% of sensitive and in 66.7% of refractory patients, a dose reduction and/or delay was required. The investigators concluded that additional development of this regime (cisplatin combined with topotecan) using better-tolerated schedules is warranted [2].

In our study, we tested a 3-day schedule of cisplatin 20 mg/m^2 combined with topotecan 0.9 mg/m^2 both given for three consecutive days. This schedule was based on a phase I study, conducted in one of our centers [3]. This schedule was generally well tolerated. No toxic deaths occurred, grade IV neutropenia occurred in 5 (15%) patients and grade IV thrombocytopenia in 1 (3%) patient. No other grade IV toxicities were reported. From 140 cycles of chemotherapy administered in our study, 120 cycles were given at full dose. No treatment delays occurred and the median duration between cycles was 21 days. It is also interesting that myelotoxicity was lower in our study, compared to the single-agent topotecan given at 1.5 mg/m^2/day for five consecutive days [1, 4, 5, 14, 19].

In conclusion, this 3-day schedule of cisplatin combined with topotecan, was well tolerated, produced modest response rates but good survival and TTP both in sensitive and refractory patients with relapsed SCLC. It would be interesting to test this combination in platinum-nieve patients with recurrent SCLC and in untreated SCLC patients.

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