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Topotecan–carboplatin–etoposide combination as 1st line treatment in patients with small cell lung cancer

K. Zarogoulidis[a], E. Mylonaki[b], P. Kakavelas[b], P. Zarogoulidis[a], Th. Tsiouda[a], E. Rapti[d], H. Lithoxopoulou[e], V. Zarogoulidou[e], Th. Kontakiotis[c,*], Hellenic Pulmonary Oncology Study Group (HE.P.O.G.)

[a] *Lung Tumour Research Section, University Pulmonary Clinic, Aristotle Univ. of Thessaloniki, G. Papanicolaou Hospital, Greece*
[b] *2nd Pulmonary Department, G. Papanicolaou Hospital, Thessaloniki, Greece*
[c] *Bronchoscopy Unit, G. Papanicolaou Hospital, Thessaloniki, Greece*
[d] *7th Pulmonary Department, Sotiria Hospital, Athens, Greece*
[e] *Lung Cancer Research Section, Aristotle University Pulmonary Clinic, "G. Papanikolaou" Hospital, Exohi 57010, Thessaloniki, Greece*

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ABSTRACT

Purpose: To test toxicity, tolerability, time to progression, survival and response rate in the 3-day administration of topotecan (T) followed by carboplatin (C), and then etoposide (E) in a study for small cell lung cancer (SCLC) treatment.
Patients: 44 chemotherapy-naive patients with SCLC (median age 63.5, PS 0–1). ED was present in 28 patients.
Methods: Each treatment cycle consisted of T (0.8 mg/m^2 on days 1–3), C (AUC = 5, day 3) and a standard oral dose of E (100 mg on days 15–17). Cycles were repeated every 32 days and up to eight were performed. Responders received radiotherapy to the primary site (50 Gy) after the 4th cycle and complete responders also received PCI.
Results: Complete response (CR) was achieved in 4 patients, partial response (PR) in 18, stable disease in 10 and PD in 12. Median survival was 280 (±36.7) days and median time to progression 137 days. 11 patients developed grade 3/4 neutropenia and 3 patients grade 3/4 anaemia. Non-haematological toxicity was mild.
Conclusion: In contrast to ORR, PFS and survival were quite similar to those of SCLC patients suffering from ED treated by a platinum–etoposide regimen. The T/C/E combination was well tolerated and with low toxicity, but without improvement in the ORR and survival in comparison to platinum analogue regimes.

1. Introduction

Topotecan (T) is a water-soluble analogue of camptothecin that specifically inhibits the activity of topoisomerase I by stabilizing the topoisomerase I-DNA complex, resulting in lethal DNA strand breaks. Topotecan was found to have substantial activity as a single-agent in a phase II study including 48 chemotherapy-naive extensive stage of small cell lung cancer (SCLC) patients, demonstrating an objective response rate of 39% [1]. Preclinical studies of combining topo I and II inhibitors have also yielded promising results. However, the simultaneous administration of topotecan and etoposide (E) resulted in an antagonistic response. Besides that, inhibition of topo I by topotecan resulted in a compensatory increase in topo II levels associated with increasing sensitivity of tumours to subsequent treatment with etoposide [2].

Etoposide is a potent topo II inhibitor and its effect on this enzyme is schedule dependent. Clinical studies suggested that prolonged exposure to low doses of etoposide is more effective than when given over a short time [3,4]. In vitro maximum synergy occurs for the sequence of topotecan followed by etoposide (as compared with the opposite sequence) [5,6]. Thus there is a pharmacologic rationale for the sequence of topotecan followed by etoposide. In vitro topotecan exhibited synergistic effect with cisplatin [7]. The sequence of platinum followed by topotecan has more haematological toxicity than topotecan followed by cisplatin or carboplatin [8–11]. Clinical synergism is better observed when etoposide follows platinum in SCLC [12]. In a randomized phase II study of cisplatin and topotecan, the 3-day treatment was not inferior to the standard 5-day treatment [13]. On the other hand adding a blood–brain barrier (BBB)-penetrating drug, with the initial cycle, such as topotecan having an activity against SCLC may

* Corresponding author at: 13 P. Kavda, Panorama 55236, Thessaloniki, Greece. Tel.: +30 2310 992433; fax: +30 2310 992433.
E-mail address: kontak@auth.gr (Th. Kontakiotis).

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possibly result in a more effective treatment and prevention of CNS relapse [14–18].

Licitra et al. [19] studied topotecan infusion for 72 h, followed by etoposide administration on days 8–10. Some responses and occasional increases of topo II level in tumour tissue were observed, accompanied by severe myelosuppression.

In a phase II trial in NSCLC Hammond et al. [20] tested the sequence of 72 h continuous infusion of topotecan followed by etoposide p.o. on days 7–9. They observed three responses out of 19 patients, as well as a 33% 1-year survival. These results seemed interesting for a non-platinum-based regimen.

In a small phase I study, Miller et al. [21] administered topotecan 0.4 mg/m^2 for 7 days followed by carboplatin AUC 4–6 on day 8 and oral etoposide 50 mg/day on days 9–20 repeated every 28 days for up to six cycles. The investigators reported one complete and three partial responses (PRs) among six evaluated patients with extensive stage SCLC. Grade 4 neutropenia was the only dose-limiting toxicity occurring at a carboplatin dose AUC = 5 and all other toxicities were considered mild, suggesting that this is an active and well tolerated regimen in SCLC.

Regarding these considerations, we decided to test the sequence of 3 days topotecan followed by carboplatin, and then etoposide in a study for SCLC treatment.

The main objectives of this study are to estimate the impact of topotecan on survival, TTP in patients with SCLC of ED and LD stage. Another objective is to record toxicity and tolerability, and response rate in these patients.

2. Patients and methods

46 chemotherapy-naive patients were enrolled in the study. Three clinics participated in this study, two from G. Papanikolaou Hospital of Thessaloniki and one from Sotiria Hospital of Athens. The 2nd Pulmonary Department of Papanikolaou Hospital recruited 16 patients, the University Pulmonary Clinic of Papanikolaou Hospital recruited 20 patients and the Sotiria Hospital of Athens recruited 10 patients. No more patients were enrolled as the regimen did not appear to improve survival and response rate. One of them refused to continue and one abandoned the study because of excessive gastrointestinal side effects. Patients who were eligible in this multi-centre phase I–II trial were those who were up to 75 years old and had histological or cytological confirmation of SCLC. They had to have ECOG performance status 0–1, normal renal, hepatic and adequate cardiac function, with no arrhythmias or congestive heart failure and life expectancy $\geq$12 weeks. Upon enrolment, they provided a complete medical history and underwent physical examination. Height, weight and weight loss (if any) in the previous 3 months were recorded. Patients with weight loss >10% in the previous 3 months were excluded.

The protocol was approved by the Hospitals Ethical Committees. Informed consent was obtained from all screened patients.

2.1. Treatment plan

The intention according to clinical experience in our department was to give up to eight cycles of CHT consisting of topotecan 1 mg/m^2 on days 1, 2, 3 combined with carboplatin AUC = 5.5 over 30 min on day 3, and a standard oral dose of etoposide 100 mg on days 15, 16, 17. Oral etoposide was preferred to I.V. etoposide so that patients could continue their treatment with etoposide at home without having to travel often to our hospital as 45% of them lived quite far. Blood examinations were performed weekly in order to evaluate the need of supportive treatment as the onset on nadir occurred as early as day 12 [8]. Biochemical profile was performed before every new CHT cycle, as well as chest radiographs to estimate response or progression to therapy. We restaged our patients either after PD diagnosed by the radiograph or after the 4th cycle in order to decide for radiotherapy and 1 month after CHT completion. Responders received radiotherapy to the primary site (50 Gy) after the 4th cycle, and PCI was provided in complete responders. Palliative radiotherapy and haematopoietic growth factors were used as appropriate. 2–3 weeks after radiotherapy completion patients received two CHT cycles additionally.

According to patients' situation, additional investigation and/or palliative treatment were used as necessary. Patients experiencing early progression were treated with salvage CHT according to each collaborating centre practice. After the completion of the 1st cycle, three out of the initial seven patients developed grade 3 (two patients) or 4 (one patient) neutropenia leading us to omission of etoposide administration during the 1st cycle. This led to a decrease in the dose of topotecan to 0.8 mg/m^2 and carboplatin to AUC = 5 for the subsequent cycles of treatment given to these seven patients and to all other patients, as well as to an extension of the CHT cycle from 28 to 32 days.

2.1.1. Antiemetic treatment

Before CHT, methylprednisolone (16 mg) and ondansetron (32 mg) were given orally 3 and 1 h respectively on days 1 and 2. On day 3 hydrocortisone 125 mg was also added 1 h before CHT.

2.1.2. Treatment evaluation and follow-up

An extra evaluation of the patient response was performed every 3 months and 1 month after the last CHT by a panel consisted of one researcher from each collaborating centre and one independent radiologist who did not take part in the above trial. All patients underwent bone scan and chest, abdomen and brain CT. Patients with complete response (CR) had also a second look bronchoscopy. After discontinuation of treatment, patients were evaluated every month in order to access survival and disease free status. All patients were analyzed for efficacy, safety, response, progression free survival and survival.

2.1.3. Statistical methods

Survival analysis was performed with the Kaplan–Meier test. Significances were evaluated through Log Rank, Breslow and Tarone-Ware tests.

3. Results

A total of 44 patients were registered between January 2001 and April 2005. The final analysis was performed in 2007. 16/44 patients suffered from limited disease (LD) and 28/44 form extensive disease (ED).

Baseline investigations before treatment initiation included: complete blood count with differential and platelet count, complete biochemical profile, ECG, chest films, CT of the chest and abdomen, CT of the brain (or magnetic resonance imaging, if necessary), isotope bone scan and bronchoscopy. In symptomatic negative bone scan patients extra X-rays or Bone MRIs were performed.

Patient characteristics, metastatic site and number of metastases at the time of enrolment are shown in Tables 1 and 2. Patients with brain metastases at presentation received cranial radiotherapy simultaneously to the first cycle of chemotherapy (CHT) (29 Gy over 10 days from 7th day to the 21st day of the 32nd day of each cycle).

A total of 222 of CTH cycles were given (medium five cycles per patient, 95% CI 1–8). The overall response rate (ORR) was 50% [CR 4/44 (9%) and PR 18/44 (40.9%)]. For LD patients ORR was 68.7% (CR 4/16 + PR 7/16 patients). Disease was stable in 10/44 patients and progressive disease (PD) was observed in 12/44 patients. The detailed results are shown in Table 3. 14 LD patients underwent