Phase II study of topotecan and paclitaxel for patients with previously untreated extensive stage small-cell lung cancer

S. Ramalingam¹, C. P. Belani¹*, R. Day¹, B. A. Zamboni¹, S. A. Jacobs¹ & J. R. Jett¹²

¹University of Pittsburgh Cancer Institute, Pittsburgh, PA; ²Mayo Clinic, Rochester, MN, USA

Introduction
Small-cell lung cancer (SCLC) accounts for ~15–20% of all cases of lung cancer diagnosed in the USA [1]. A majority of the patients have extensive stage disease (ED-SCLC) at the time of diagnosis [1]. Combination chemotherapy regimen of a platinum compound and etoposide is considered the ‘standard of care’ for patients with ED-SCLC in the USA. Despite initial sensitivity to chemotherapy, >80% of the patients die from recurrent disease within 2 years [2]. Hence there is a need to develop novel agents or combinations to improve the outcome for patients with this disease.

Topotecan is an inhibitor of topoisomerase-1 enzyme which exhibits anti-tumor activity against several solid tumors [3, 4]. It has been approved by the Food and Drug Administration for treatment of SCLC patients who progress after initial response (sensitive) to first-line chemotherapy. The proven activity of topotecan in the second-line setting makes it worthy of evaluation for first-line chemotherapy. The combination of topotecan and paclitaxel is active as initial therapy in SCLC, but the efficacy is similar to ‘standard therapy’. This combination was associated with a high incidence of myelosuppression and febrile neutropenia, at the doses evaluated.

Background: This phase II study was conducted to evaluate the safety and efficacy of the combination of paclitaxel and topotecan for patients with extensive stage small-cell lung cancer (ED-SCLC).

Patients and methods: Previously untreated ED-SCLC patients with Eastern Cooperative Oncology Group performance status ≤2 were eligible. Treatment consisted of topotecan 1 mg/m² (first three patients received 1.25 mg/m²), on days 1–5, and paclitaxel 135 mg/m² over 24 h on day 5, every 4 weeks. Prophylactic granulocyte colony-stimulating factor was administered to all patients.

Results: Thirty-two patients received a median of four cycles of chemotherapy. Grade 4 anemia, neutropenia and thrombocytopenia occurred in 31, 31 and 18 patients, respectively. Thirty episodes of febrile neutropenia occurred in 22 patients. Grade 3 fatigue, esophagitis, stomatitis and hypotension occurred in one patient each. Of 26 patients eligible for response evaluation, there were six complete and 12 partial responses (overall response rate 69%). The median survival was 54 weeks. The 1-, 2- and 3-year survival rates were 50%, 10% and 3%, respectively.

Conclusions: The combination of topotecan and paclitaxel is active as initial therapy in SCLC, but the efficacy is similar to ‘standard therapy’. This study demonstrated a response rate of 34% with a median survival of 43 weeks. In this ‘window of opportunity’ trial patients were crossed over to standard first-line therapy if there was no response to single-agent paclitaxel. The Mayo clinic study also utilized the same dose and schedule of paclitaxel, but the response rate was higher (53%) [6]. In addition, there is known pre-clinical synergy between paclitaxel and topotecan [7] and both have non-overlapping toxicity profiles. Hence we conducted a phase II clinical trial to evaluate the efficacy of the combination of topotecan and paclitaxel for patients with previously untreated ED-SCLC.

Patients and methods
The objectives of the study were to evaluate the response rate, toxicity and overall survival for patients with ED-SCLC treated with topotecan and paclitaxel. Patients with previously untreated ED-SCLC were eligible to participate in the study. Extensive stage was defined by the presence of metastatic disease outside the chest, cytologically proven malignant pleural or pericardial effusion or involvement of contralateral supraclavicular/hilar nodes that cannot be included in a single radiation port. Other eligibility criteria included pathological confirmation of diagnosis, age ≥18 years, presence of measurable disease and normal bone marrow [absolute neutrophil count (ANC) ≥2000/µl, platelet count >100 000/µl], liver [serum alkaline phosphatase ≤3 times the institutional upper limit of normal (ULN)], serum total bilirubin ≤1.5 times ULN, serum aspartate aminotransferase ≤3 times ULN] and renal function (serum
creatinine ≤ULN). The exclusion criteria were: central nervous system (CNS) metastasis, obstructive pneumonia, clinically significant infection, uncontrolled angina pectoris, life-threatening cardiac arrhythmias, recent myocardial infarction, electrocardiographic evidence of bundle branch block, superior vena cava syndrome, major paraneoplastic syndrome, recent major surgery (within 3 weeks prior to enrolment), prior radiotherapy or prior malignancies except non-melanomatous skin cancer or carcinoma in situ of uterine cervix. All patients signed written informed consent to participate in the study.

**Treatment**

The first three patients who were enrolled in the study received topotecan 1.25 mg/m²/day intravenously (i.v.) over 30 min on days 1–5 of each 4-week treatment cycle. Paclitaxel 135 mg/m² was administered i.v. on day 5 as a 24-h infusion, following topotecan. Due to the occurrence of febrile neutropenia in two of three patients, the dose of topotecan was reduced to 1 mg/m²/day on days 1–5, while the dose of paclitaxel remained 135 mg/m². Treatment cycles were repeated every 4 weeks. Dexamethasone, diphenhydramine and ranitidine were administered as pre-medications with each dose of paclitaxel. All patients received prophylactic therapy with granulocyte colony-stimulating factor (G-CSF; 5 µg/kg/day, subcutaneous) daily, beginning 24 h after the dose of paclitaxel until recovery of ANC to ≥10 000/µl. Patients who experienced a complete response (CR) received a total of six cycles of therapy, while those with partial response (PR), minor response or stable disease continued therapy until they developed CR or progressive disease. Patients who developed CNS metastasis during the course of the study received whole-brain radiotherapy and were subsequently continued on protocol therapy. Patients who developed progressive disease (outside the CNS) were treated with cisplatin and etoposide combination provided their clinical status permitted further intervention.

**Dose modifications for toxicity**

Dose modification of paclitaxel and topotecan by 30% was made if any of the following occurred during the previous cycle: ANC <500/µl lasting >5 days, fever associated with ANC <500/µl, severe infection or platelet count <30 000/µl. For ANC <2000/µl or platelet count <100 000/µl, treatment was delayed until recovery of the counts. Delay in treatment up to 4 weeks until normalization (and subsequent reduction in dose of paclitaxel by 30%) was necessary for AST >5 times ULN or total bilirubin >1.5 times ULN. Dose of paclitaxel was also reduced by 30% for patients who experienced grade 2 neurotoxicity, while those who had grade 2 neurotoxicity were discontinued from protocol therapy. The dose of topotecan was held for any elevation in serum creatinine greater than normal until return to normal levels. Protocol therapy was discontinued after delay in treatment of longer than 4 weeks.

### Table 1. Study design operating characteristics

<table>
<thead>
<tr>
<th>True response rates</th>
<th>$P_{PR} + P_{CR}$</th>
<th>$P_{CR}$</th>
<th>$P_{PR} + 2P_{CR}$</th>
<th>$P$ (reject regimen)</th>
<th>$P$ (early termination)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15</td>
<td>0.15</td>
<td>0.30</td>
<td>0.99</td>
<td>0.52</td>
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<td>1.00</td>
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<tr>
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<td>0.25</td>
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<tr>
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<td>0.19</td>
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<td>0.70</td>
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</table>

The utility, a linear function of the third column, equals one (favorable) in the bottom two lines, zero (neutral) in the middle two, and negative one (unfavorable) in the top two lines.

**Patient evaluation**

The following tests were performed at baseline: history and physical exam, complete blood count, serum chemistry [including serum creatinine, aspartate amino transferase (AST), alkaline phosphatase, total bilirubin, electrolytes], chest radiograph, computed tomography (CT) scan of chest and upper abdomen, CT scan or magnetic resonance imaging of brain and electrocardiogram. Isotope bone scan was necessary for any patient with bony pain or elevation of serum calcium or alkaline phosphatase. Patients were evaluated every 4 weeks at the time of re-treatment. Toxicity was graded by National Cancer Institute Common Toxicity Criteria (NCI CTC) guidelines. CT scans were performed after cycles three, five and seven to assess for response. Chest radiographs were performed before each cycle of chemotherapy. The World Health Organization criteria were used to assess responses.

### Statistical methods

A two-stage design was utilized in conducting the study. As the importance of partial responses in SCLC is questionable, the primary end point of the study counted complete responses twice as heavily as partial responses: the weighted response summary was PR rate + 2 × CR rate. In the first stage, 17 patients were enrolled, and data were reviewed to decide if the study should be terminated due to inactivity of the treatment. If the weighted response summary was no bigger than four (e.g. two CRs or four PRs), the study was to terminate early; otherwise the study would accrue to the total planned sample size of 41. The final reporting decision was to conclude that the treatment is effective if the final weighted response summary exceeded 22/41 (0.54). The study plan was chosen to have satisfactory type I and type II errors at important design points, and to have reasonable Bayesian decision theoretic characteristics using as the implied utility function $P_{PR} + 2P_{CR} − 0.5)/0.2$. This design protects patients from inappropriate treatment, and the type I error is adjusted to preserve statistical validity. The operating characteristics are described in Table 1.

While the criteria for continuing the study were achieved, accrual difficulties led to early termination at a total sample size of 32. Because $P$ values and confidence intervals have questionable validity when the planned design is not achieved, a Bayesian analysis is also presented (Figure 1). Results were insensitive to the choice of prior distributions. Time-to-progression, treatment failure and death were summarized using the Kaplan–Meier methods. Toxicities were summarized by worst toxicity grade and type experienced by the patients.
Results

Patient characteristics

This study was conducted at the University of Pittsburgh Cancer Institute and its community network between January 1995 and August 1999. The median age of the patients was 64.7 years (41.8–80.2 years). The majority (91%) of the patients had an ECOG performance status of 0 or 1. Fifteen patients had intra-thoracic metastasis, while 13 patients had metastasis to the liver in addition to intra-thoracic disease. Bone, spleen, adrenal gland and pancreas were involved in one patient each.

Toxicity

All the patients enrolled to the study were eligible for toxicity assessment. A total of 136 cycles of chemotherapy were administered during the study. The median number of chemotherapy cycles was four. Thirteen patients received six or more cycles of therapy. Two patients developed hypersensitivity reaction to paclitaxel during the first cycle of therapy and were discontinued from further protocol therapy. Another patient developed cardiac arrhythmia with the second cycle of paclitaxel and was removed from the study. Hematological toxicities were the most commonly reported adverse events for the study participants (Table 2). Grade 3 or higher leukopenia was noted in 31 patients (97%), while 13 patients had metastasis to the liver in addition to intra-thoracic disease. Bone, spleen, adrenal gland and pancreas were involved in one patient each.

Efficacy

Seventeen patients were entered into the first stage of the study. Four patients achieved a complete response and there were seven partial responders. The efficacy of the regimen met the predefined criteria for further continuation of the study. Twenty-six of the total 32 patients were evaluable for response. As mentioned earlier, three patients were non-evaluable as they did not complete two cycles of therapy due to hypersensitivity reaction to paclitaxel; one patient died after the first cycle of therapy; two patients discontinued treatment after the first cycle. There were a total of six complete responses and 12 partial responses with an overall response rate of 69% (Table 4). Seven patients developed progression of disease after the first three cycles of chemotherapy. The overall median survival was 54 weeks with a 1-year survival rate of 50% (Figure 1). Disease response was seen at all metastatic sites.

Discussion

The results of our phase II study demonstrate the effectiveness of topotecan and paclitaxel combination as first-line therapy for
patients with ED-SCLC. However, despite the use of prophylactic G-CSF, there was a high incidence of febrile neutropenia with the regimen. Non-hematological toxicities were relatively mild. As in our study, myelosuppression was the predominant toxicity noted with the paclitaxel–topotecan combination [8–11]. In most of these trials, paclitaxel was administered as a 3-h infusion while in the present trial it was infused over 24 h. When topotecan is administered orally at a dose of 1.75 mg/m² for five consecutive days followed by paclitaxel (175 mg/m²) as a 3-h infusion, grade 3 neutropenia has been noted in only 40% of the patients, as opposed to 97% incidence observed in the present study [11]. The higher incidence of neutropenia in our study may be a result of schedule of administration of paclitaxel (24-h infusion), as opposed to short infusions (3-h) noted in other studies.

The overall response rate of 69% noted in our study compares favorably with the efficacy of the existing ‘standard’ regimen of cisplatin–etoposide [12–14]. Response rates of 45, 68, 71 and 100%, respectively, have been reported in the other studies that have evaluated the efficacy of topotecan–paclitaxel combination as first-line therapy for ED-SCLC [8–11]. The latter study that reported responses in all the participants included 15 patients only [10]. From these studies, it appears that the combination of topotecan and paclitaxel does not represent an improvement over the regimen of cisplatin–etoposide. Irinotecan, also an inhibitor of topoisomerase-I, has also shown efficacy in SCLC. A recently reported randomized phase III trial, performed in Japan, reported provocative results with the combination of irinotecan–cisplatin for patients with previously untreated ED-SCLC [15]. Patients on the cisplatin–irinotecan arm had a response rate of 85%, while those in the control arm, who were treated with cisplatin–etoposide, demonstrated a response rate of only 65%. The overall survival was also more favorable for the cisplatin–irinotecan arm (12.8 months versus 9.4 months). The study was closed early due to the superior results noted in the experimental arm. Based on the results of this study, two ongoing randomized trials are comparing the efficacy of cisplatin–irinotecan with the standard regimen of cisplatin–etoposide in the USA. If proven effective in these randomized trials, the use of cisplatin–irinotecan may represent the next major advance in the treatment of ED-SCLC.

Despite incremental improvements in survival over the years, the overall outlook still remains poor for patients with ED-SCLC. Three drug chemotherapy combinations have not demonstrated any benefit over the ‘standard doublet’ and they are associated with prohibitive toxicity [16]. Maintenance therapy with topotecan following four cycles of cisplatin–etoposide also failed to improve outcome for patients with ED-SCLC [17]. Other approaches, such as high-dose chemotherapy or alternating chemotherapy regimens, have also yielded disappointing results [12, 18, 19]. Thus, the search for an ‘optimal’ regimen for the management of patients with ED-SCLC continues.

Acknowledgements


References


