The Role of Topotecan in the Treatment of Small Cell Lung Cancer

JULIE R. BRAHMER, DAVID S. ETTINGER
The Johns Hopkins Oncology Center, Baltimore, Maryland, USA

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ABSTRACT
Topotecan is a chemotherapeutic agent that is active in the treatment of small cell lung cancer (SCLC). As a first-line agent in chemotherapy-naive patients with extensive disease SCLC, topotecan has a 39% response rate. As a second-line drug in SCLC patients with “sensitive” disease and “refractory” disease, the response rate is greater than 38% and less than 10%, respectively. The combination of topotecan and paclitaxel exhibits a promising overall response rate of 92% in chemotherapy-naive patients with extensive disease SCLC. Further studies are warranted with topotecan used in combination with other agents, including radiation therapy in patients with SCLC. The Oncologist 1998;3:11-14

INTRODUCTION
Lung cancer continues to be the leading cause of cancer-related mortality among men and women in the United States. Small cell lung cancer (SCLC) represents about 20%-25% of all lung cancers, making SCLC the seventh most frequent cause of cancer deaths [1]. Patients with SCLC frequently present with widely metastatic disease; only 30%-40% of patients present with limited-stage disease (LD). LD-SCLC is defined as disease confined in only one hemithorax, with or without regional lymph nodes (hilar or mediastinal), with or without ipsilateral supraclavicular lymph node involvement, and without ipsilateral pleural effusions. Extensive disease (ED) is defined as disease that has spread beyond these boundaries. This distinction is important in regard to treatment and prognosis. Limited disease is potentially curable: the response to combined modality therapy is as high as 85%-95%, with the complete remission rate approximately 50%-60% [1]. The median survival for these patients is 20 months, with the two-year survival of 40% [1]. Despite improvement in the treatment of LD-SCLC, unfortunately, there has been little for ED-SCLC. There is a need to develop new agents as well as new combination chemotherapeutic regimens to treat SCLC.

TOPOTECAN
Topotecan is a drug originating from a family of chemotherapeutic agents that inhibit the DNA topoisomerase I enzyme (Table 1). The DNA topoisomerase I enzyme is responsible for relaxing a supercoiled DNA helix during DNA synthesis. Topoisomerase I inhibitors inhibit the religation step of the enzymatic reaction by stabilizing the DNA enzyme complex [2]. It then causes accumulation of persistent single strand DNA breaks. After the inhibition of the enzyme, it is not clear how the camptothecins cause cell death. Camptothecin, the parent drug, is a plant alkaloid extract derived from the oriental tree Camptotheca acuminata. Topotecan is a water-soluble analog (Fig. 1).

Topotecan is excreted in urine and also is concentrated in bile. O’Reilly et al. found that dose adjustments should be made in patients with reduced renal function [3] (Table I). Patients who had been heavily pretreated with other chemotherapy agents and lower creatinine clearances had worse toxicities at 1.5 mg/m²/d given i.v. over 30 min for five days. Cycles were repeated every 21 days. In patients with creatinine clearances of 20-39 ml/min, and 40-59 ml/min, the dose of topotecan should be reduced to 0.5 mg/m²/d and 1.0 mg/m²/d, respectively [3]. The dose of topotecan does not have to be adjusted for abnormal liver function as long as the bilirubin is less than 10 mg/dl [2].

Topotecan is a relatively well-tolerated drug. Hematologic toxicity, mainly neutropenia, is the dose-limiting toxicity [2]. Anemia and thrombocytopenia also occur. The hematologic nadir is around day 14 and usually recovers by day 21. These hematologic toxicities do not
Topotecan and Small Cell Lung Cancer

Topotecan and Small Cell Lung Cancer appear to be cumulative [3]. Other toxicities include fatigue and malaise. Mild toxicities include alopecia, nausea/vomiting, stomatitis, diarrhea, and elevation of liver function tests (mainly AST and ALT) [2].

The trials with topotecan in lung cancer have mainly focused on the treatment of extensive stage SCLC; the drug has been evaluated both in SCLC patients who were previously untreated as well as those who have received prior therapy. In addition, topotecan has been combined with paclitaxel to treat patients with ED-SCLC. This paper will review the studies of topotecan on the treatment of SCLC (Table 2).

**TOPOTECAN AS A FIRST-LINE AGENT**

A study done by the Eastern Cooperative Oncology Group (ECOG) investigated topotecan as an initial treatment of extensive stage SCLC [4]. Forty-eight chemotherapy-naive patients with extensive SCLC were given topotecan as a single agent at 2.0 mg/m²/d for five days every 21 days. None of the 48 patients had a complete remission (CR), but 19 of 48 had a partial remission (PR), for a response rate of 39%. The median duration of response was 4.8 months. The median survival was 10 months, which is the average survival of patients with extensive stage SCLC. The one-year survival rate was 39%.

In this study, there was a correlation between the topotecan levels and myelosuppression. The main toxicity was hematologic. Of the first 13 patients entered into the study, 92% had grade 3 or 4 neutropenia. However, with G-CSF added, only 29% of 35 patients treated with topotecan developed grade 3 or 4 neutropenia. Grade 3 or 4 thrombocytopenia also occurred in 38% of patients. Other grade 3 or 4 toxicities included nausea and vomiting occurring in four patients, while grade 3 or 4 toxicities occurred in one patient each with seizures, rash, hyperbilirubinemia, foot drop, stomatitis, esophagitis, and duodenitis.

Other studies are looking to evaluate topotecan in combination with other chemotherapeutic agents. Jett et al. reported at the Eighth World Conference on Lung Cancer meeting in Dublin on the effectiveness of the combination of topotecan and paclitaxel to treat chemotherapy-naive patients with ED-SCLC [5]. Of 12 evaluable patients treated, two achieved a CR and nine achieved a PR, for an overall response rate of 92%. The one-year survival was 50% and the two-year survival was 25%. Their preliminary conclusion was that the combination of topotecan and paclitaxel is highly active against untreated SCLC patients and yielded similar responses to current front-line chemotherapy agents. The study was ongoing.

Currently, there is a trial being conducted by ECOG (PROTOCOL 7593). It is a randomized phase three trial in ED-SCLC, comparing topotecan and G-CSF versus observation after prior treatment with cisplatin plus etoposide. Patients with ED-SCLC receive four cycles of etoposide, 120 mg/m² i.v. days 1, 2 and 3 plus cisplatin 60 mg/m² i.v. on day 1. Cycles are repeated every three weeks. Patients with progression of disease are taken off study. Patients who have responded or have stable disease after four cycles of etoposide and cisplatin are randomized to either observation or receive topotecan 1.5 mg/m² i.v. daily for five days with cycles repeated every three weeks for four cycles. The study was activated in March 1995 and is ongoing. As yet, there are no results reported.

**TOPOTECAN AS A SECOND-LINE AGENT**

Topotecan is an effective second-line agent in patients with SCLC. Perez-Soler et al. investigated the use of topotecan in patients with SCLC refractory to etoposide and cisplatin [6]. The investigators used the idea of upregulation of topoisomerase I enzyme in patients who were previously treated with topoisomerase II inhibitors such as etoposide (VP-16).
Etoposide is thought to potentially upregulate the topoisomerase I enzyme, and thus topoisomerase I inhibitors may then be more effective as second-line agents. Thirty-two patients with refractory SCLC previously treated with VP-16 and cisplatin were given 1.25 mg/m$^2$/d for five days every 21 days. Three of 28 patients achieved a PR, for a response rate of 11%. This rate is comparable to other response rates of other second-line regimens which vary from 8%-19% [6].

Median survival was 20 weeks and the one-year survival rate was only 3.5%. It should be noted that only 44 of 81 courses could be given at the full dose level. Most of the other courses had to be given at lower than normal dose levels secondary to hematologic toxicities.

A more recent study by Ardizzoni et al. assessed topotecan as a second-line treatment for patients with SCLC, but divided the patients by having either previously sensitive disease or refractory disease [7]. The sensitive group of SCLC patients was defined as having responded to the initial chemotherapy and then progressed three months or greater from the completion of the therapy. The refractory group were patients who relapsed or progressed less than three months after receiving the first-line regimen. Of 97 patients treated with single-agent topotecan at 1.5 mg/m$^2$/d for five days every 21 days, 2 of 47 refractory patients achieved a PR, and 1 of 47 achieved a CR. Of 45 sensitive patients, 11/45 achieved a PR and 6/45 achieved a CR. The overall response rate was 21.7%, with 6.4% and 37.8% in the refractory and sensitive groups, respectively. The median survival time for all patients was 5.4 months, with the median survival of responding patients being 12.5 months. The study demonstrates that topotecan is an excellent second-line chemotherapeutic agent in patients with sensitive disease. There were several other interesting findings in this particular study. The patients with documented brain metastasis (seven patients) and who responded systemically to topotecan (five patients) also responded in the CNS sites. This may be significant since brain metastasis is a common occurrence in patients with SCLC. In addition, the type of prior chemotherapy was not statistically significant in influencing the topotecan treatment outcome.

A comparable study was reported in an abstract by Eckardt et al. [8]. In this study of topotecan as second-line therapy in patients with SCLC, 74 patients received topotecan; 36 patients were part of the sensitive group, while 38 patients were refractory to therapy. Three of 36 patients achieved a CR, and 4 of 36 patients achieved a PR, for a 19% overall response rate in sensitive patients. Only one of the 38 refractory patients achieved a PR. The investigators' conclusion also confirmed that topotecan is associated with an encouraging response rate in patients who are sensitive to prior chemotherapy.

A SmithKline Beecham pharmaceutical company-sponsored phase III randomized study comparing

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<tr>
<td>Patient population</td>
<td>Chemo-naive patients with extensive stage SCLC</td>
<td>Chemo-naive patients with SCLC</td>
<td>Patients with resistant disease to etoposide &amp; cisplatin</td>
<td>Previously treated patients</td>
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<td>Dosage of topotecan</td>
<td>2.0 mg/m$^2$/d for 5 days every 21 days</td>
<td>1 mg/m$^2$/d × 5 with paclitaxel 135 mg/m² i.v. over 24 h on day 5</td>
<td>1.25 mg/m$^2$/d for 5 days every 21 days</td>
<td>1.5 mg/m$^2$/d for 5 days every 21 days</td>
<td>1.5 mg/m$^2$/d for 5 days every 21 days</td>
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<td>Number of patients</td>
<td>48</td>
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<td>32 (only 28 patients were assessed)</td>
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<td>PR</td>
<td>19/48</td>
<td>9/12</td>
<td>3/28</td>
<td>S = 11/45; R = 2/47</td>
<td>S = 4/36; R = 1/38</td>
<td>16/64</td>
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<td>CR</td>
<td>0/48</td>
<td>2/12</td>
<td>0/28</td>
<td>S = 6/45; R = 1/47</td>
<td>S = 3/36; R = 0</td>
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<td>Overall response rate</td>
<td>39%</td>
<td>92%</td>
<td>11%</td>
<td>21.7%</td>
<td>S = 19%</td>
<td>25%</td>
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<td>Median survival</td>
<td>10 months</td>
<td>1 yr. = 50%</td>
<td>20 weeks</td>
<td>5.4 months</td>
<td>S = 26.6 weeks</td>
<td>21.7 weeks</td>
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<td>1 yr. = 39%</td>
<td>2 yr. = 25%</td>
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<td>1 yr. = 3.5%</td>
<td>R = 20.4 weeks</td>
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S = patients with sensitive disease; R = patients with refractory disease.
topotecan (1.5 mg/m²/d) versus CAV (cyclophosphamide 1,000 mg/m², doxorubicin 45 mg/m², and vincristine 2 mg) as second-line therapy of SCLC was presented at the Eighth World Conference on Lung Cancer [9]. There were 64 patients in the topotecan arm, with 16/64 PRs—a response rate of 25%. Of 61 patients in the CAV arm, there were 9/61 PRs—a response rate of 15%. Median survival time was comparable with topotecan-treated patients, 21.7 weeks, and CAV-treated patients, 23.1 weeks. The toxicities were similar, with the exception that topotecan caused slightly more anemia (18% versus 6% of courses of CAV) and thrombocytopenia (32% versus 9% in patients treated with CAV). The authors concluded that single agent topotecan, as second-line therapy in sensitive patients, is similar in efficacy to the CAV regimen, with similar toxicities.

**CONCLUSIONS**

These studies show that topotecan is both an effective second-line agent in the treatment of SCLC, especially in patients with chemo-sensitive disease, and is a promising first-line drug. Topotecan is reasonably well tolerated, with myelosuppression being the major dose-limiting toxicity. Studies are needed utilizing topotecan in combination with other agents to treat patients with ED-SCLC and LD-SCLC. In the latter group of patients, the drug used alone or in combination together with radiation therapy is warranted.

**REFERENCES**


