Recent Advances with Topotecan in the Treatment of Lung Cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe phase I studies evaluating the pharmacokinetics and early safety data of single-agent oral topotecan.
2. Discuss the results and implications of clinical trials evaluating oral topotecan for small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).
3. Explain why topotecan is a good candidate for combination with other novel anticancer agents.

ABSTRACT

Topotecan is a semisynthetic derivative of camptothecin that specifically targets topoisomerase I. It has well-established antineoplastic properties and has been successfully combined with other antineoplastic agents with activity dependent on DNA disruption, such as cisplatin and etoposide. Topotecan is indicated for the treatment of small cell lung cancer (SCLC) sensitive disease after failure of first-line chemotherapy and metastatic ovarian carcinoma after failure of initial or subsequent chemotherapy. Since the approval of topotecan for the second-line treatment of SCLC, studies have been conducted in the first-line setting. Recent studies demonstrate the utility of i.v. topotecan in combination with cisplatin for untreated SCLC. Further, an oral formulation of topotecan is currently under investigation and may provide added convenience for patients. Oral topotecan has been studied in the first- and second-line settings for both SCLC and non-small cell lung cancer (NSCLC). Three recent phase III trials have demonstrated the activity of oral topotecan. In the first study of chemotherapy-naïve patients with extensive-disease SCLC, oral topotecan plus cisplatin provided efficacy and safety similar to those of etoposide plus cisplatin. In a second study of patients with relapsed SCLC, treatment with oral topotecan showed a statistically significant and clinically meaningful longer overall survival time and improvement in dyspnea and quality of life compared with best supportive care alone in all prognostic groups. Finally, in previously treated patients with NSCLC, single-agent oral topotecan was shown to be noninferior in 1-year survival rate relative to the current standard of i.v. docetaxel. In future studies, oral topotecan will represent a good candidate for combination therapy with other i.v. or oral chemotherapy agents, monoclonal antibodies, and small molecule tyrosine kinase inhibitors. The Oncologist 2007;12:1194–1204
INTRODUCTION
Lung cancer is a significant global health issue, being both the most commonly diagnosed cancer and the most common cause of cancer-related death worldwide. Globally, lung cancer accounts for an estimated 1.4 million cancer cases and 1.2 million deaths each year [1]. Similar incidence and mortality rates are seen in developed and developing nations. The highest incidence rates occur for men in Eastern Europe and North America and for women in North America and Northern Europe [1]. In the U.S., small cell lung cancer (SCLC) accounts for approximately 15% of lung cancer cases [2].

Although surgery and radiation play integral roles in lung cancer management, chemotherapy is the mainstay of treatment for SCLC and is increasingly being used in non-small cell lung cancer (NSCLC). Platinum-based regimens are the standard first-line strategy in both settings for either early-stage or advanced disease. The agents used as second-line therapy vary by setting [2, 3].

Topotecan, a semisynthetic derivative of camptothecin, is a topoisomerase I inhibitor with well-established antineoplastic properties. In the mid-1990s, i.v. single-agent topotecan was shown to have activity against relapsed ovarian cancer [4] and SCLC [5]. This activity led to approval by the U.S. Food and Drug Administration (FDA) of single-agent topotecan for the treatment of metastatic ovarian carcinoma after failure of initial or subsequent chemotherapy, and for the treatment of SCLC sensitive disease after failure of first-line chemotherapy. Most recently, topotecan, in combination with cisplatin, was approved for use in stage IV-B recurrent or persistent cervical cancer [6]. The principal dose-limiting toxicity of i.v. topotecan is myelosuppression, which is short lived, noncumulative, and reversible; nonhematologic toxicities are manageable [5]. For SCLC and ovarian cancer, the approved dose of i.v. topotecan is 1.5 mg/m2 given as a 30-minute i.v. infusion, daily for five consecutive days, every 21 days. However, multiple trials have evaluated alternative doses and schedules, including lower starting doses of 1.25 or 1.0 mg/m2 given for 5 days, 3-day schedules, and weekly bolus schedules [7–9]. i.v. topotecan has been used as a single agent and in combination regimens for the treatment of various tumor types. Topotecan is currently recommended by the National Comprehensive Cancer Network as the first choice in treating chemotherapy-sensitive SCLC, specifically for disease that has relapsed within 2–6 months after primary treatment [2].

Since the approval of topotecan for use in relapsed SCLC, various studies have been conducted in the first-line setting. An oral formulation of topotecan has been investigated and provided added convenience for patients. Oral topotecan has been studied in the first- and second-line settings for both SCLC and NSCLC. This paper reviews the role of topotecan in the treatment of lung cancer, focusing on recent data with i.v. topotecan in first-line SCLC and the new oral formulation in both SCLC and NSCLC.

I.V. TOPOTECAN FOR UNTREATED SCLC
Median survival times from studies evaluating conventional cisplatin plus etoposide regimens as first-line treatment for patients with extensive-disease (ED)-SCLC are approximately 9–10 months [10–13]. Results from studies discussed below suggest that using topotecan in combination regimens in this setting is an effective and well-tolerated option.

Recent studies evaluating topotecan in first-line SCLC have primarily examined its use in combination with either cisplatin or etoposide. Results of a phase II study in 36 patients with limited or extensive disease suggested that sequential administration of i.v. topotecan (0.75 mg/m2 daily for 5 days) and oral etoposide (50 mg twice daily for 7 days) as 21-day cycles is effective for SCLC [14]. The median progression-free survival duration was 7.3 months and the median survival time was 12.0 months. The incidences of grade 3 or 4 neutropenia and thrombocytopenia were 25% and 11%, respectively; two patients died from neutropenic sepsis.

The topotecan–etoposide combination was compared with a topotecan–cisplatin combination, with results suggesting similar efficacy [15]. In that randomized phase II study, 82 patients with previously untreated ED-SCLC received either i.v. topotecan (1.25 mg/m2 per day) on days 1–5 plus cisplatin (50 mg/m2) on day 5 or i.v. topotecan (0.75 mg/m2 per day) on days 1–5 plus i.v. etoposide (60 mg/m2 per day) on days 1–5. Response rates and median survival times were similar in the two groups (63.4% versus 61.0% and 9.6 months versus 10.1 months, respectively). Hematologic toxicities in the topotecan–cisplatin arm versus the topotecan–etoposide arm, respectively, were grade 3 or 4 anemia (46.4% versus 20.0%) and grade 4 neutropenia (56.1% versus 65.0%). The incidence of sepsis was 0% with topotecan plus cisplatin versus 9.8% with topotecan plus etoposide. Secondary to the significant myelosuppression of the topotecan–cisplatin combination, investigators have studied shorter schedules of topotecan in combination with cisplatin [7, 16, 17], including a 3-day administration schedule of topotecan that appears to be comparable with the standard 5-day schedule [7]. A randomized phase II study in 86 patients with ED-SCLC compared a 1.0-mg/m2 dose of topotecan on days 1–5 with a 1.5-mg/m2 dose on days 1–3, each with cisplatin (75 mg/m2) on the last day of topotecan treatment. While the efficacies were similar, the 3-day regimen may offer a more tolerable option. The me-
median survival times in the 5- and 3-day arms were 8.7 months and 7.6 months, respectively. There was no significant difference in overall survival (p = .68), and response rates were 62% and 60%, respectively. Grade 3 or 4 toxicities in the 5- and 3-day arms, respectively, included leukocytopenia (64% versus 48%), anemia (43% versus 21%), and thrombocytopenia (52% versus 40%).

Topotecan has been evaluated in a consolidation approach to untreated SCLC. A randomized phase III trial by the Eastern Cooperative Oncology Group (ECOG) evaluated topotecan following cisplatin plus etoposide in patients with previously untreated ED-SCLC [18]. Four cycles of cisplatin plus etoposide were given to 402 patients; those with response or stable disease were then randomized to either continue chemotherapy with topotecan (1.5 mg/m²) daily for 5 days every 3 weeks for four cycles (n = 112) or proceed to observation alone (n = 111). The progression-free survival interval was significantly longer in the topotecan arm (median, 3.7 months with topotecan versus 2.3 months with observation alone; p < .001). The overall survival duration was not significantly different between the two groups (median, 9.3 months with topotecan versus 8.9 months with observation; p = .43). Administration of topotecan did not worsen quality of life; no significant differences occurred in Trial Outcome Index or Functional Assessment of Cancer Therapy–Lung scores.

Finally, a phase III trial comparing two different schedules of the cisplatin–etoposide–topotecan combination has been completed [19]. The study employed either sequential administration—cisplatin (75 mg/m²) on day 1 and etoposide (100 mg/m² per day) on days 1–3 for four cycles followed by topotecan (1.5 mg/m² per day) on days 1–5 for four cycles—or alternating administration of the same doses of i.v. cisplatin and etoposide (cycles 1, 3, 5, and 7) and topotecan (cycles 2, 4, 6, and 8) in 284 chemotherapy-naïve patients with ED-SCLC. The preliminary analysis indicated comparable activity and safety in the two comparison groups, with no significant differences between groups in response, overall survival, time to progression (TTP), or response duration. For the sequential versus alternating groups, the overall response rates were 53% versus 55%; the median survival times were 10.2 versus 9.5 months; the median TTP were 6.0 versus 6.8 months; and the median response durations were 5.5 versus 5.2 months, respectively. Grade 3 or 4 hematologic toxicities were neutropenia (51% and 52%), anemia (12% and 11%), febrile neutropenia (7% and 9%), and thrombocytopenia (19% and 20%). There were seven toxicity-related deaths (four in the sequential arm and three in the alternating arm). Taken together, these studies add useful information about the use of i.v. topotecan in the first-line treatment of SCLC and provide a basis for further investigation of topotecan as a potential new agent in the treatment of this disease.

**Development of Oral Topotecan**

An oral version of topotecan was developed to improve convenience and accessibility for patients. Indeed, many patients prefer oral chemotherapy. A 1997 survey of 103 patients with incurable cancer showed that, given a choice of agents with similar efficacy, most patients would prefer oral agents over i.v. chemotherapy [20]. Reasons for this preference include convenience, problems with i.v. access or needles, having control over the environment for taking chemotherapy, and the need for travel to receive i.v. chemotherapy. Compliance with oral topotecan in clinical trials, to the extent that this can be evaluated by pill counts, has been high. In a retrospective analysis of compliance data from three randomized phase III trials of oral topotecan in lung cancer, compliance according to pill counts was in the range of 90.8%–98.6% [21].

Quality of life is an important issue for patients with lung cancer. In another survey of patients with advanced NSCLC, given the choice between supportive care and chemotherapy, only 22% selected chemotherapy if it provided a survival benefit of 3 months, whereas 68% chose chemotherapy if it substantially reduced symptoms without prolonging survival [22]. Advantages of oral agents include eliminating the need for i.v. lines that cause discomfort and possibly lead to infections, the potential for fewer side effects than the injectable counterparts, and perhaps easier integration into combination regimens.

Phase I studies evaluating the pharmacokinetics and early safety data of single-agent oral topotecan have been completed (Table 1) [23–31]. Single-dose studies determined that the absolute bioavailability of the oral formulation is 30%–44% [23–25] and is not affected by food intake [23]. A multiple-dose study found that approximately 57% of the oral dose is eliminated unchanged in the urine and feces [26]. A population pharmacokinetic analysis revealed that renal creatinine clearance and, to a limited extent, performance status (PS) are factors that significantly affect oral topotecan clearance [27].

In multiple-dose phase I studies, several dosing schedules of single-agent topotecan were examined for toxicity and pharmacokinetics. Together these studies suggested the following recommended dosing schema: 14 mg/m² on day 1 every 21 days [25], 0.5 mg/m² twice daily for 21 days every 28 days [28], 2.3 mg/m² per day or 4 mg/day for 5 days every 21 days [29], and 1.4 mg/m² per day or 0.7 mg/m² twice daily for 10 days every 21 days [30]. The dose-limiting toxicity was diarrhea with the longer schedule (dosing for 21 days) versus hematologic toxicity (granulo-
cytopenia) with the shorter schedule (dosing for 1 or 5 days). Both diarrhea and granulocytopenia occurred with the 10-day schedules. These toxicities were self-limiting and noncumulative. Finally, a pharmacokinetic and pharmacodynamic comparison of the four different multiday schedules using data from the patients in these studies found that (a) the area under the concentration–time curve (AUC) per week and AUC per course were not significantly different among the schedules, (b) the 5-day schedule had the least inter- and intrapatient variability, and (c) the 10- and 21-day schedules were associated with unpredictable, and sometimes severe, diarrhea [31]. Thus, the 5-day schedule (2.3 mg/m² per day or 4 mg/day for 5 days every 21 days) was recommended as the preferred regimen for future clinical trials [31].

Phase I trials that evaluated oral topotecan given in combination with other chemotherapeutic agents have identified the maximum-tolerated dose of oral topotecan with cisplatin, capecitabine, and carboplatin plus paclitaxel [32–35]. In a randomized, crossover design, 49 patients received oral topotecan at escalating doses daily for 5 days every 21 days with i.v. cisplatin (75 mg/m²) on either day 1 or day 5 of topotecan [32]. Consistent with previously reported data with i.v. topotecan and cisplatin [36], myelotoxicity was significantly more severe when cisplatin preceded topotecan. As such, the recommended maximum-tolerated dose of oral topotecan is lower in the cisplatin–topotecan sequence—topotecan (1.25 mg/m² per day) for 5 days preceded by cisplatin (75 mg/m²) on day 1 once every 3 weeks versus topotecan (2.0 mg/m² per day) for 5 days followed by cisplatin (75 mg/m²) on day 5. Evaluation of an all-oral combination of topotecan and capecitabine in 19 patients

### Table 1. Phase I studies with single-agent oral topotecan

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Design</th>
<th>Topotecan dose and route</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herben et al. (1999) [23]</td>
<td>18</td>
<td>Randomized, two-period crossover, single-dose</td>
<td>Period 1: oral 2.3 mg/m² with or without high-fat breakfast; period 2: oral capsules, 2.3 mg/m² or i.v. 1.4 mg/m²</td>
<td>Food does not affect extent of absorption; mean F, 42% ± 13%; 90% CI, 37%–47%</td>
</tr>
<tr>
<td>Schellens et al. (1996) [24]</td>
<td>12</td>
<td>Crossover, single-dose</td>
<td>Oral solution, 1.5 mg/m² day 1, then i.v. 1.5 mg/m² day 1</td>
<td>Mean F, 30% ± 7.7%; range, 21%–45%</td>
</tr>
<tr>
<td>Kuhn et al. (1995) [25]</td>
<td>11</td>
<td>Randomized, single-dose</td>
<td>Oral solution, 14 mg/m² or i.v. 17.5 mg/m²</td>
<td>Mean F, 44%</td>
</tr>
<tr>
<td>Herben et al. (2002) [26]</td>
<td>9</td>
<td>Randomized, crossover, multiple-dose</td>
<td>Oral, 2.3 mg/m² or i.v. 1.5 mg/m², each daily × 5 days</td>
<td>Percent unchanged in urine and feces, 20% and 33% oral, 49% and 18% i.v.</td>
</tr>
<tr>
<td>Leger et al. (2004) [27]</td>
<td>190</td>
<td>Retrospective data collection; population model (NONMEM)</td>
<td>i.v. (n = 72) or oral (n = 118)</td>
<td>CrCl and PS are significant covariates affecting clearance</td>
</tr>
</tbody>
</table>

### Dosing studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Topotecan dose and route</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creemers et al. (1997) [28]</td>
<td>Prospective, multiple-dose</td>
<td>0.15–0.6 mg/m² b.i.d. × 21 days every 28 days</td>
<td>DLT, diarrhea; MTD, 0.5 mg/m² b.i.d. × 21 days every 28 days</td>
</tr>
<tr>
<td>Gerrits et al. (1998) [29]</td>
<td>Prospective, multiple-dose</td>
<td>1.2–2.7 mg/m² or 4 mg daily × 5 days every 21 days</td>
<td>DLT, granulocytopenia; MTD, 2.3 mg/m² or 4 mg daily × 5 days every 21 days</td>
</tr>
<tr>
<td>Gerrits et al. (1998) [30]</td>
<td>Prospective, multiple-dose</td>
<td>1.0–1.6 mg/m² daily × 10 days, every 21 days or 0.5–0.8 mg/m² b.i.d. × 10 days every 21 days</td>
<td>DLT, myelosuppression and diarrhea; MTD, 1.4 mg/m² daily or 0.7 mg/m² b.i.d. × 10 days every 21 days</td>
</tr>
<tr>
<td>Gerrits et al. (1999) [31]</td>
<td>Pharmacokinetic evaluation of three studies above</td>
<td>Daily × 5 days every 21 days (n = 29); daily × 10 days every 21 days (n = 19); b.i.d. × 10 days every 21 days (n = 20); b.i.d. × 21 days every 28 days (n = 31)</td>
<td>5-day schedule preferred for future clinical trials based on toxicity and pharmacokinetic evaluation</td>
</tr>
</tbody>
</table>

*aAll oral topotecan. Abbreviations, b.i.d., twice daily; CI, confidence interval; CrCl, creatinine clearance; DLT, dose-limiting toxicity; F, bioavailability; MTD, maximum-tolerated dose; NONMEM, nonlinear mixed-effects model; PS, performance status.*
led to a recommended regimen of topotecan (1.5 mg/m² per day) for 5 days on days 1–5 of each week for 2 weeks and capecitabine (1,800 mg/m² twice daily) on days 1–14 of a 21-day cycle in future trials [34]. A study of 13 patients receiving escalating doses of topotecan on days 1–5 in combination with paclitaxel (175 mg/m²) and carboplatin (AUC, 5) on day 1 found significant myelotoxicity at all dose levels of topotecan (0.75, 1.0, and 1.25 mg/m²), and the authors could not recommend any of the doses for further study [33]. However, a subsequent phase I–II study in patients with ovarian cancer administered the triplet in a “reverse schedule,” with the same doses of paclitaxel plus carboplatin on day 5 of oral topotecan dosing (rather than day 1) [35]. In the phase I portion, a topotecan dose of 2.0 mg/m² for 5 days was reached; however, in the phase II portion, a dose reduction to 1.75 mg/m² was required after the first course as a result of febrile neutropenia. The triplet was well tolerated after the dose reduction.

**Oral Topotecan in SCLC**

Phase II and III studies have been conducted with oral topotecan in the first- and second-line treatment of SCLC (Table 2) [10, 37–40]. Of particular note are two recent randomized phase III trials that demonstrate the activity of oral topotecan both in a combination regimen as first-line treatment and as monotherapy in the second-line treatment of patients with SCLC [10, 40].

**First-Line Oral Topotecan in SCLC**

A phase II feasibility study examined oral topotecan as first-line monotherapy in 41 patients with ED-SCLC who were ineligible for standard therapy (because of factors such as age or concomitant illness; 88% with PS scores of 1–2) [39]. Patients initially received 2.0 mg/m² per day for 5 days every 3 weeks, but the dose level was reduced to 1.7 mg/m² per day as a result of myelosuppression. The overall response rate was 30%, including one complete response. The incidence of grade 3 or 4 neutropenia was 72% at the 2.0-mg/m² dose and 57% at the 1.7-mg/m² dose. These data suggest that oral topotecan is active in this setting.

**Phase III Trial**

In a subsequent randomized, phase III trial, the combination of oral topotecan and cisplatin was compared with the standard etoposide–cisplatin regimen in previously untreated patients with ED-SCLC [10]. Treatment consisted of oral topotecan (1.7 mg/m² per day) for 5 days with i.v. cisplatin (60 mg/m²) on day 5 (TC, n = 389) or i.v. etoposide (100 mg/m² per day) for 3 days with i.v. cisplatin (80 mg/m²) on day 1 (PE, n = 395) every 21 days. The primary endpoint of the study, overall survival, was not significantly different between arms (p = .48). The hazard ratio adjusted for interim analyses was 1.05 (95% confidence interval [CI], 0.90–1.24). The median survival times were 39.3 weeks with TC versus 40.3 weeks with PE. The 1-year survival rates were similar between TC and PE (31% in both groups). The 95% CI for the coprimary endpoint of difference in the 1-year survival rate between TC and PE was −6.5 to 6.5, indicating that TC was not inferior to PE in a 1-year survival rate based on a 10% noninferiority margin. The median TTP for TC and PE were 24.1 weeks and 25.1 weeks, respectively. Response rates were 63% with TC and 69% with PE. Of grade 3 or 4 hematologic toxicities, neutropenia occurred more frequently with PE (84% versus 59%), while anemia and thrombocytopenia occurred more frequently with TC (38% versus 21% and 38% versus 23%, respectively). Fever and infection occurring within 2 days of grade 4 neutropenia was observed in 10% of patients on PE versus 4% on TC. Differences between arms were observed for nonhematologic toxicities. Patients on TC had a higher incidence of diarrhea (33% for TC versus 18% for PE), but a lower incidence of serum creatinine elevations (12% for PE versus 5% for TC) and alopecia (40% for PE versus 24% for TC). Overall, this phase III study demonstrated similar efficacy and tolerability between oral topotecan plus cisplatin and the standard etoposide–cisplatin combination as first-line treatment for patients with ED-SCLC.

**Second-Line Oral Topotecan in SCLC**

The rationale for evaluating oral topotecan in relapsed SCLC is based on the efficacy of the i.v. formulation in this setting. Intravenous topotecan is the only single agent approved for second-line SCLC and is currently the agent of choice for treatment of patients with SCLC that has relapsed within 2–6 months after completing first-line chemotherapy [2]. This recommendation is supported by data from a randomized trial in which i.v. topotecan was compared with cyclophosphamide, doxorubicin, and vincristine (CAV) in 211 patients with relapsed SCLC considered sensitive to chemotherapy (defined in this trial as relapse ≥60 days after the end of chemotherapy) [41]. The primary endpoint of difference in response rate between topotecan and CAV was 6.0% in favor of topotecan, with a 95% CI of −5.9 to 18, indicating that, at the lower limit of the CI, topotecan may be inferior to CAV by at most 5.9%. No significant differences between i.v. topotecan and CAV were observed in the response rate (24.3% versus 18.3%), TTP (median, 13.3 versus 12.3 weeks; p = .552), or overall survival time (median, 25.0 versus 24.7 weeks; p = .795). However, several disease-related symptoms (dyspnea, fatigue, anorexia, hoarseness, and interference with daily ac-
Table 2. Clinical studies with oral topotecan in small cell lung cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Treatment</th>
<th>Response rates</th>
<th>Survival and progression</th>
<th>Grade 3 or 4 hematologic toxicity</th>
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<tr>
<td><strong>First-line treatment</strong></td>
<td></td>
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</tr>
<tr>
<td>Eckardt (2001) [39], phase II</td>
<td>41</td>
<td>Oral topotecan, 1.7–2.0 mg/m² per day × 5 days every 21 days</td>
<td>ORR, 30%; CR, 3%; PR, 27%; SD, NA; CBR, NA (preliminary analysis)</td>
<td>NA</td>
<td>N, 57%–72%; A, 32%–29%; T, 52%–36%</td>
</tr>
<tr>
<td>Eckardt et al. (2006) [10], phase III</td>
<td>389</td>
<td>Oral topotecan, 1.7 mg/m² per day × 5 days, with i.v. cisplatin, 60 mg/m² on day 5 every 21 days</td>
<td>ORR, 63%; CR, 6%; PR, 57%; SD, 10%; CBR, 73%</td>
<td>MST, 39.3 wks; 1-yr, 31%; TTP, 24.1 wks</td>
<td>N, 59%; A, 38%; T, 83%</td>
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<tr>
<td></td>
<td>395</td>
<td>i.v. etoposide, 100 mg/m² per day × 3 days, with i.v. cisplatin, 80 mg/m² on day 1 every 21 days</td>
<td>ORR, 69%; CR, 5%; PR, 64%; SD, 12%; CBR, 81%</td>
<td>MST, 40.3 wks; 1-yr, 31%; TTP, 25.1 wks</td>
<td>N, 84%; A, 21%; T, 23%</td>
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<td><strong>Second-line treatment</strong></td>
<td></td>
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<tr>
<td>von Pawel et al. (2001) [37], phase II</td>
<td>52</td>
<td>Oral topotecan, 2.3 mg/m² per day × 5 days every 21 days</td>
<td>ORR, 23%; CR, 2%; PR, 21%; SD, 19%; CBR, 42%</td>
<td>MST, 32 wks; TTP, 14.9 wks</td>
<td>N, 57%; A, 31%; T, 53%</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>i.v. topotecan, 1.5 mg/m² per day × 5 days every 21 days</td>
<td>ORR, 15%; CR, 4%; PR, 11%; SD, 30%; CBR, 45%</td>
<td>MST, 25 wks; TTP, 13.1 wks</td>
<td>N, 94%; A, 30%; T, 49%</td>
</tr>
<tr>
<td>Eckardt et al. (2007) [38], phase III</td>
<td>153</td>
<td>Oral topotecan, 2.3 mg/m² per day × 5 days every 21 days</td>
<td>ORR, 18%; CR, NA; PR, NA; SD, 18%; CBR, 36%</td>
<td>1-yr, 33%; MST, 33 wks</td>
<td>N, 47% (grade 4); A, 23%; T, 29% (grade 4)</td>
</tr>
<tr>
<td></td>
<td>151</td>
<td>i.v. topotecan, 1.5 mg/m² per day × 5 days every 21 days</td>
<td>ORR, 22%; CR, NA; PR, NA; SD, 23%; CBR, 45%</td>
<td>1-yr, 29%; MST, 35 wks</td>
<td>N, 64% (grade 4); A, 31%; T, 18% (grade 4)</td>
</tr>
<tr>
<td>O’Brien et al. (2006) [40], phase III</td>
<td>71</td>
<td>Oral topotecan, 2.3 mg/m² per day × 5 days every 21 days with BSC</td>
<td>ORR, 7%; CR, 0; PR, 7%; SD, 44%; CBR, 51%</td>
<td>MST, 25.9 wks; TTP, 16.3 wks</td>
<td>N, 61%; A, 25%; T, 38%</td>
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<tr>
<td></td>
<td>70</td>
<td>BSC alone</td>
<td>NA</td>
<td>MST, 13.9 wks c</td>
<td>NA</td>
</tr>
</tbody>
</table>

*p = .02 for overall TTP versus oral topotecan.

*p = .001 versus oral topotecan for grade 4 neutropenia (67% for i.v. versus 35% for oral).

*p = .01 for overall survival versus oral topotecan.

Abbreviations, A, anemia; BSC, best supportive care; CBR, clinical benefit rate (CR + PR + SD); CR, complete response; MST, median survival time; N, neutropenia; NA, not available; ORR, overall response rate; PR, partial response; SD, stable disease; T, thrombocytopenia; TTP, time to progression.
tivity) improved to a significantly greater extent with topotecan than with CAV. Some safety advantages were observed with topotecan as well. While grade 3 or 4 thrombocytopenia and anemia occurred more frequently with topotecan, grade 4 neutropenia occurred less frequently than with CAV. Additionally, fewer dose reductions for nonhematologic toxicities occurred in the topotecan arm. A subsequent study demonstrated activity with topotecan in patients previously treated for SCLC who relapsed with symptomatic brain metastases [42]. Of the 30 patients in the single-arm phase II study, eight had prior whole-brain irradiation (WBI). Responses in cerebral metastases were observed in 33% of patients, including four of the eight patients who had undergone WBI. These data support the current role of i.v. topotecan in relapsed SCLC and the investigation of the oral formulation in this setting.

To evaluate whether oral topotecan could alternatively be used in chemotherapy-sensitive SCLC, i.v. and oral topotecan were compared in a phase II trial [37] and further explored in a phase III trial [10] (Table 2) [10, 37–40]. In these randomized studies, patients with relapsed, sensitive SCLC (defined as relapse >90 days after the end of chemotherapy) received second-line therapy with either oral topotecan (2.3 mg/m² per day) or i.v. topotecan (1.5 mg/m² per day) for 5 days every 21 days. Efficacy parameters indicated similar activity between the two treatments and possibly a lower incidence of severe neutropenia with the oral formulation. From the phase III trial, response rates and median survival times for oral versus i.v. topotecan were 18.3% versus 21.9% and 33 weeks versus 35 weeks, respectively [38]. The incidences of grade 4 neutropenia were 47% versus 64% for the oral and i.v. formulations, respectively. In the phase II trial, the incidences of grade 4 neutropenia were 35% versus 67% for the oral and i.v. formulations, respectively [37]. These data suggest that oral topotecan has similar efficacy to the i.v. formulation and is a suitable alternative to the i.v. route in patients with relapsed SCLC, with the added advantage of convenient administration.

**Phase III Trial: Superior Survival in Relapsed Advanced SCLC Compared with Best Supportive Care**

The phase III trial, designed to assess whether active chemotherapy has a role in second-line SCLC, evaluated oral topotecan versus best supportive care (BSC) in patients with relapsed SCLC [40]. In this open-label study, 141 patients were randomized to receive oral topotecan (2.3 mg/m² per day) for 5 days every 3 weeks plus BSC or BSC alone. A clinically and statistically significant improvement in the primary endpoint of overall survival was observed in the oral topotecan arm (p = .01). The unadjusted hazard ratio for oral topotecan relative to BSC was 0.64 (95% CI, 0.45–0.90), indicating a 36% lower risk for death in the oral topotecan group. The median survival time was 86% longer in the topotecan arm than in the BSC arm (25.9 weeks versus 13.9 weeks). The 6-month survival rates were 49% in the topotecan arm and 26% in the BSC arm. On entry, patients were stratified according to the TTP since first-line therapy (< or >60 days). Importantly, the survival advantage for topotecan was maintained in both strata: namely, patients with resistant disease (TTP ≤60 days) and patients with sensitive disease (TTP >60 days). The overall response rate to topotecan was 7%. Importantly, an additional 44% experienced stable disease. As shown in Table 2, this clinical benefit rate of 51% (representing the sum of the percentages of patients experiencing an objective response and stable disease) is consistent with the range of 36%–45% observed with oral or i.v. topotecan in other phase II and III clinical trials in second-line SCLC [37, 38]. The median TTP in the topotecan arm was 16.3 weeks. Response and progression data were not collected for the BSC arm. Quality of life (measured with the EuroQoL-5 Dimensions [EQ-5D] questionnaire) deteriorated significantly faster in patients receiving BSC alone. The rate of deterioration per 3-month interval in EQ-5D scores was −0.20 (95% CI, −0.27 to −0.12) on BSC compared with −0.05 (95% CI, −0.11 to 0.02) on topotecan. The difference in rate of change was significant (+0.15; 95% CI, 0.05–0.25).

Oral topotecan also significantly improved the symptom of dyspnea, clinically important in this patient population. This finding is consistent with the study of i.v. topotecan versus CAV, in which dyspnea was improved to a significantly greater extent with topotecan than with CAV [41]. The most common toxicities related to oral topotecan were hematological (grade 3 or 4 neutropenia, 61%; grade 3 or 4 thrombocytopenia, 38%; grade 3 or 4 anemia, 25%). All-cause mortality within 30 days of starting the study was not higher in the topotecan group (7% for topotecan versus 13% for BSC). The most commonly occurring nonhematologic toxicity was diarrhea in the topotecan group (6%) and dyspnea in the BSC group (9%). These data suggest that treatment with oral topotecan should be considered for all patients with relapsed SCLC, including those with resistant disease. Until this study, the role of chemotherapy in resistant disease was not well defined, and some evidence previously suggested that chemotherapy may not be beneficial in such patients [43]. This study made an important contribution by being the first to show that active chemotherapy can in fact prolong survival in patients with resistant SCLC and improve quality of life in patients with relapsed SCLC.

SCLC is an aggressive and fatal disease. Novel active
Therapies are urgently needed in all subsets of patients with this disease. Taken together, the studies with oral topotecan support a role for this new agent in the treatment of SCLC.

**Oral Topotecan in Advanced NSCLC**

A doublet platinum-containing chemotherapy regimen (with or without bevacizumab) is considered the standard of care for the first-line treatment of advanced NSCLC [3, 44]. Upon progression, established second-line agents include docetaxel, pemetrexed, and erlotinib [3]. Oral topotecan has been evaluated in phase II and III trials in NSCLC (Table 3). Phase II trials show activity of first-line oral topotecan, and a phase III trial in the second-line setting shows that oral topotecan may offer a new option in this setting.

### First-Line Oral Topotecan for Advanced NSCLC

The rationale for studying oral topotecan in the first-line setting is based on data from single-agent trials supporting the activity of the i.v. formulation in previously untreated advanced NSCLC. Intravenous topotecan, dosed daily for 5 days every 3 weeks, produced response rates ranging up to 15% and median survival times of 32–38 weeks [45–47].

Two phase II trials of oral topotecan have been conducted in untreated patients with NSCLC. Monotherapy was evaluated in 30 patients with inoperable stage III or IV NSCLC and an ECOG PS score of 0 (7%), 1 (70%), or 2 (23%) [48]. The dose of oral topotecan was escalated starting with 2.3 mg/m² per day up to 3.1 mg/m² per day and administered for five consecutive days every 3 weeks for up to six cycles. No responses were observed; however, 43% of patients achieved stable disease. The median survival time was 39.9 weeks, the 1-year survival rate was 33%, and the median TTP was 12.3 weeks.

### Second-Line Oral Topotecan for Advanced NSCLC

Recent data from a large randomized phase III trial show that oral topotecan is not inferior to i.v. docetaxel in the treatment of patients with relapsed or refractory NSCLC.
Patients were randomized to oral topotecan (2.3 mg/m² per day) for 5 days (n = 414) or a standard regimen of i.v. docetaxel (75 mg/m²) on day 1 (n = 415) every 3 weeks. The 1-year survival rates for oral topotecan versus docetaxel were 25.1% versus 28.7%; the 95% CI for the primary endpoint of difference in 1-year survival rate between oral topotecan and docetaxel was −9.6 to 2.5, indicating that oral topotecan was not inferior to docetaxel in 1-year survival rate based on a prespecified 10% noninferiority margin. Overall survival was in favor of docetaxel (log-rank p = .06). The unadjusted hazard ratio was 1.16 (95% CI, 0.99–1.36), indicating a 16% higher risk for death in the topotecan arm. For oral topotecan versus docetaxel, respectively, the median survival times were 27.9 weeks versus 30.7 weeks, 1-year survival rates were 25.1% versus 28.7%, and median TTP were 11.3 weeks versus 13.1 weeks. The response rate was 5% in both arms. Based on the 1-year survival rate, oral topotecan met the criteria for noninferiority to docetaxel in this trial. The quality of life profile favored docetaxel relative to topotecan; however, the magnitude of the difference was small and may not be clinically significant. Grade 3 or 4 toxicities differed between treatments; neutropenia occurred more frequently with docetaxel (60% versus 50%), while anemia and thrombocytopenia occurred more frequently with oral topotecan (26% versus 10% and 26% versus 7%, respectively). This study demonstrated that topotecan may provide an oral alternative for patients with relapsed, advanced NSCLC. Together, these studies in advanced NSCLC show that oral topotecan represents a feasible treatment option in this setting and offers the advantage of convenient administration.

**Topotecan as a Candidate for Combination with Novel Agents**

Recent literature suggests that topotecan is a good candidate for combination with additional categories of antineoplastic agents. The specific targeting of topoisomerase 1 by topotecan appears to lead to a decrease in hypoxia-inducible factor (HIF)-1 transcriptional repression, downregulation of HIF-1−dependent gene expression, and inhibition of vascular endothelial growth factor (VEGF) mRNA expression [51], suggesting that the combination of topotecan with VEGF inhibitors may be synergistic. Topoisomerase 1 can evade targeting by topotecan by ubiquitination, leading to downregulation of topoisomerase 1 [52]. At least in vitro, this process can be inhibited by proteasome inhibitors [53], suggesting that combinations with bortezomib should be explored. Finally, tyrosine kinase inhibitors also inhibit breast cancer resistance protein, which pumps topotecan out of cancer cells [54], suggesting that combinations with tyrosine kinase inhibitors may be particularly efficacious and worthy of future evaluation.

**Conclusions**

A growing body of data provides support for the use of topotecan as a viable option in treating lung cancer. Intravenous topotecan is currently indicated for the treatment of relapsed, sensitive SCLC. Recent studies demonstrate the potential utility of i.v. topotecan as first-line treatment of SCLC.

An oral topotecan formulation has been developed. The dose-limiting toxicity of single-agent oral topotecan is grade 4 neutropenia, which appears somewhat less frequently than with i.v. topotecan. Oral topotecan (alone or in combination) may be a viable option for patients with lung cancer who prefer oral treatment to i.v. therapy. Three recent phase III trials have demonstrated the activity of oral topotecan. In chemotherapy-naïve patients with ED-SCLC, oral topotecan plus cisplatin provided efficacy and safety that were similar to those of etoposide plus cisplatin. In patients with relapsed SCLC, treatment with oral topotecan showed a statistically significant and clinically meaningful longer overall survival duration than with BSC alone, a benefit maintained in subgroups of patients with either chemotherapy-resistant or chemotherapy-sensitive disease. In that same study, oral topotecan also improved quality of life over that seen with BSC alone in the study population. In previously treated patients with NSCLC, single-agent oral topotecan was shown to be noninferior in 1-year survival relative to the current standard of i.v. docetaxel based on a 10% noninferiority margin. In future studies, oral topotecan represents a good candidate for combination therapy with other i.v. or oral chemotherapy agents, monoclonal antibodies, proteosome inhibitors, and small molecule tyrosine kinase inhibitors.

**References**


38 Eckardt JR, von Pawel J, Pujol JL et al. Phase III study of oral compared