Update on the Role of Topotecan in the Treatment of Non-Small Cell Lung Cancer

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ABSTRACT
Non-small cell lung cancer (NSCLC) is an aggressive disease that is generally resistant to chemotherapy. As a result, the prognosis for patients with NSCLC is poor. Currently, platinum-based regimens are the standard of care for patients with advanced NSCLC. However, these regimens are associated with severe and often cumulative hematologic and non-hematologic toxicities, limiting dose intensity. Therefore, novel chemotherapeutic agents and combination regimens may improve the outcome for these patients. A variety of new agents and combinations have been investigated in the treatment of NSCLC. However, to date, no clearly superior single-agent or combination regimen has emerged. Topotecan (Hycamtin®; GlaxoSmithKline; Philadelphia, PA), a topoisomerase I inhibitor, is currently approved for the treatment of patients with relapsed small cell lung cancer (SCLC) and is associated with manageable, noncumulative, hematologic toxicities. In addition, topotecan demonstrates a favorable nonhematologic tolerability profile compared with agents currently used in the treatment of patients with NSCLC. The success of topotecan in patients with SCLC has made it an attractive option in the NSCLC setting. Topotecan-based combination regimens in the first-line treatment of NSCLC have demonstrated promising antitumor activities with favorable toxicity profiles. Many topotecan combination regimens have induced stable disease, a response that may offer meaningful clinical benefit in the palliative treatment of patients with advanced disease. Topotecan plus gemcitabine (Gemzar®; Eli Lilly and Company; Indianapolis, IN) and single-agent topotecan may be particularly appropriate for patients in the second-line setting, in which palliation of symptoms is an important outcome of chemotherapy. Herein, the future role of topotecan in the first- and second-line treatment of NSCLC and the potential role of resistance mechanisms obtained from in vivo dose-response studies in designing future combination regimens are discussed.
INTRODUCTION

The current American Society of Clinical Oncology guidelines for the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) recommend platinum-based chemotherapy [1, 2]. As single agents, both cisplatin (Platinol®; Bristol-Myers Squibb; Princeton, NJ) and carboplatin (Paraplatin®; Bristol-Myers Squibb) produce response rates of only ~10% [3]. To take advantage of potential synergistic activity, cisplatin and carboplatin have been combined with other chemotherapy agents in the hope of increasing tumor response. Cisplatin or carboplatin in combination with agents such as etoposide (Vepesid®; Bristol-Myers Squibb) and paclitaxel (Taxol®; Bristol-Myers Squibb) produce response rates of 12%-63% and median survival times of ~30-40 weeks [4-6]. In a large trial of 1,207 patients with advanced NSCLC treated with platinum-based combination therapy, the median survival time of all patients was 8.0 months, with 33% alive at 1 year [4]. In addition to the disappointing overall patient survival, current standard platinum-based regimens may cause nausea and vomiting, hematologic toxicities, hypersensitivity (for platinum-taxane combinations), and cumulative nephrotoxicity and neuropathy, which is severe and debilitating in some patients. Platinum-based regimens may be particularly poorly tolerated in elderly patients or patients with poorer performance statuses [4].

Because of the marginal response rates and poor tolerability of the standard platinum-based regimens, a number of other agents, including vinorelbine (Navelbine®; GlaxoSmithKline; Philadelphia, PA), docetaxel (Taxotere®; Aventis Pharmaceuticals Inc.; Bridgewater, NJ), gemcitabine (Gemzar®; Eli Lilly and Company; Indianapolis, IN), and irinotecan (Camptosar®; Pfizer Pharmaceuticals; New York, NY), have been investigated in the treatment of patients with NSCLC. Single-agent vinorelbine has demonstrated antitumor activity in the first-line treatment of advanced NSCLC, with overall response rates of 8%-37% [7-10]. In addition, vinorelbine in combination with cisplatin is associated with superior response and survival rates compared with cisplatin alone [11]. Vinorelbine in combination with docetaxel has also demonstrated antitumor activity, with response rates of 23%-51% [12, 13]. Gemcitabine in combination with cisplatin has been shown to be effective in the first-line treatment of patients with advanced NSCLC [2]. Finally, single-agent gemcitabine, docetaxel, and irinotecan, although associated with some antitumor activity, do not have established roles in the first-line setting [9, 13]. Unfortunately, despite the generally superior toxicity profiles and promising antitumor activities of these newer agents compared with the standard platinum-based regimens, no clearly superior single-agent or combination regimen has emerged [4, 6].

The continued poor outcome of patients with NSCLC indicates that the current recommended regimens are falling short. In addition, many of the chemotherapy agents used regularly to treat NSCLC are associated with severe nonhematologic toxicities that are often cumulative and nonreversible and impair quality of life in this essentially palliative setting. Therefore, agents with novel mechanisms of action and superior safety profiles need to be investigated in this patient population. Topotecan (Hycamtin®; GlaxoSmithKline), a topoisomerase I inhibitor, is currently approved for the treatment of relapsed small cell lung cancer (SCLC) and has recently shown activity in the NSCLC setting [14-16]. This review summarizes the recent findings on topotecan in the treatment of these patients and explores the potential role of topotecan in the treatment of patients with NSCLC.

TOPOTECAN IN THE TREATMENT OF NSCLC

Rationale for Topotecan

The recommended dose of topotecan is 1.5 mg/m² via a 30-minute i.v. infusion on days 1-5 of a 21-day cycle. In SCLC, topotecan is associated with overall response rates of approximately 10%-30% [17-20]. In chemotherapy-sensitive SCLC, topotecan was associated with an overall response rate of 24%, or 6% greater than the rate in patients treated with CAV chemotherapy (cyclophosphamide, doxorubicin [Adriamycin®; Bedford Laboratories; Bedford, OH], and vincristine [Oncovin®; Eli Lilly and Company]) [18]. An overall response rate of 24% has also been reported with topotecan in chemotherapy-resistant SCLC [20], although some other trials have reported lower response rates. Adverse events occurring during topotecan treatment for chemotherapy-resistant SCLC were predictable, manageable, and noncumulative. Myelosuppression was the primary adverse event, consisting of grade 4 neutropenia in 49% of patients, grade 4 anemia in 10% of patients, grade 4 thrombocytopenia in 44% of patients, and grade 4 febrile neutropenia in 15% of patients [20]. Prophylactic treatment with growth factors such as G-CSF may reduce the duration and severity of hematologic toxicities, permitting treatment of patients who otherwise could not receive chemotherapy because of comorbidities and/or a poor performance status. Nonhematologic toxicities associated with topotecan were mild to moderate in severity, noncumulative, and reversible. Given the established antitumor activity and favorable safety profile of topotecan in SCLC, topotecan has been studied in both the first- and second-line settings in patients with NSCLC.
Single-Agent Topotecan in First-Line Therapy of NSCLC

**i.v. Topotecan**

Studies of single-agent topotecan in the first-line treatment of NSCLC are summarized in Table 1 [21-25, 28]. In a study by Lynch et al. [21], patients with metastatic NSCLC received i.v. topotecan at a dose of 2.0 mg/m² on days 1-5 of a 21-day cycle. Two cycles were administered before response was evaluated. Enrollment was halted after 20 of a planned 30 patients were enrolled because no clinical responses were observed; however, 11 (55%) patients achieved stable disease (SD), and the median survival time of 30 weeks was comparable with that obtained with combinations of agents in similar patient populations [4]. Because therapy for patients with advanced lung cancer is primarily palliative, it has been argued that a high SD rate is a clinically meaningful response [26]. Indeed, the distinction between partial response (PR) and SD may not be useful [26], as the overall survival times are not different for patients with PRs and those with SD (Fig. 1) [27].

Grade 3/4 leukopenia, thrombocytopenia, and febrile neutropenia were reported in 19 (95%), three (15%), and three (15%) patients, respectively [21]. The high dose of topotecan (2.0 mg/m²) compared with the currently recommended dose (1.5 mg/m²) was likely a factor in the high incidence of hematologic toxicities. In a later phase II study [28], previously untreated NSCLC patients received i.v. topotecan at a dose of 1.5 mg/m² on days 1-5 of a 21-day cycle. Of 40 evaluable patients, six (15%) achieved PRs for durations of 8-61 weeks, and 10 (25%) achieved SD. The overall median survival time was 38 weeks, and 30% of patients were still alive at 1 year.

Alternative topotecan dosing schedules have also been explored in previously untreated NSCLC patients. In a phase II study, Weitz et al. [22] compared the standard i.v. topotecan dosing regimen with a 1.3-mg/m²/day dose of topotecan administered by continuous i.v. infusion (CIV) over 72 hours, every 4 weeks. An overall response rate of 11% was reported for the standard regimen and a 5% response rate was reported for the CIV regimen. In patients receiving standard topotecan dosing, grade 3/4 leukopenia and thrombocytopenia occurred in 60% and 16%, respectively; in patients receiving CIV dosing, these toxicities

### Table 1. Clinical trials of single-agent topotecan in first-line NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Dose and schedule</th>
<th>Overall response (%)</th>
<th>Stable disease (%)</th>
<th>Median survival (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch et al. 1994</td>
<td>20</td>
<td>i.v. topotecan, 2.0 mg/m² on days 1-5</td>
<td>0</td>
<td>55</td>
<td>30</td>
</tr>
<tr>
<td>of a 21-day cycle</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Perez-Soler et al.</td>
<td>40</td>
<td>i.v. topotecan, 1.5 mg/m² on days 1-5</td>
<td>15</td>
<td>25</td>
<td>38</td>
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<tr>
<td>1996</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>of a 21-day cycle</td>
<td></td>
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</tr>
<tr>
<td>Weitz et al. 2000</td>
<td>38</td>
<td>i.v. topotecan, 1.5 mg/m² on days 1-5</td>
<td>11</td>
<td>NR</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>CIV topotecan, 1.3 mg/m²/day over</td>
<td>5</td>
<td>NR</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>72 hours, every 4 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mainwaring et al.</td>
<td>25</td>
<td>CIV topotecan, 0.5 or 0.6 mg/m²/day</td>
<td>8</td>
<td>NR</td>
<td>41</td>
</tr>
<tr>
<td>1997</td>
<td></td>
<td>for 21 days, every 28 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kindler et al. 1998</td>
<td>26</td>
<td>CIV topotecan, 0.5 or 0.6 mg/m²/day</td>
<td>4</td>
<td>23</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for 21 days, every 28 days</td>
<td></td>
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<tr>
<td>White et al. 1999</td>
<td>30</td>
<td>Oral topotecan, 2.3 mg/m²/day on days 1-5</td>
<td>11</td>
<td>37</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>of a 21-day cycle</td>
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</tbody>
</table>

Abbreviation: NR = not reported.

*Minor response.

**Figure 1.** Kaplan-Meier curves showing similar overall survival rates for NSCLC patients with PRs and those with SD. Abbreviation: PD = progressive disease. Adapted from Johnson [27].
occurred in 43% and 38%, respectively. CIV infusion (although at a lower dose) was also studied by Mainwaring et al. [23] and Kindler et al. [24]. Topotecan was administered via a CIV infusion at a dose of 0.5 or 0.6 mg/m²/day for 21 days every 28 days, and response rates of 4%-8% were reported [23, 24]. Kindler et al. [24] also reported SD in an additional 23% of patients, and 23 of 58 (40%) symptoms recorded in the 52 patients at baseline had resolved by the end of best response.

**Oral Topotecan**

In a phase II study, patients received oral topotecan (2.3 mg/m²/day) on days 1-5 of a 21-day cycle, with dose modification after cycle 1 dependent on tolerability [25]. Oral topotecan may be better tolerated and more convenient for some patients than bolus i.v. injection. Dose escalation to 2.7 mg/m²/day was possible in 83% of patients. Minor responses occurred in 3 of 27 (11%) evaluable patients, and 10 (37%) patients had SD. The median survival time was 41 weeks and was comparable with that of other agents used in NSCLC. Oral topotecan was well tolerated: 14 (52%) patients experienced grade 3/4 neutropenia, four (15%) experienced grade 3/4 anemia, and one (4%) experienced grade 3 thrombocytopenia. Oral topotecan provided clinically significant symptom palliation and a tolerability profile that warrants further study in NSCLC patients who require palliative therapy. Additionally, the convenience of oral topotecan makes it an appropriate option for combination therapy, especially with agents that have nonoverlapping toxicities.

**Topotecan-Based Combination First-Line Therapies**

Topotecan has also been studied in first-line NSCLC treatment in combination with other agents including platinum agents, vinorelbine, gemcitabine, etoposide, and taxanes. Recent studies of topotecan-based combination therapies are summarized in Table 2 [14-16, 29-33].

**Topotecan Plus Platinum**

Platinum compounds were among the first agents to be studied in combination with topotecan. Raymond et al. [29] conducted a phase I study in which topotecan dose escalation was studied in combination with a fixed dose of cisplatin. Fifteen patients were enrolled; 14 were evaluable for toxicity analyses. Topotecan was administered at an initial dose of 0.75 mg/m² (30-minute i.v. infusion) on days 1-5 of a 21-day cycle along with a single dose of cisplatin (75 mg/m²)

### Table 2. Clinical trials of topotecan combinations in first-line NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Dose and schedule</th>
<th>Overall response (%)</th>
<th>Stable disease (%)</th>
<th>Median survival (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raymond et al. 1997</td>
<td>15</td>
<td>i.v. topotecan, 0.75 mg/m² on days 1-5 of a 21-day cycle; cisplatin, 75 mg/m², single dose on day 1</td>
<td>31</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pujol et al. 2001</td>
<td>47</td>
<td>i.v. topotecan, 0.5 mg/m² on days 1-5 of a 21-day cycle; carboplatin AUC 5 mg/ml/min on day 1 of each cycle</td>
<td>13</td>
<td>36</td>
<td>&gt;33</td>
</tr>
<tr>
<td>Stupp et al. 2001</td>
<td>42</td>
<td>i.v. topotecan, 0.5-1.0 mg/m² on days 1-5 of a 21-day cycle; vinorelbine, 20-30 mg/m² on days 1 and 5</td>
<td>42</td>
<td>NR</td>
<td>56</td>
</tr>
<tr>
<td>Joppert et al. 2003</td>
<td>53</td>
<td>i.v. topotecan, 1.0 mg/m² on days 1-5 of a 28-day cycle; i.v. gemcitabine, 1,000 mg/m² on days 1 and 15</td>
<td>17</td>
<td>23</td>
<td>30</td>
</tr>
<tr>
<td>Guarino et al. 2002</td>
<td>30</td>
<td>i.v. topotecan, 0.5-2.0 mg/m², cisplatin, 20 mg/m², and gemcitabine, 1,000 mg/m², on days 1, 8, and 15 of each 28-day cycle</td>
<td>38</td>
<td>NR</td>
<td>38</td>
</tr>
<tr>
<td>Dowlati et al. 2001</td>
<td>19</td>
<td>Topotecan, 0.85 mg/m²/day as a 72-hour CIV infusion on days 1-3, and oral etoposide, 100 mg BID on days 7-9 of a 21-day cycle</td>
<td>5</td>
<td>11</td>
<td>NR</td>
</tr>
<tr>
<td>Dobbs et al. 2000</td>
<td>18</td>
<td>Oral topotecan, 1.0-1.5 mg/m² on days 1-5 of a 21-day cycle; i.v. paclitaxel, 175 mg/m² over 3 hours on day 1</td>
<td>28</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Eckardt et al. 2001</td>
<td>53</td>
<td>Oral topotecan, 1.0-1.5 mg/m² on days 1-5 of a 21-day cycle; i.v. paclitaxel, 175 mg/m² over 3 hours on day 1</td>
<td>12</td>
<td>27</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviation: NR = not reported.
on day 1. All 11 patients treated at this dose level of topotecan experienced at least one episode of grade 4 neutropenia; in six of those patients, the absolute neutrophil count was <50 × 10^9/l for >5 days, and two of those patients also experienced grade 4 thrombocytopenia. At the next topotecan dose level (1.0 mg/m^2), grade 4 neutropenia for >5 days occurred in all three evaluable patients, and one of those patients died from subsequent neutropenic sepsis. Although four of the 13 (31%) patients who completed the study achieved PRs, the duration of response was short, and the toxicity profile suggested synergistic toxicity at even the lowest dose levels.

Carboplatin displays a more manageable toxicity profile than cisplatin [4], with substantially less nephrotoxicity, neurotoxicity, and ototoxicity. Thus, topotecan has also been investigated in combination with carboplatin. In a phase II study, Pujol et al. [16] enrolled 47 patients with unresectable stage III or IV NSCLC. Patients received i.v. topotecan (0.5 mg/m^2) on days 1-5 of a 21-day cycle plus carboplatin on day 1 of each cycle at an estimated area under the concentration-time curve (AUC) of 5 mg/ml/minute. Carboplatin was administered 3 hours after the end of the topotecan infusion. Preliminary response data included a 13% overall response rate, and an additional 36% of patients had prolonged SD. The median survival time was >33 weeks, and 32% of patients were alive at 1 year. Grade 3/4 neutropenia and thrombocytopenia occurred in 53% and 58% of patients, respectively, and were not cumulative. Sepsis was documented in only one course. Toxicities were manageable; G-CSF, platelet transfusions, and RBC transfusions were administered in 4%, 4%, and 13% of courses, respectively. Nonhematologic toxicities were generally mild to moderate in severity. Overall, the manageable and noncumulative toxicities of the regimen and the encouraging preliminary response and SD rates suggest that further study is warranted.

**Topotecan Plus Gemcitabine**

A phase II study of topotecan in combination with gemcitabine was conducted in patients with previously untreated advanced NSCLC. Joppert et al. [31] administered topotecan (1.0 mg/m^2) on days 1-5 of a 28-day cycle plus gemcitabine (1,000 mg/m^2) on days 1 and 15, both drugs by a 30-minute i.v. infusion, with treatment continuing until progression or unacceptable toxicity. Of 47 evaluable patients, eight (17%) achieved PRs and 11 (23%) achieved SD; the 1-year survival rate was 39% and the median survival time was 30 weeks (range <4-78 weeks). Grade 3/4 hematologic toxicities included neutropenia (53%), anemia (18%), thrombocytopenia (12%), and febrile neutropenia (6%). Topotecan plus gemcitabine appeared to be better tolerated than topotecan in combination with platinum; however, this combination also exhibited lower antitumor activity than the platinum-based topotecan regimen.

In a single-center, dose-escalation phase II trial, Guarino et al. [30] administered a triplet regimen of i.v. topotecan (0.5-2.0 mg/m^2), cisplatin (20 mg/m^2), and gemcitabine (1,000 mg/m^2) on days 1, 8, and 15 of a 28-day cycle to patients with stage IIIB/IV NSCLC. Because of dose-limiting thrombocytopenia at week 3, gemcitabine was administered only on days 1 and 15 in subsequent cycles. Eleven of 29 (38%) evaluable patients had PRs; the median survival time was 38 weeks (range 4-110 weeks), and the 1-year survival rate was 33%, with two patients still alive at 108+ to 110+ weeks of follow-up. The triplet was generally well tolerated; there were no reports of grade 4 neutropenia or febrile neutropenia and only one case of grade 4 leukopenia. Although topotecan dose escalation proceeded to the 2.0-mg/m^2 target, the authors recommended the 1.75-mg/m^2 dose for further evaluation. The low toxicity and comparable or better response with topotecan/cisplatin/gemcitabine relative to many other NSCLC treatment regimens suggest that this triplet regimen should be investigated further. Guarino et al. [30] recommended including quality-of-life end points in phase II studies of this triplet regimen to determine whether the prolonged survival observed was also associated with symptom palliation.
Topotecan Plus Etoposide

Inhibition of topoisomerase I often leads to increases in topoisomerase II levels and may increase the susceptibility of tumor cells to topoisomerase II inhibitors such as etoposide. In vitro and preclinical studies have shown schedule-dependent synergy between topotecan and etoposide [34]. A phase II study examined the efficacy and safety of this combination in patients with advanced NSCLC [32]. Topotecan was administered at a dose of 0.85 mg/m²/day as a 72-hour CIV infusion on days 1-3, and oral etoposide, 100 mg twice daily (BID), was administered on days 7-9 of a 21-day cycle. One (5%) patient had a PR and two (11%) experienced SD. The 1-year survival rate was 33%. Hematologic toxicities included grade 4 neutropenia in 7% of courses. The authors noted that the lack of efficacy in their study may have been related to the short-lived (<24 hours) effect of topoisomerase II elevation after topoisomerase I inhibition; thus, it may be necessary to administer etoposide much earlier in a combined regimen with topotecan [32].

Topotecan Plus Paclitaxel

Oral topotecan has also been investigated in combination with paclitaxel in the first-line setting. In a phase I/II trial, oral topotecan plus i.v. paclitaxel was administered to chemotherapy-naïve patients with stage III/IV NSCLC [33]. To establish the maximum tolerated dose (MTD) for topotecan in combination with paclitaxel, 18 patients were enrolled in the phase I portion of the trial. Oral topotecan was administered at a starting dose of 1.0 mg/m² on days 1-5 of a 21-day cycle and escalated by 0.25 mg/m² in subsequent cohorts if tolerability permitted. Paclitaxel (175 mg/m²) was administered on day 1 of each cycle. Hematologic toxicities included grade 3/4 neutropenia in 61% of patients, grade 3 anemia in 6% of patients, and no grade 3/4 thrombocytopenia. One (6%) patient experienced a DLT of febrile neutropenia in cohort 3 (one febrile neutropenia, one fatal neutropenic sepsis). The MTD of 1.25 mg/m² was recommended for the ongoing phase II portion of the study. Combined response data for all cohorts included one (6%) complete response, three (17%) PRs, and one (6%) unconfirmed PR.

Similar results were also reported in another phase I/II trial of oral topotecan plus i.v. paclitaxel [14]. Eighteen patients were enrolled in the phase I portion of that study. Although one episode of febrile neutropenia was reported with the 1.0-mg/m² topotecan dose, no DLTs were reported with the 1.25-mg/m² topotecan dose; one episode of febrile neutropenia and one death from neutropenic sepsis were reported with the 1.5-mg/m² topotecan dose. Similar to the previous trial [33], the MTD of topotecan was defined as 1.25 mg/m². A total of 41 patients (six in phase I, 35 in phase II) received 147 cycles at the MTD. Pooled phase I and II incidences of grade 3/4 neutropenia and anemia were 68% and 18%, respectively. Nonhematologic toxicities were mild to moderate and self-limiting. Preliminary responses from both portions of the study include 12% of patients with PRs and 27% with SD.

Topotecan Second-Line Therapies

For the second-line therapy of NSCLC, the emphasis is on palliation of symptoms and maintenance of quality of life. With its favorable nonhematologic toxicity profile, topotecan may be an appropriate agent in the palliative setting. Recent studies of topotecan in combination with other agents in this patient population are summarized in Table 3 [35-37].

Gemcitabine also has a superior nonhematologic toxicity profile compared with platinum-based regimens. Therefore, the combination of topotecan plus gemcitabine may be feasible for patients with previously treated NSCLC. Rinaldi et al. [35, 36] have reported results from phase I and phase II trials investigating topotecan plus gemcitabine. The first phase I/II trial established the MTD for topotecan as

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Dose and schedule</th>
<th>Overall response (%)</th>
<th>Stable disease (%)</th>
<th>Median survival (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rinaldi et al. 2001 [35]</td>
<td>19</td>
<td>i.v. topotecan, 0.75 mg/m² on days 1-5 of a 21-day cycle; i.v. gemcitabine, 400 mg/m² on days 1 and 5</td>
<td>18*</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>Rinaldi et al. 2002 [36]</td>
<td>35</td>
<td>i.v. topotecan, 0.75 mg/m² on days 1-5 of a 21-day cycle; i.v. gemcitabine, 400 mg/m² on days 1 and 5</td>
<td>11</td>
<td>23</td>
<td>28</td>
</tr>
<tr>
<td>Larocca et al. 2003 [37]</td>
<td>24</td>
<td>i.v. topotecan, 2.0-2.75 mg/m², followed by i.v. gemcitabine, 800-2,000 mg/m², on days 1 and 15 of a 28-day cycle</td>
<td>4</td>
<td>17</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Of 17 patients with measurable disease.
0.75 mg/m² and for gemcitabine as 400 mg/m² when topotecan was administered on days 1-5 and gemcitabine was administered on days 1 and 5 of a 21-day cycle [35]. Of 19 patients treated, 3 of 17 (18%) with measurable disease achieved PRs and 6 of 19 (32%) achieved SD. A second trial using the MTD doses and schedule for this combination regimen reported PRs in 4 of 35 (11%) patients and SD in 8 (23%) patients [36]. Particularly interesting was that 3 of 17 (18%) patients with refractory disease (progression during first-line treatment) had responses, with 18% having SD for four or more courses. Grade 4 neutropenia and thrombocytopenia were observed in 14% and 9% of patients, respectively. Grade 3 fatigue was reported in one (3%) patient and grade 2 nonhematologic toxicities were reported in eight (23%) patients. Although the nonhematologic toxicities were generally mild to moderate in severity, such adverse effects may be of greater concern in the second-line setting because of the emphasis on quality of life.

A third study of topotecan in combination with gemcitabine enrolled both SCLC and NSCLC patients [37]. Patients naïve to topotecan and gemcitabine and refractory to at least one chemotherapy regimen were treated with i.v. topotecan (2.0-2.75 mg/m²) followed by i.v. gemcitabine (800-2,000 mg/m²) on days 1 and 15 of a 28-day cycle. Grade 3/4 neutropenia was reported in 11 of 35 (31%) patients, and grade 3 thrombocytopenia was reported in one (3%) patient. There was a low incidence of severe nonhematologic toxicities: grade 3 nausea and vomiting in one (3%) patient and grade 3 oral mucositis in one (3%) patient. One of 24 (4%) patients had a PR (NSCLC patient) and four (17%) patients had SD. The MTD has not been reached and further dose escalation is in progress.

A number of ongoing studies are evaluating various dosing and administration schedules and novel combinations of topotecan with other agents for second-line therapy of NSCLC. These studies include: a randomized, phase III study of oral topotecan versus docetaxel; a phase I study of weekly topotecan in combination with weekly docetaxel [38], which has led to a phase III study of weekly topotecan plus weekly docetaxel; a phase I study of weekly topotecan with docetaxel every 3 weeks; and a phase III study of docetaxel with or without topotecan. The results of these trials are pending.

**FUTURE ROLE OF TOPOTECAN IN NSCLC**

Topotecan has displayed encouraging utility in the treatment of NSCLC, a disease well known for its resistance to chemotherapy. Incremental increases in responses, survival, and quality of life are considered advances in the treatment of this difficult disease. Although overall response rates with single-agent topotecan have been relatively low in some studies, SD rates, when reported, are frequently high. Because NSCLC is a disease for which—given the current treatment state of the art—cure is not possible for patients with advanced disease, delays in disease progression are desirable, especially if nonhematologic toxicities are mild and hematologic toxicities are manageable and noncumulative. In patients with advanced disease, SD may be a meaningful clinical response; therefore, single-agent topotecan may be particularly appropriate in the second-line setting.

Topotecan in combination with a number of established and novel antitumor agents has demonstrated superior antitumor activity compared with single-agent topotecan and allows for the reduction of the dose intensity of other agents, and thereby the potential for the nonhematologic toxicities associated with these agents. Some of the more encouraging responses have been obtained when topotecan was combined with etoposide, a high degree of schedule dependency was indicated and antitumor activity was less promising at the doses and schedules studied. In addition, toxicities were problematic when topotecan was combined with platinum or taxanes. The ideal regimen combining topotecan and other agents has yet to be defined.

The future of NSCLC treatment—indeed, the future of treatment for many malignancies—may well be defined by a more rational approach that accounts for tumor biology and resistance mechanisms. A better understanding of tumor resistance mechanisms may assist in optimizing the dose and schedule of chemotherapy agents used in lung cancer therapy. We hypothesized that the shape of dose-response curve (log percent cell survival versus dose) might reflect the major mechanisms of resistance that limit efficacy of a chemotherapy agent in a particular tumor type (Fig. 2) [39]. We proposed that resistance that was due to excess of a factor (e.g., P-glycoprotein or glutathione) would arise from gene amplification or overexpression and would be reflected as a shoulder on the dose-response curve (Fig. 2E). This would be analogous to competitive inhibition of drug effect and might be amenable to therapy with high-dose chemotherapy or with resistance-modulating agents to increase therapeutic efficacy. "Nonsaturable passive resistance" would arise from gene mutation or factor alteration and would be reflected as a less steep slope on the dose-response curve (Fig. 2C), analogous to what one would see with decreased affinity of a drug for a receptor or target. "Saturable passive resistance" would arise from gene downregulation or deletions and would be due to a deficiency or saturation of a factor. It would be analogous to noncompetitive inhibition of drug effect and, graphically, this would appear as a flat dose-response curve or one with a steep initial curve followed by a plateau (Fig. 2D). Therefore, it may be predicted that high-dose chemotherapy or therapy with resistance-modulating agents would not be effective.
against saturable passive resistance. In the future, in vivo studies could be designed in an attempt to define these dose-response relationships and identify resistance mechanisms in patients with NSCLC and other malignancies. The data derived from such studies could yield important information on resistance mechanisms present in various tumor types and could be used to select agents, doses, and schedules to maximize the therapeutic index.

**SUMMARY**

Combination regimens with topotecan for the first-line treatment of NSCLC may be appropriate for patients who cannot tolerate standard platinum-based first-line treatments because of the associated nonhematologic and hematologic toxicities. In combination with a number of other agents, topotecan has demonstrated response rates equivalent to those of standard therapy, with manageable, noncumulative, hematologic toxicities and a favorable nonhematologic toxicity profile. Many trials of topotecan have also demonstrated high SD rates, which may be seen as a meaningful clinical benefit in patients with advanced NSCLC. Additionally, non-hematologic toxicities, which often have a disproportionate effect on patient quality of life and willingness to continue treatment, are usually mild and manageable with topotecan therapy. Topotecan has also demonstrated activity comparable with that of other agents in the second-line treatment of patients with NSCLC.

Topotecan in combination with investigational agents that have different mechanisms of action and nonoverlapping toxicities may have synergistic antitumor activities and may be therapeutic options for the future in this patient population. Dose-response characteristics and knowledge of resistance mechanisms may help to define the optimum dose and schedule of topotecan in combination with other agents.

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**REFERENCES**


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**ADDITIONAL READING**

