Topotecan Continuous Infusion: CA-125 Responses Including Patients Pretreated with Other Schedules of Topotecan

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The article entitled “Hematologic Safety and Tolerability of Topotecan in Recurrent Ovarian Cancer and Small Cell Lung Cancer: An Integrated Analysis” by Armstrong et al. in the October 2005 issue of The Oncologist [1] summarizes the data from eight phase II and phase III clinical studies of topotecan (Hycamtin®; GlaxoSmithKline, Philadelphia) given to 879 patients that had stage III/IV ovarian cancer or extensive small cell lung cancer. This analysis supported the use of topotecan at 1.5 mg/m² per day on days 1–5, every 3 weeks, and concluded that the “results suggest that topotecan may be safely administered for multiple courses” with the primary major side effect being myelosuppression, which was noncumulative.

In the same issue, Markman [2] commented that the extreme fatigue of the daily dosing regimen at 1.5 mg/m² per day cannot be overlooked and suggested that lower doses (1–1.25 mg/m² per day) may help improve the side-effect profile. Safra et al. [3] have recently provided evidence for favorable response rates and median time on study with weekly topotecan. We would like to call attention to the tolerance and efficacy of topotecan by continuous infusion at 0.4 mg/m² per day for 14–21 days every 4 weeks in heavily pretreated patients with ovarian cancer.

Phase I/pharmacologic and phase II studies of protracted infusion schedules of topotecan as a single agent or in combination with other agents, such as cisplatin, pegylated liposomal doxorubicin, or oxaliplatin [4–9], by our group have already been published. Moreover, we have documented the ability to combine a full 14-day infusion with cisplatin in a highly active first-line regimen [6].

Finally, we have shown that the 14-day schedule of topotecan with oxaliplatin is less toxic and is active in the pretreated setting [9].

The preclinical background for protracted-infusion schedules was provided by Peter Houghton and coworkers [10, 11]. The logistics of such schedules have improved by the availability of more “user-friendly” 7-day Baxter infusers (rather than battery-run pumps) and by the use of long-acting and effective antiemetics in the HT3 family and aprepitant. Our recent clinical experience with protracted-infusion topotecan in patients with recurrent ovarian or primary peritoneal cancer, after failing multiple agents including other schedules of topotecan, may therefore be of interest.

Ten platinum-resistant patients with epithelial ovarian cancer and a median age of 60 years (Table 1) recently received topotecan after disease progression on several prior regimens. Six women had received topotecan administered via different schedules (weekly i.v., daily i.v. × 5 days, and oral), while the other four had been exposed to a median of two nonplatinum agents after induction. All received topotecan as a single agent in a 14-day schedule every 28 days at a dose of 0.4 mg/m² per day, with subsequent schedule adjustments for subjective intolerance (fatigue, nausea) or myelosuppression. Grade 3 and 4 toxicities of this infusion regimen in the 10 patients included grade 3 thrombocytopenia in three patients and grade 3 neutropenia in three patients (two of whom also had grade 3 platelet toxicity), all without complications. Red cell transfusions were required every other cycle by three patients, five patients experienced grade 2 fatigue, and subtotal alopecia was also commonly noted. One of the longest responders, patient 1, had failed...
Table 1. Patient characteristics and outcome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Prior chemotherapy; topotecan (reason for change)</th>
<th>Topotecan (protracted infusion) No. of cycles</th>
<th>CA-125 response: baseline→ nadir</th>
<th>Subsequent course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>Carboplatin/paclitaxel; i.p. floxuridine; i.p. cisplatin/carboplatin; Pegylated liposomal doxorubicin; Gemcitabine/carboplatin; Topotecan weekly × 3 doses (CA-125 increase); Docetaxel; Vinorelbine; Ifosfamide</td>
<td>14+</td>
<td>1098→97&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Added erlotinib at cycle 14 for CA-125 increase only; CA-125 in the 300 range over the last three cycles</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>Carboplatin/paclitaxel; Carboplatin/gemcitabine; Gemcitabine; Pegylated liposomal doxorubicin; Topotecan weekly × 12</td>
<td>6</td>
<td>5,445→3,663</td>
<td>CT scan progression prompted change to bevacizumab</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>Carboplatin/paclitaxel; Pegylated liposomal doxorubicin/gemcitabine; Gemcitabine; Carboplatin; Paclitaxel weekly; Topotecan daily × 5 doses (progression on CT scan)</td>
<td>2 cycles as single agent, 1 cycle with oxaliplatin</td>
<td>61→105</td>
<td>Progressive disease—small bowel obstruction</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>Carboplatin/paclitaxel; Carboplatin/docetaxel; Pegylated liposomal doxorubicin; Topotecan weekly × 3 doses (CA-125 increase)</td>
<td>2 cycles as single agent, 1 cycle with pegylated liposomal doxorubicin</td>
<td>1236→165&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Added pegylated liposomal doxorubicin for persistent ascites, but no response and progression afterward</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>Topotecan oral plus cisplatin × 1 cycle (GI intolerance); Carboplatin/paclitaxel; i.p. cisplatin/floxuridine; Carboplatin/pegylated liposomal doxorubicin; Pegylated liposomal doxorubicin/oxaliplatin; Gemcitabine</td>
<td>3</td>
<td>47→48.9</td>
<td>Progression in liver; now on retrial of oxaliplatin/pegylated liposomal doxorubicin</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>Carboplatin/paclitaxel; Pegylated liposomal doxorubicin; Topotecan weekly × 8 doses (CA-125 increase); Gemcitabine</td>
<td>3</td>
<td>350→289</td>
<td>Disease progression; now on oxaliplatin/pegylated liposomal doxorubicin</td>
</tr>
<tr>
<td>7</td>
<td>82</td>
<td>Carboplatin/paclitaxel; Carboplatin/docetaxel</td>
<td>16</td>
<td>165→27&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Complete response—off treatment</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>Carboplatin/paclitaxel; Docetaxel; Carboplatin/pegylated liposomal doxorubicin; Pegylated liposomal doxorubicin</td>
<td>9 (initial 2 cycles given with pegylated liposomal doxorubicin, which was discontinued because of hematologic toxicity)</td>
<td>636→113&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Rising CA-125 and progressive disease on PET/CT scan; oxaliplatin started</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>i.p. cisplatin/floxuridine; Carboplatin/paclitaxel; Gemcitabine/cisplatin</td>
<td>4+</td>
<td>120→18.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Continuing on current regimen</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>Carboplatin/paclitaxel; Gemcitabine/pegylated liposomal doxorubicin; Methotrexate/mitomycin; Carboplatin/pegylated liposomal doxorubicin; Gemcitabine</td>
<td>3+</td>
<td>61.2→29.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Continuing on topotecan infusion for 9 days every 4 weeks</td>
</tr>
</tbody>
</table>

<sup>a</sup>Satisfies definition of CA-125 partial response [15].

Abbreviations: CT, computed tomography; GI, gastrointestinal; IP, intraperitoneal; PET, positron emission tomography.
multiple agents, including carboplatin, pegylated liposomal doxorubicin, gemcitabine, and weekly topotecan, after recurring from her initial induction; she had a gradual decline in CA-125 to a nadir of <10% from the original value, relief of pelvic symptoms, and improved findings on imaging (short of a partial response by Response Evaluation Criteria in Solid Tumors criteria).

From this experience, we conclude that the 14-day protracted infusion of topotecan is active, even after multiple courses of chemotherapy, with noncumulative and predictable toxicity. Intriguing is the possibility that this schedule might be more effective than intermittent schedules in the presence of resistance mechanisms mediated by the ABCG2 (BCRP) transporter [12]. Negative views on protracted infusion schedules [13] might be reassessed in light of our experience [14].

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DISCLOSURES

The authors indicate no potential conflicts of interest.

REFERENCES


IN REPLY

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I appreciate the letter and information from Dr. Muggia [1]. As he notes, their group has a long history studying the use of topotecan as a continuous infusion in the treatment of ovarian cancer. In the past, the requirement for cumbersome infusion devices made this a less appealing approach. However, as indicated, advances in biotechnology allow for easier infusion using this approach, which continues to be under investigation. Of note, an oral formulation of topotecan is currently under investigation [2, 3]. It is hypothesized that continuous oral dosing of topotecan may have similar pharmacokinetics to and possibly the beneficial antitumor effects of continuous infusion i.v. topotecan. This remains an active area of investigation.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The author indicates no potential conflicts of interest.

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2. Rose PG, Markman M, Bell JG et al. Sequential prolonged oral topotecan and prolonged oral etoposide as second-line therapy in ovarian or peritoneal carcinoma: a phase I Gynecologic Oncology Group study. Gynecol Oncol 2006 Jan 10; [Epub ahead of print].

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IN REPLY

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In their letter, Muggia et al. [1] describe their experience with a “protracted continuous i.v. infusion schedule” of topotecan in the management of ovarian cancer. The authors suggest this may be an alternative strategy to either the U.S. Food and Drug Administration-approved regimen of 1.5 mg/m² per day for 5 days, or a lower dose of 1.0–1.25 mg/m² per day for 5 days, or a “weekly” topotecan treatment program.

While the information presented in this letter and in previous publications is certainly of interest, it is important to note the absence of data from phase III randomized trials demonstrating either the superior efficacy of this approach or even a reduction in toxicity compared with other strategies. Further, even the provocative data presented in this letter regarding the biological activity of the drug in previously heavily pretreated patients does not provide evidence that other, possibly far simpler, management programs might not have produced equivalent effects.

Exploration of novel methods of drug delivery should be strongly encouraged, for it is possible the clinical utility of specific anticancer drugs can be substantially improved through such efforts (e.g., the demonstrated superior impact of i.p. cisplatin in ovarian cancer). However, ultimately, the genuine benefits of such strategies must be documented in prospective randomized trials, especially when they are associated with the time, effort, cost, and toxicity of prolonged continuous infusional topotecan.

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