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Alternate Dosing Schedules for Topotecan in the Treatment of Recurrent Ovarian Cancer

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Key Words. Infusion · Intravenous · Ovarian neoplasms · Recurrence · Topotecan

ABSTRACT

Topotecan has demonstrated efficacy in the treatment of both platinum-sensitive and platinum-resistant recurrent ovarian cancer. However, the optimal dosing for topotecan has not been established. The standard dosing regimen is 1.5 mg/m²/day on days 1-5 of a 21-day cycle, with response rates ranging from 13%-33%. Although the resulting hematologic toxicities are reversible and noncumulative, this schedule is associated with significant myelosuppression. Ongoing clinical phase I and II trials have evaluated alternative dosing schedules such as the 21-day 24-hour continuous intravenous (c.i.v.), the 3-day i.v. bolus, the weekly 72-hour c.i.v., the weekly 24-hour c.i.v., and the weekly bolus i.v. regimens. Prolonged exposure to topotecan has been shown to increase the efficacy of topotecan, whereas shorter regimens decrease exposure to the drug and therefore decrease toxicity. Preliminary studies investigating the weekly bolus i.v. regimen have demonstrated response rates comparable with those achieved with the standard dosing regimen, with a lower frequency of severe toxicity. Although randomized, controlled comparative trials are necessary to determine relative efficacy, results from studies utilizing other alternative regimens are less encouraging, especially for lower-risk patients with platinum-sensitive ovarian cancer who are likely to tolerate higher doses of topotecan. Optimizing the dosing regimen will also increase the quality of life for the patient through increased efficacy, decreased toxicity, and increased convenience of administration. Continued investigation of the weekly i.v. bolus is needed to fully elucidate the contribution of this regimen to the current armamentarium used in the treatment of patients with relapsed ovarian cancer.

INTRODUCTION

Topotecan, a semisynthetic, water-soluble derivative of camptothecin, is an inhibitor of topoisomerase I [1]. This derivative is more stable and has decreased toxicity compared with its parent compound [2-4]. Topoisomerase I is a nuclear enzyme that relieves torsional strain on supercoiled DNA by causing single-stranded breaks during replication. Topotecan forms a stable complex with topoisomerase I and...
prevents the religation of the cleaved DNA. This lack of religation leads to double-stranded DNA breaks during replication and eventually results in apoptosis. Topotecan is currently approved for the treatment of metastatic ovarian cancer.

Data from phase II trials showed that topotecan has efficacy in both platinum-sensitive and platinum-resistant ovarian cancer [5-11]. Based on these studies, a 30-minute i.v. infusion of 1.5 mg/m²/day on days 1-5 of a 21-day cycle, for a minimum of 4 cycles was established as the standard dosing schedule for topotecan administration. With this standard dosing regimen, response rates to topotecan in patients with platinum-sensitive recurrent ovarian cancer range from 19%-33%, whereas response rates in patients with platinum-resistant ovarian cancer range from 12%-18% (see Herzog et al, pp 3-10, for a review of the role and response of topotecan in recurrent ovarian cancer [12]). The standard schedule of topotecan administration is generally well tolerated, although tolerability is reduced in patients who have been heavily pretreated or have diminished creatinine clearance. Myelosuppression is the dose-limiting toxicity (DLT), with grade 3/4 neutropenia occurring in 40%-90% of patients and grade 3/4 thrombocytopenia occurring in 30%-60% of patients. However, these hematologic toxicities are of short duration and are noncumulative. Nonhematologic toxicities including fatigue and gastrointestinal toxicities are generally mild and not dose limiting (see Dunton et al, pp 11-19 [13]).

Although the success of the current standard dosing regimen of topotecan is well documented, there remains considerable interest in optimizing the topotecan dosing schedule. Studies show that a response to topotecan treatment may be related to the frequency and duration of exposure to the drug [14, 15]. Further, there is a continued desire to reduce the levels of myelosuppression. Alternative schedules may provide higher tumor response rates and diminished myelosuppression compared with the standard dosing schedule. In addition, an optimal dosing schedule may improve the patient’s quality of life by providing more convenience. An alternate schedule may also provide flexibility for integration of topotecan into novel combination regimens. This review will discuss the efficacy and tolerability of several alternative dosing schedules that have been investigated. These alternative dosing schedules include a 21-day 24-hour continuous i.v. (c.i.v.), a 3-day i.v. bolus, a weekly 72-hour c.i.v., a weekly 24-hour c.i.v., and a weekly i.v. bolus regimen.

**TOPOTECAN ALTERNATE DOSING SCHEDULES**

**21-Day c.i.v. Topotecan**

Drugs with S-phase specificity often have a threshold exposure period required for cytotoxicity. Therefore, frequent or prolonged dosing regimens are often favored for S-phase-specific drugs over less frequent or shorter dosing regimens. Because topotecan targets topoisomerase I activity during the S-phase of the cell cycle, topotecan cytotoxicity was thought to be S-phase specific and schedule dependent. In a preclinical study, continuous topotecan was effective in inhibiting tumor colony formation by explanted tumor specimens [14]. A prolonged exposure to topotecan is likely to increase the probability of exposing cells in the S-phase of the cell cycle, which would likely increase the number of cells that would undergo apoptosis. Therefore, prolonged topotecan exposure has the potential for improving the antitumor activity of this agent.

A 21-day, 24-hour c.i.v. regimen was investigated early in the development of alternative dosing schedules because of the potential improvement in antitumor activity with prolonged topotecan exposure. Patients with histologically confirmed malignant solid tumors that were refractory to standard therapy who had measurable or assessable disease were enrolled in a phase I study to investigate the tolerability of continuous topotecan [16]. Patients were treated with 24-hour c.i.v. topotecan for 21 days, starting at a dose of 0.2 mg/m²/day for 7 days, and eventually escalating to 21 days of administration. Cycles were repeated every 28 days. The maximum tolerated dose (MTD) for this 21-day schedule was 0.53 mg/m²/day. Three of six patients with ovarian cancer who had been heavily pretreated with chemotherapy (i.e., platinum and paclitaxel) demonstrated a partial response (PR) when treated with this prolonged topotecan infusion. The DLTs included thrombocytopenia and neutropenia occurring at the dose of 0.70 mg/m²/day for 21 days.

The apparent effectiveness of topotecan in a 24-hour, 21-day c.i.v. regimen in patients with ovarian cancer prompted the New York Gynecologic Oncology Group to further investigate the efficacy of this schedule. In a phase II study, 24 patients with recurrent ovarian cancer previously treated with a platinum-based therapy were enrolled [17]. Topotecan was administered as a 0.4-mg/m²/day c.i.v. infusion for 21 days, with cycles repeated every 28 days. The overall response (OR) rate was 38%, including 8 of 23 patients (35%) with measurable disease achieving a PR, and one patient with assessable disease achieving a PR. Patients with platinum-refractory tumors had a response rate of 33%. Those patients relapsing early or later with platinum-sensitive tumors achieved PR rates of 40% and 38%, respectively. The median time to progression for all patients in the study was 26 weeks. Grade 3 neutropenia was observed in 28% of patients, whereas grade 4 neutropenia was observed in 4% of patients. Grade 4 thrombocytopenia was observed in 4% of patients, and anemia was common, with 52% of patients requiring transfusion. However, nonhematologic toxicities were mild. Randomized comparative studies are
required to determine if the high response rates observed in this study are attributable to the dosing schedule.

The results of the Hochster et al. [17] study suggested that the 24-hour, 21-day c.i.v. regimen might be an attractive alternative for topotecan dosing. However, Gore et al. [18] reported that of 35 recurrent ovarian cancer patients treated with 0.4 mg/m²/day topotecan given as a 24-hour i.v. infusion for 21 days, only 9% achieved a PR, with a median time to progression of 16 weeks. The major toxicity was myelosuppression, with grade 4 neutropenia occurring in 9% of patients. Median survival was 43.6 weeks. Prolonged infusion decreased the incidence of severe neutropenia but increased the incidence of grade 3/4 anemia. Differences in performance status, tumor bulk, and response to first-line therapy have been suggested as possible reasons for the varied response rates [18]. The inconvenience of a 24-hour c.i.v. infusion, which requires the implantation of a semipermanent venous access device and the use of an ambulatory infusion pump and tubes, and possible catheter-related complications and infections, make this dosing regimen less than ideal.

3-Day i.v. Bolus Topotecan

A 3-day i.v. bolus schedule was designed to lower hematologic toxicity yet provide antitumor response comparable to the 5-day regimen. Further, a 3-day regimen would be conducive to combination therapy with other agents administered on a 3-day schedule such as carboplatin and paclitaxel. In a phase I, dose-escalation trial, 20 patients with recurrent epithelial cancer of the ovary, fallopian tube, or peritoneum following treatment with a platinum-based agent and paclitaxel were given topotecan doses beginning at 2.5 mg/m² given as a 30-minute i.v. infusion on days 1-3 of a 21-day cycle [19]. Grade 4 neutropenia was observed in 85% of patients during cycle 1; however, neutropenia was readily managed with G-CSF support. Grade 4 thrombocytopenia occurred in 2% of patients during cycle 1. Neurotoxicity was dose limiting at 4.25 mg/m²; two patients experienced debilitating lethargy at this dose level. However, neurotoxicity was not related to hemoglobin, performance status, renal function, or prior therapy. Based on the results of this trial, the MTD for a 3-day regimen was set at 3.75 mg/m². This study demonstrated that topotecan was well tolerated when administered as a 30-minute i.v. infusion on days 1-3 of a 21-day cycle. This investigation was followed by several phase II studies to further characterize this dosing regimen.

In the first published phase II study, 29 patients with ovarian cancer refractory to platinum and paclitaxel were treated with 1.5 mg/m²/day topotecan given as a 30-minute i.v. bolus on days 1-3 of a 21-day cycle (Table 1) [20]. Grade 4 neutropenia was the major toxicity observed in 24% of patients. Neutropenic fever and grade 3 thrombocytopenia were each experienced by 10% of patients. Blood transfusions and G-CSF support because of severe neutropenia and neutropenic fever were rarely needed; only four patients (14%) and three patients (10%) required a blood transfusion or G-CSF support, respectively. No patients required platelet transfusions and there were no serious infections. Dose reductions were required in 28% of patients. However, despite the expected myelosuppression, dose escalation was possible in four patients (14%). A clinically relevant PR was achieved in two patients (7%) and stable disease (SD) was achieved in six patients (21%).

Recently, three other studies have investigated the 3-day topotecan regimen in ovarian cancer patients. In an open-label, multicenter phase II trial, 30 patients with platinum-sensitive ovarian cancer or primary peritoneal cancer were treated with topotecan 1.0-2.0 mg/m²/day on days 1-3 of a 21-day course [21]. Of these patients, 29 had received prior chemotherapy, and none had received prior radiotherapy. Grades 3 and 4 neutropenia were experienced by 60% and 30% of patients, respectively. Grade 3 leukopenia was reported in 33% of patients and grade 4 thrombocytopenia in only 3% of patients. Of the 29 evaluable patients, 14% achieved an OR including 2 complete responses (CRs) and 2 PRs. An additional 55% of patients achieved SD.

Two other studies have shown improved response rates in similar patient populations. Herzog et al. [22] reported on 28 platinum-sensitive patients treated with topotecan 2.0 mg/m²/day on days 1-3 of a 21-day course in a phase II study. A total of 156 cycles of chemotherapy were administered. Grade 3/4 neutropenia and leukopenia were reported in 53% and 20% of cycles, respectively. Grade 3/4 thrombocytopenia was reported in only 2% of courses. Of the 26 evaluable patients, 23% achieved an OR and an additional 50% of

Table 1. Phase II studies investigating the 3-day topotecan regimen in ovarian cancer patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Evaluable n</th>
<th>RR %</th>
<th>SD %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markman et al., 2000 [20]</td>
<td>29</td>
<td>7</td>
<td>21</td>
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<tr>
<td>Miller et al., 2002 [21]</td>
<td>29</td>
<td>14</td>
<td>55</td>
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<tr>
<td>Herzog et al., 2002 [22]</td>
<td>26</td>
<td>23</td>
<td>50</td>
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<tr>
<td>Brown et al., 2002 [23]</td>
<td>28</td>
<td>26</td>
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Abbreviations: RR = response rate; SD = stable disease.
patients had SD. Similar efficacy results were reported by Brown et al. [23]. In that study, 33 patients with recurrent ovarian cancer were treated with topotecan 2.0 mg/m²/day using the 3-day topotecan regimen. Grade 3 and 4 neutropenia were reported in 29% and 25% of courses, respectively, whereas grade 4 thrombocytopenia was only reported in 1% of courses. An OR rate of 26% was observed in the 28 evaluable patients, with an additional 25% of patients achieving SD. These phase II studies demonstrated that the 3-day topotecan regimen was more convenient and less toxic compared with the 5-day regimen. However, the potential equivalence of tumor activity between the 3-day and 5-day regimens will require further investigation.

**Weekly Topotecan Regimens**

Although grade 4 nonhematologic toxicity is rare with the standard 5-day topotecan schedule, this regimen is associated with noncumulative and reversible hematologic toxicity, which can prevent the combination of topotecan with other agents. It was thought that a weekly schedule would be associated with reduced myelosuppression compared with the 5-day regimen. Further, because there was interest in combining topotecan with agents such as gemcitabine, which are administered on a weekly schedule, a weekly topotecan regimen was an attractive alternative dosing schedule. However, a weekly schedule would be counterintuitive to the proposed S-phase specificity of topotecan. Therefore, preclinical studies investigated the efficacy of weekly topotecan prior to its use in clinical trials. In one preclinical study, human colon carcinoma xenografts were transplanted into mice that were then treated with topotecan twice weekly—the pharmacologic equivalent of weekly treatment in humans. In two separate experiments, five of six and three of five mice obtained a CR [24]. In another study, mice with systemic B16 melanoma treated with topotecan achieved an increase in median survival time of 56% (oral administration) and 49% (intraperitoneal administration) [25]. Similarly, mice bearing subcutaneously transplanted Lewis lung carcinoma demonstrated 90% inhibition of tumor growth at day 13, as well as an 86%-110% increase in life span [25]. These preclinical data suggested that weekly topotecan might be efficacious in humans. Further, gemcitabine and irinotecan (another topoisomerase I inhibitor) are both S-phase-specific agents that are active when administered on a weekly basis, suggesting the S-phase specificity of topotecan would not be an obstacle in designing a weekly topotecan regimen. Therefore, several weekly dosing regimens were evaluated.

**Weekly 72-Hour c.i.v. Infusion Topotecan**

To investigate a weekly 72-hour c.i.v. regimen, 24 patients with platinum-resistant and paclitaxel-resistant ovarian cancer were enrolled in a phase II study and were treated with 2.0 mg/m²/week topotecan given by 72-hour c.i.v. (Table 2) [26]. Eligible patients were allowed two prior chemotherapy regimens, with at least 3 weeks elapsed since any prior therapy. Of the 23 evaluable patients, two (9%) achieved a PR and six patients (26%) achieved SD. The median time to progression was 2 months, with a median survival of 9 months. Pharmacokinetic analyses showed that patients who responded had the highest steady-state topotecan lactone concentrations compared with patients with stable or progressive disease. Grade 3/4 anemia, neutropenia, and thrombocytopenia were each experienced by 17%, 13%, and 9% of patients, respectively. In this preliminary study, topotecan demonstrated modest antitumor activity. Although randomized, controlled studies are necessary to directly compare the efficacy of different regimens, the 9% response rate of the weekly 72-hour c.i.v. regimen was somewhat less than the response rate of 12%-18% reported in platinum- and paclitaxel-resistant patients treated with the standard dosing regimen. Nevertheless, the activity of a weekly 72-hour c.i.v. regimen in patients with platinum- and paclitaxel-sensitive ovarian cancer remains to be determined.

**Weekly 24-Hour c.i.v. Topotecan**

In addition to a weekly 72-hour c.i.v. topotecan schedule, a weekly 24-hour c.i.v. regimen has also been investigated. In an early phase I pharmacokinetic study, 32 patients were given 1.0-2.0 mg/m²/day topotecan as a 24-hour i.v. infusion every...
Most patients (88%) had received prior chemotherapy and the median performance status was 1. Dose-limiting neutropenia occurred at topotecan doses ≥1.75 mg/m²/week. However, grade 4 thrombocytopenia only occurred in patients who had been heavily pretreated. Nonhematologic toxicity was mild and controlled by prochlorperazine. Pharmacodynamic analyses showed that the area under the curve of total drug and the concentration of the lactone form of the drug correlated with neutropenia. Based on the results of this study, the recommended dose for phase II trials was 1.5 mg/m²/week topotecan by 24-hour c.i.v. infusion.

The National Cancer Institute of Canada Clinical Trials Group conducted a comparative phase II study in patients with recurrent ovarian cancer to compare the weekly 24-hour c.i.v. infusion schedule with the standard 5-day schedule [11]. Topotecan was administered as either a 1.75-mg/m², 24-hour c.i.v. infusion once a week for 4 weeks, or as the standard dosing schedule of 1.5 mg/m²/day on days 1-5 of a 21-day cycle. Patients were required to have failed no more than two prior treatment regimens, one of which had to be a platinum-containing regimen. A total of 66 patients were enrolled in the study and 63 were assessable for response (32 patients in the weekly 24-hour c.i.v. arm and 31 patients in the standard 5-day arm). The response rate in patients receiving topotecan administered as a weekly 24-hour infusion was 3%, which is substantially lower than the 23% response rate observed in patients receiving the standard schedule. However, when patients with SD are included in the analysis, 47% and 52% of patients achieved clinical benefit when treated with a weekly 24-hour c.i.v. or standard 5-day regimen, respectively. The median time to progression was 1.8 months for patients receiving weekly 24-hour c.i.v. topotecan compared with 2.9 months in patients receiving the standard dosing schedule. However, the overall survival for both treatment arms was similar, with a median survival of 12.4 months and 11 months for patients treated with the weekly 24-hour c.i.v. or standard 5-day regimen, respectively. As expected, myelosuppression was lower in patients treated with a weekly 24-hour c.i.v. regimen compared with the standard dosing regimen; neutropenia occurred in 52% of patients treated with weekly 24-hour c.i.v. and in 94% of patients receiving the standard dosing schedule. Despite the improved hematologic profile, the similar proportion of patients experiencing clinical benefit, and the similar overall survival of patients treated with the weekly 24-hour c.i.v. regimen, the significant decrease in response rate in this study suggested further studies are needed to determine if the weekly 24-hour c.i.v. topotecan dosing regimen is effective in the treatment of ovarian cancer.

**Weekly i.v. Bolus Topotecan**

The safety and efficacy of weekly i.v. bolus topotecan in patients with recurrent ovarian cancer were first investigated in a phase I study by Homesley et al. [28]. The 35 enrolled patients had platinum-sensitive or platinum-resistant disease and had received one or two prior chemotherapy regimens. In this dose-escalation study, topotecan was administered at a starting dose of 1.5 mg/m² every week, with incremental increases of 0.5 mg/m² applied every 21 days, provided the dose was well tolerated. The MTD was 6.0 mg/m²/week and the maximum recommended dose for further study was 4 mg/m²/week. Four of the 32 evaluable patients (13%) achieved a PR and six patients (19%) achieved SD at topotecan doses of ≥2 mg/m². DLTs included grade 2 anemia, chronic fatigue, and grade 2 gastrointestinal toxicity. In contrast to the 5-day regimen, myelotoxicity and thrombocytopenia were not dose limiting in patients given weekly topotecan.

Currently, in an ongoing, open-label, multicenter, phase II study, we are further evaluating the weekly i.v. bolus topotecan regimen in patients with platinum-sensitive recurrent ovarian and peritoneal cancer [29]. Patients are allowed one prior platinum-containing chemotherapy regimen and must have bidimensionally measurable disease. Patients with serum CA-125 elevation alone are excluded. Enrolled patients receive topotecan at a starting dose of 4.0 mg/m² as an i.v. bolus over 30 minutes. Weekly doses are decreased by 0.5-mg/m² increments to 2.5 mg/m²/week if patients experience uncomplicated grade 3/4 hematologic or nonhematologic toxicity. The dose is reduced by 1.0 mg/m² if patients experience complicated hematologic toxicity. If patients fail to recover from hematologic toxicity, treatment is omitted for 1 week to allow for recovery. To date, 21 patients with recurrent stage IIIC/IV ovarian cancer (n = 19), stage IIC ovarian (n = 1), or bulky primary peritoneal cancer (n = 1) have been enrolled. Seventeen patients are currently evaluable for response; four patients were removed prior to assessing tumor response (three patients failed to experience absolute neutrophil count recovery within 2 weeks and one patient was removed because of gastrointestinal toxicity). Seven patients (41%) have achieved a PR, with a median time to response of 7.7 weeks. The median time to progression was 20.6 weeks, and the progression-free interval for responders was 28.3 weeks. An additional six patients (35%) have achieved SD; however, it is too early to assess the progression-free interval for these patients. The progression-free interval for all evaluable patients was 18.3 weeks.

All 21 patients were assessable for toxicity. Weekly topotecan was well tolerated. Of the 293 planned treatments, 261 (89%) have been administered on time, with 12 treatments (5%) delayed or omitted due to absolute neutrophil count <1,500/µl, 11 (4%) due to patient noncompliance, five (2%) due to platelets <100,000/µl, two (<1%) due to fatigue, and two (<1%) due to other illness. Grade 4 hematologic toxicity was rare, with only one patient experiencing grade 4...
neutropenia. Nonhematologic toxicity included grade 3 fatigue (two patients) and grade 3 diarrhea (one patient). The low toxicity in this study is surprising given that over 3 weeks of administration, the maximum dose of topotecan in this study was 12 mg/m², which is much higher than the total dose of topotecan (7.5 mg/m² over 3 weeks) in the 5-day regimen.

Weekly administration of topotecan is an active regimen in the treatment of ovarian cancer. Although fatigue may be severe and dose limiting, this regimen is generally well tolerated, with only moderate myelosuppression. In addition, a weekly regimen is more convenient than the standard 5-day regimen and may be more easily integrated into combination regimens. Based on the preliminary results of our trial, we recommend a starting dose of 4.0 mg/m²/week with dose modifications for patients with renal impairment, and we recommend a treatment-free week every 4-6 weeks to allow patients to recover from nonhematologic toxicity.

DISCUSSION

Many alternate dosing schedules of topotecan are being investigated in phase I and phase II trials for the treatment of recurrent ovarian cancer. Two equally important goals for developing these alternative regimens are to increase the response rate, which is 13%-33% for the standard treatment regimen, and to improve the hematologic toxicity profile, which ranges from 40%-90% for grade 3/4 neutropenia and 30%-60% for grade 3/4 thrombocytopenia. Another goal in optimizing dosing schedules is to increase the convenience and quality of life for patients.

Although the 21-day c.i.v. infusion regimen showed a higher response rate and a lower rate of toxicity compared with the standard regimen in one trial, the antitumor activity observed in other trials has been generally disappointing [17, 18]. The disparity in antitumor activity may be attributed, in part, to modulation of the topoisomerase I enzyme. For instance, in non-small cell lung cancer cell lines, continuous exposure to topotecan resulted in a reduction of topoisomerase I levels. Additionally, topoisomerase I levels did not return to pretopotecan levels until 7 days after drug removal [15]. Further, there was a concomitant increase in resistance to the cytotoxic effects of topotecan as topoisomerase I levels decreased. In light of these findings, the mixed results observed in studies of 21-day c.i.v. infusion are not surprising. Further study is required to determine if continuous or prolonged exposure to topotecan has a place in clinical practice.

Studies investigating the 3-day regimen have shown varied results. This regimen was reported to have relatively low response rates in two studies [20, 21], and relatively high response rates in two other studies in relapsed ovarian cancer patients [22, 23]. Therefore, the efficacy and tolerability of the 3-day topotecan dosing regimen need to be further evaluated.

Despite low hematologic toxicity, the weekly schedules with 2 mg/m² administered over 72 hours and 1.75 mg/m² administered over 24 hours were both associated with low response rates. This poor response may be due to the low maximal drug concentration subsequent to the long infusion time. Therefore, the contribution of these regimens in the treatment of patients with relapsed ovarian cancer is likely to be limited. Nevertheless, they may find a place in combination therapy in selected patient populations.

Weekly topotecan is active at doses >2 mg/m² and should be started at a dose of 4 mg/m². The weekly i.v. bolus regimen provides larger maximal drug concentration values compared with the standard 5-day dosing regimen. The standard regimen of 1.5 mg/m²/day on days 1-5 of a 21-day cycle provides 7.5 mg/m² per cycle. By comparison, a cycle of the weekly i.v. bolus regimen (topotecan 4 mg/m²/week) provides 12 mg/m² topotecan over a 21-day cycle. As a result, preliminary response rates in patients receiving topotecan by the weekly i.v. bolus schedule seem to provide comparable efficacy and an improved hematologic toxicity profile compared with the standard dosing regimen. The improved hematologic toxicity profile of the weekly i.v. bolus regimen may allow greater tolerability in combining topotecan with other antitumor agents. An added benefit of the weekly i.v. bolus regimen is its greater convenience when compared with the 5-day regimen. Nevertheless, randomized controlled studies are necessary to directly compare the weekly i.v. bolus regimen with the standard 5-day regimen.

The prospects of alternative dosing schedules for the use of topotecan in patients with recurrent ovarian cancer look promising. Further work in this area should focus on continued development of these alternative dosing regimens with topotecan alone and in combination with other agents.

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REFERENCES


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