Update on the Treatment of Cervical and Uterine Carcinoma: Focus on Topotecan

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Key Words. Cervical neoplasms · Cisplatin · Radiotherapy · Topotecan · Uterine neoplasms

Abstract

Carcinomas of the uterine cervix and corpus are significant causes of morbidity and mortality among women in the U.S. and are expected to contribute 10,700 deaths in 2002. Despite the widespread use of cytologic screening and improvements in early diagnosis, mortality rates have changed little over the past 25 years, and the management of cervical and uterine cancers remains a significant unmet medical need. Currently available modalities, including radiotherapy and cisplatin-based chemotherapy, provide suboptimal control of disease, and there are no effective treatments for recurrent disease. The antitumor activity and tolerability of a number of novel agents, including topoisomerase I inhibitors, vinca alkaloids, taxanes, and gemcitabine, have been of considerable interest in treatment of these cancers. This review discusses current trends in the treatment of cervical and endometrial carcinomas, focusing on the potential role of topotecan in the treatment of non-ovarian gynecologic malignancies. The Oncologist 2002;7(suppl 5):36-45

Learning Objectives

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

1. Identify the need for new chemotherapeutic agents in the treatment of advanced gynecologic malignancies.
3. Identify other gynecologic malignancies in which the use of topotecan is currently being explored.

Introduction

Carcinomas of the uterine cervix and corpus are significant causes of death for women suffering from gynecologic malignancies in the U.S. and are expected to account for an estimated 10,700 deaths (cervical, 4,100; uterine, 6,600) in 2002 [1]. Additionally, 13,000 and 39,300 new cases of cervical and uterine cancer, respectively, will be diagnosed in 2002 [1]. The 5-year overall survival (all stages) of patients with carcinoma of the uterine cervix and corpus is generally favorable at 70% and 84%, respectively [1, 2]. However, the 5-year survival rates for patients with regional or distant cervical cancer (49% and 15%, respectively) or endometrial cancer (63% and 26%, respectively) are less encouraging [2].

With the advent of the Papanicolaou (Pap) smear, the incidence of cervical cancer has dramatically declined, and mortality from cervical cancer has decreased by >70% since 1940. However, women who have multiple sexual
partners, have first coitus at a young age, bear children at a young age, or have had a partner with promiscuous sexual behavior have an increased risk of developing cervical cancer [3]. Further, a strong correlation between human papillomavirus (HPV) and the incidence of cervical cancer has been established, with HPV DNA being detected in 93% of cervical carcinomas [4]. Women who are not diagnosed with cervical cancer through screening typically present with advanced disease. A high proportion of these patients have persistent and recurrent disease with locoregional and/or distant metastases despite first-line radiation therapy. Therefore, there is an unmet need for active treatment options in patients with recurrent cervical cancer.

As with cervical cancer, most cases of endometrial carcinoma are diagnosed at an early stage. Most newly diagnosed endometrial carcinomas are confined to the uterus, and treatment with hysterectomy alone is associated with cure rates of 80%-90%. However, two-thirds of the recurrences seen in women whose primary tumor was confined to the uterus are systemic recurrences. Further, patients with advanced disease usually experience recurrence after hysterectomy and radiotherapy, and two-thirds of these patients experience abdominal and systemic recurrence. Most patients with advanced recurrent disease should be assessed for treatment with cytotoxic agents. Unfortunately, treatment of systemic disease with current chemotherapy agents is largely palliative. Therefore, there is a need for the development of new agents for the treatment of patients with advanced recurrent endometrial cancer.

Although there is clearly an unmet need for new therapies in the management of advanced non-ovarian gynecologic malignancies, a number of agents have shown activity in these diseases. In this review, we will discuss the efficacy of these therapies with a focus on topotecan (Hycamtin®; GlaxoSmithKline; Philadelphia, PA), a novel topoisomerase I inhibitor.

CERVICAL CANCER

Several factors influence the prognosis of patients with cervical cancer, including histologic type and stage of disease. Squamous cell carcinoma constitutes between 80%-90% of cervical cancers, with the remaining cases composed of pure adenocarcinoma or mixed adenosquamous carcinoma. Staging of the disease to determine the tumor volume, nodal involvement, extent of local invasion, and the extent of regional involvement is important in designing a treatment strategy for these patients. Surgical staging is the most accurate method in determining the extent of disease. However, there is little evidence of improved overall survival with routine surgical staging [5]. Recently, computed tomography and positron emission tomography have been used to assess the extent of disease. Both of these imaging methods have demonstrated sensitivity in predicting nodal and local involvement; however, the routine use of these imaging methods remains controversial [6-8].

Current First-Line Treatment Strategies

Early invasive disease (stages IA2, IB1, and small stage IIA with no parametrial involvement) is managed with radical hysterectomy or radiation therapy, which results in a 5-year survival rate of 80%-90% [9]. In contrast, advanced disease (stages IIB2 through IV) is rarely managed with surgery because of regional involvement and a high rate of local relapse. Instead, brachytherapy and external-beam pelvic irradiation, alone or in combination with chemotherapy, are used to treat patients with advanced disease. Five-year survival rates for patients with stage IIB, III, or IVA tumors are 65%, 40%, and <20%, respectively [9].

Recently, several studies have demonstrated that radiation therapy with concomitant chemotherapy results in improved overall survival. Concomitant cisplatin-based chemotherapy (acting as a sensitizer) with radiotherapy in patients with early-stage or locally advanced cervical cancer significantly increases overall survival compared with radiotherapy alone [10-15]. For example, the estimated 5-year survival rate in patients with stage IB, IIA, or IIB cervical cancer who were treated with radiotherapy and cisplatin plus 5-fluorouracil was 73% compared with 58% in patients treated with radiotherapy alone (p = 0.004) [11]. The results of these trials led the National Cancer Institute to issue a clinical announcement that strongly suggested the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in cervical cancer patients who require radiation therapy [16, 17]. Nevertheless, despite this shift in the standard of care, most patients with advanced cervical cancer will experience recurrent or persistent disease.

Although significant progress has been made in the treatment of patients with cervical cancer using cisplatin-based chemotherapy regimens given concomitantly with radiotherapy, there is still an unmet need for new treatment options in this patient population. Further, because persistent and recurrent cervical cancer are not usually responsive to reirradiation, first-line treatment offers the best possibility for a cure. Therefore, several new cytotoxic agents have been recently investigated in the first-line treatment of cervical cancer patients (Table 1) [18-23]. In chemotherapy-naïve patients with advanced or recurrent squamous cervical carcinoma, treatment with paclitaxel 170-250 mg/m² results in a response rate of 17%-23% [18, 19]. Treatment with weekly vinorelbine 30 mg/m² in previously untreated patients with recurrent cervical cancer resulted in an overall response rate (ORR) of 45% [23]. Therefore, the
activity of these agents and others should be investigated as radiosensitizers in the first-line setting.

**Current Salvage Treatment Strategies**

In patients with relapsed cervical cancer, radiotherapy is usually directed to nonirradiated areas for palliation of symptoms. In addition, most cervical cancer patients who relapse often recur at both local and distant sites. Therefore, systemic chemotherapy is an important option for these patients. Cisplatin is the most active single agent in recurrent or metastatic cervical cancer. Patients with advanced or recurrent cervical cancer who have been treated with cisplatin have achieved ORRs of 17%-38% [24-27]. However, these responses are partial and short lived, and median overall survival is only 6-7 months [25]. A few studies have also investigated new antineoplastic agents in recurrent cervical cancer. Weekly gemcitabine 800 mg/m² treatment in patients previously treated with one prior chemotherapy regimen resulted in an ORR of only 8% [21]. In contrast, treatment with irinotecan, a topoisomerase I inhibitor, resulted in an ORR of 21% in cervical cancer patients who had failed first-line chemotherapy [22]. Therefore, the use of new chemotherapeutic agents, particularly topoisomerase I inhibitors, should be further investigated in the salvage setting.

**Topotecan in Cervical Cancer**

Topotecan is a topoisomerase I inhibitor that is currently approved for the treatment of recurrent ovarian cancer (for in-depth analysis of topotecan in ovarian cancer, see Herzog et al., pp 3-10 [28]). Topotecan causes double-stranded DNA breaks during replication, which eventually lead to cell death. Early investigations suggested that topotecan is a radiosensitizer. Kim et al. [29] reported the cell-killing synergy of radiation and topotecan in a dose-dependent manner in murine fibrosarcoma cells. Topotecan also demonstrated radiation-sensitizing activity in human head-and-neck squamous cell carcinoma cell lines [30], a radioresistant human melanoma cell line [31, 32], glioblastoma cell lines, [33, 34], and a non-small cell lung cancer cell line [34]. Subsequently, concurrent radiotherapy and administration of topotecan were assessed in patients with inoperable non-small cell lung cancer [35]. Of the 12 patients enrolled in this small trial, five were alive after 12 months of follow-up.

Recently, Boabang et al. [36] demonstrated that topotecan has significant cytotoxic effects in several squamous cell carcinoma cell lines of the cervix and vulva and may potentiate the cytotoxic activity of cisplatin, etoposide, and paclitaxel in some cell lines. The results of the previously mentioned studies suggested that topotecan may act as a radiation sensitizer in vivo and prompted the investigation of topotecan in cervical cancer. In a feasibility study conducted in previously irradiated cervical cancer patients, topotecan 0.5 mg/m²/day (days 1-5 of a 21-day course) administered with low-dose brachyradiotherapy was well tolerated [37]. However, significant toxicity was observed at a topotecan dose level of 1.0 mg/m². In contrast, Dunton et al. [38] reported in a recent phase I trial that topotecan 1.0 mg/m² on days 1-5 of a 21-day course was safely administered with concomitant standard external-beam radiotherapy in previously untreated patients. The difference between these two studies may be explained by the patient treatment histories. Further studies are needed to fully characterize the radiosensitizing activity of topotecan in patients with cervical cancer.

The use of topotecan as first-line or second-line chemotherapy in patients with cervical cancer has also been

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### Table 1. Efficacy of various agents in the treatment of advanced cervical cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Treatment history</th>
<th>Evaluable patients n</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGuire et al., 1996</td>
<td>Paclitaxel</td>
<td>No prior chemotherapy</td>
<td>52</td>
<td>17%</td>
</tr>
<tr>
<td>Kudelka et al., 1996</td>
<td>Paclitaxel</td>
<td>No prior chemotherapy except as radiation sensitizer; 92% prior RT</td>
<td>22</td>
<td>23%</td>
</tr>
<tr>
<td>Kudelka et al., 1996</td>
<td>Docetaxel</td>
<td>No prior chemotherapy except as radiation sensitizer; 65% prior RT</td>
<td>16</td>
<td>13%</td>
</tr>
<tr>
<td>Schilder et al., 2000</td>
<td>Gemcitabine</td>
<td>1 prior chemotherapy regimen</td>
<td>25</td>
<td>8%</td>
</tr>
<tr>
<td>Verschraegen et al., 1997</td>
<td>Irinotecan</td>
<td>88% prior RT; refractory to first-line chemotherapy</td>
<td>42</td>
<td>21%</td>
</tr>
<tr>
<td>Lacava et al., 1997</td>
<td>Vinorelbine</td>
<td>Previously untreated</td>
<td>42</td>
<td>45%</td>
</tr>
</tbody>
</table>

Abbreviation: RT = radiotherapy.
investigated in several phase II studies (Table 2) [39-43]. 

Noda et al. [39] first reported on the antitumor activity of topotecan 1.2 mg/m²/day on days 1-5 of a 21-day course in cervical cancer patients. Of the 22 evaluable patients in that study, the ORR was 18%, including 4 partial responses (PRs) in patients with squamous cell cervical cancer. Grade 4 leukopenia occurred in 33% of previously untreated patients and in 37% of previously treated patients. Grade 4 anemia did not occur in previously untreated patients but was reported in 25% of previously treated patients. In another study of topotecan 1.0 mg/m²/day on days 1-5 of a 21-day cycle, Abu-Rustum et al. [40] reported an ORR of 17% in 12 recurrent cervical cancer patients who had been previously treated with platinum-based chemotherapy. In a larger study of 43 chemotherapy-naïve patients, topotecan (1.5 mg/m²/day on days 1-5 of a 21-day course) treatment resulted in an ORR of 19%, including 3 (7%) complete responses (CRs) and 5 (12%) PRs [41]. Grade 4 neutropenia and thrombocytopenia were reported in 68% and 18% of patients, respectively. Nonhematologic toxicity was not dose limiting. Similar results were reported in a Gynecologic Oncology Group (GOG) study that enrolled 45 patients with recurrent squamous cell carcinoma of the cervix who were allowed one prior chemotherapy regimen [42]. Of 40 evaluable patients, five (13%) achieved an overall response (OR) and 15 (38%) achieved stable disease with topotecan (1.5 mg/m²/day on days 1-5 of a 21-day course). In these previously treated patients, the median progression-free interval was 2.1 months and the median overall survival was 6.6 months. Grade 4 neutropenia and thrombocytopenia were experienced by 68% and 39% of patients, respectively. Nonhematologic toxicities associated with single-agent topotecan were mild and not dose limiting.

Topotecan in combination with other agents has also been investigated in patients with recurrent cervical cancer. We investigated topotecan in combination with cisplatin in previously untreated patients. In our phase II trial, patients were treated with cisplatin 50 mg/m² by a 1-hour i.v. infusion on day 1 and topotecan 0.75 mg/m² by 30-minute i.v. infusion on days 1-3 of a 21-day cycle [43-45]. A total of 35 patients were enrolled. Of the 32 evaluable patients, nine (28%) responded to treatment including 3 CRs and 6 PRs. An additional nine patients (28%) achieved stable disease. Median survival was 10 months, with three patients in lasting remission at the time of the report. As anticipated, the most common toxicity was hematologic, with 30% and 10% of cycles associated with grade 3/4 neutropenia and thrombocytopenia, respectively. The antitumor activity of topotecan in combination with cisplatin in cervical cancer patients has prompted the design of a randomized phase III trial that is currently ongoing (Fig. 1).

Table 2. Efficacy of topotecan in cervical cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment history</th>
<th>Treatment</th>
<th>Evaluable patients</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noda et al., 1996 [39]</td>
<td>24% with no prior chemotherapy; 76% with prior chemotherapy</td>
<td>Topotecan 1.2 mg/m²/day on days 1-5 of 21-day cycle</td>
<td>22</td>
<td>18%</td>
</tr>
<tr>
<td>Abu-Rustum et al., 2000 [40]</td>
<td>Prior platinum-based chemotherapy</td>
<td>Topotecan 1 mg/m²/day on days 1-5 of 21-day cycle</td>
<td>12</td>
<td>17%</td>
</tr>
<tr>
<td>Maderspach et al., 2001 [41]</td>
<td>No prior chemotherapy</td>
<td>Topotecan 1.5 mg/m²/day on days 1-5 of a 28-day cycle</td>
<td>43</td>
<td>19%</td>
</tr>
<tr>
<td>Bookman et al., 2000 [42]</td>
<td>15% with no prior chemotherapy; 85% with prior chemotherapy</td>
<td>Topotecan 1.5 mg/m²/day on days 1-5 of a 21-day cycle</td>
<td>40</td>
<td>13%</td>
</tr>
<tr>
<td>Fiorica et al., 2002 [43]</td>
<td>No prior chemotherapy</td>
<td>Cisplatin 50 mg/m² on day 1 and topotecan 0.75 mg/m² on days 1-3 of a 21-day cycle</td>
<td>32</td>
<td>28%</td>
</tr>
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</table>

Figure 1. Future investigations of topotecan in the treatment of cervical cancer. The lack of efficacy of a methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) combination has led to the elimination of this treatment arm.

Abbreviations: D = day; M = methotrexate; V = vinblastine; A = doxorubicin; C = cisplatin; GOG = Gynecologic Oncology Group.
The vast majority (90%) of uterine cancers is of epithelial origin. Of these, 90% are endometrial adenocarcinomas or adenosquamous carcinomas. The remaining 10% of cases are classified as papillary serous carcinoma, clear cell carcinoma, papillary endometrioid carcinoma, and mucinous carcinoma [46]. The average age at diagnosis of patients with endometrial cancer is about 60 years and most patients are postmenopausal. Patients typically present with vaginal bleeding, and before 1988, they were clinically staged. However, because of erroneous clinical staging found in up to one-third of cases, today most patients are surgically staged [46]. Treatment with hysterectomy alone is associated with a high cure rate. However, endometrial cancer patients with advanced disease or recurrent systemic disease are often treated with cytotoxic agents as salvage therapy.

**Chemotherapy Treatment of Recurrent Endometrial Cancer**

Several agents have been investigated in the treatment of advanced or recurrent endometrial carcinoma (Table 3) [47-53]. One of the first cytotoxic agents investigated was doxorubicin. *Thigpen et al.* [47] investigated doxorubicin 60 mg/m² in 43 patients with advanced or recurrent endometrial carcinoma whose disease was no longer manageable with surgery or radiotherapy. Of these patients, 11 (26%) achieved a CR and 16 (37%) achieved ≥50% reduction in measurable disease. Patients who responded to doxorubicin experienced significantly longer survival than nonresponders ($p < 0.05$). *Thigpen* and colleagues also investigated the use of cisplatin in chemotherapy-naïve patients with advanced endometrial carcinoma. Forty-nine patients with advanced or recurrent endometrial carcinoma were treated with cisplatin 50 mg/m² i.v. every 3 weeks [48]. Of these patients, 10 (20%) achieved an OR, including 2 (4%) CRs. An additional 45% achieved stable disease. Cisplatin has also been investigated as second-line therapy in these patients. In a phase II trial, 25 patients with advanced or recurrent endometrial carcinoma were treated with cisplatin 50 mg/m² every 3 weeks as salvage therapy [54]. Only 4% of patients achieved an objective response, although 80% of patients had stable disease.

The success of single agents, doxorubicin and cisplatin, prompted studies investigating the antitumor activity of a novel combination of the two agents. In a randomized phase III comparison trial, doxorubicin alone was compared with a combination of doxorubicin/cisplatin in advanced or recurrent endometrial carcinoma patients [49]. In this study, 281 patients were randomized to receive doxorubicin 60 mg/m² or doxorubicin 60 mg/m² plus cisplatin 50 mg/m² by i.v. injection every 3 weeks. The ORR of patients treated with doxorubicin alone was 27% compared with 45% in patients treated with doxorubicin/cisplatin. Of the patients treated with doxorubicin alone, 8% achieved a CR compared with 22% of patients treated with doxorubicin/cisplatin.

Although the doxorubicin/cisplatin combination regimen has been widely adopted for treatment of recurrent endometrial carcinoma, there is still a substantial need for improved treatment options. Therefore, several new cytotoxic agents (paclitaxel, etoposide, and ifosfamide) have been recently investigated in the treatment of patients with recurrent disease. In a phase II trial, 30 patients with advanced or recurrent endometrial adenocarcinoma were treated with paclitaxel 250 mg/m² with granulocyte colony-stimulating factor (G-CSF) support [50]. Of the 28 evaluable patients, 10 (35%) achieved an OR, including 4 (14%)
CRs and 6 (21%) PRs. Grade 3/4 leukopenia was experienced by 62% of patients, and grade 3 thrombocytopenia and neurotoxicity were experienced by 7% and 10% of patients, respectively.

The antitumor activity of single-agent paclitaxel in the treatment of these patients led to the investigation of treatment with paclitaxel in combination with doxorubicin and in combination with doxorubicin/cisplatin. In a large, multicenter trial, 314 patients were randomized to receive doxorubicin 60 mg/m² and cisplatin 50 mg/m² or doxorubicin 50 mg/m² and paclitaxel 150 mg/m² with G-CSF support (Study GOG-163) [53]. The ORR in patients treated with doxorubicin/paclitaxel (43%) was similar to the ORR in patients treated with doxorubicin/cisplatin (40%). Of the 168 evaluable patients treated with doxorubicin/paclitaxel, 17% and 26% achieved a CR or PR, respectively. Similarly, of the 160 evaluable patients treated with doxorubicin/cisplatin, 15% and 25% achieved a CR or PR, respectively.

The toxicities were also similar between both treatment groups. Grade 4 neutropenia and grade 3/4 thrombocytopenia were experienced by 54% and 6% of patients treated with doxorubicin/cisplatin, respectively. Grade 4 neutropenia and grade 3/4 thrombocytopenia were experienced by 48% and 9% of patients treated with doxorubicin/paclitaxel, respectively. Nonhematologic toxicities, including renal, neurologic, gastrointestinal, and cardiac toxicities, also occurred at similar incidences in both treatment groups. Results from this trial suggest that treatment with doxorubicin/paclitaxel is as effective as treatment with combined doxorubicin/cisplatin in advanced endometrial cancer patients.

Investigators also have been interested in evaluating a treatment combination of doxorubicin/cisplatin/paclitaxel. In an early phase I, dose-escalating study, Fleming et al. [55] treated 14 endometrial cancer patients with fixed-dose doxorubicin 45 mg/m² and cisplatin 60 mg/m², with increasing levels of paclitaxel. The hematologic dose-limiting toxicities were manageable with G-CSF support. In the presence of G-CSF support, neuromuscular toxicity was dose limiting, although with paclitaxel administered at 160 mg/m², only one patient experienced grade 3 myalgia and none experienced grade 2 neuropathies. Notably, no congestive heart failure occurred in patients treated with doxorubicin at 45 mg/m². The authors recommended paclitaxel at 160 mg/m² for further evaluation in this combination regimen. The GOG is currently investigating a regimen of doxorubicin 45 mg/m², cisplatin 50 mg/m², and paclitaxel 160 mg/m² in a comparative trial versus doxorubicin 60 mg/m² and cisplatin 50 mg/m² (Study GOG-177).

Other chemotherapy agents have been less effective in treating patients with advanced or recurrent endometrial carcinoma. In a phase II GOG trial, 37 patients with advanced endometrial adenocarcinoma were treated with i.v. ifosfamide 1.2 g/m² and i.v. mesna 300 mg/m² every 4 hours for 3 doses daily for 5 days, every 4 weeks [51]. Of 33 evaluable patients, 24% achieved an OR. The response rate with ifosfamide treatment is lower than that observed with doxorubicin-based therapies. In addition, the ifosfamide regimen was inconvenient. In another phase II GOG trial, oral etoposide was investigated in second-line therapy of patients with advanced or recurrent endometrial carcinoma. Twenty-five patients received oral etoposide starting at 50 mg/m²/day and increasing to 60 mg/m²/day if hematologic toxicity permitted [56]. Of 22 evaluable patients, none achieved a tumor response, indicating that oral etoposide is not effective in the second-line setting. Oral etoposide has also been investigated as first-line therapy in recurrent endometrial adenocarcinoma. In a phase II trial, 44 patients were treated with oral etoposide 50 mg daily on days 1-21 of a 28-day schedule [52]. Fourteen percent of patients treated on this regimen achieved a response, including 1 (3%) CR and 5 (11%) PRs. Although an additional four patients had unconfirmed responses, the response rate of single-agent oral etoposide in this study demonstrated modest activity compared with the response rate in patients treated with doxorubicin combinations.

Although doxorubicin-based treatments demonstrate good efficacy in recurrent endometrial carcinoma, the agent is associated with considerable toxicity, including irreversible myocardial toxicity, congestive heart failure, and necrotizing colitis. Therefore, other efficacious agents with more favorable toxicity profiles need to be developed. Topotecan is one of several novel agents under investigation for treatment of endometrial cancer.

**TOPOTECAN IN ENDOMETRIAL CANCER**

The antitumor activity of topotecan in the treatment of relapsed ovarian cancer and the preliminary activity of topotecan in cervical cancer have prompted the investigation of topotecan in the treatment of advanced or recurrent endometrial cancers. In a phase II trial, 29 patients were treated with topotecan 1.5 mg/m² day on days 1-5 of a 21-day cycle. A median of 4 (range, 2-11) courses was administered to each patient [57]. Of the 22 patients evaluable for response, one patient achieved a CR and one patient achieved a PR. An additional 12 patients (55%) had stable disease. Twenty-eight patients were evaluable for toxicity. Of these patients, 61%, 39%, and 25% experienced grade 4 neutropenia, leukopenia, and thrombocytopenia, respectively. These preliminary results suggest that single-agent topotecan might have limited activity in patients with advanced or recurrent disease.
In an ongoing study, a regimen of weekly bolus i.v. topotecan is also being investigated in advanced recurrent metastatic endometrial carcinoma. To date, 13 patients have been enrolled in this phase I/II dose-escalation trial. In a preliminary report, Finkler and Holloway [58] reported that these 13 patients have tolerated weekly bolus i.v. topotecan at dose levels of 2.5-4.5 mg/m²/week. With a median of nine doses of topotecan per patient, the maximal tolerated dose has not yet been reached. Grade 3 and 4 neutropenia were reported in 31% and 8% of patients, respectively, and grade 3 anemia and thrombocytopenia were reported in 54% and 31% of patients, respectively. Fatigue was the most common non-hematologic toxicity, with 31% and 8% of patients experiencing grade 3 and 4 fatigue, respectively. Of the 13 patients, three have achieved a PR and six patients have died because of progressive disease. The weekly dosing schedule of topotecan appears to offer improved tolerability in this patient population compared with the 5-day topotecan dosing regimen. Further investigation is required to fully characterize the efficacy of single-agent topotecan as either a 5-day or a weekly bolus schedule in this patient population.

Although topotecan used as a single agent may offer limited activity, topotecan-based combinations may be attractive options. In an ongoing phase II study, patients with stage III/IV recurrent endometrial cancer were treated with topotecan 0.75 mg/m² on days 1-5 of a 21-day cycle with cisplatin 50 mg/m² on day 5 [59]. A preliminary report on the first eight patients enrolled in the study showed promising results. Of these patients, three achieved a CR and one achieved a PR. The progression-free interval was 30.3 weeks compared with the historical progression-free interval for these patients of 8.7-17.3 weeks. The median survival of these patients was 44 weeks. An additional 12 patients will be enrolled into this study. The final results of this study will help shed light on the role of topotecan in the treatment of this intractable disease.

Topotecan also has been investigated in patients with uterine papillary serous carcinoma. In a pilot study, Chambers et al. [60] treated 15 patients with topotecan 1.5 mg/m² on days 1-5 of a 21-day course for 6 cycles. Twelve patients received topotecan as front-line therapy, and three received topotecan as second-line therapy after platinum therapy failed. The median survival for these patients was >17 months, and the median disease-free survival was >10 months. With a median follow-up of 13 months, 11 (92%) of the 12 patients receiving topotecan in front-line therapy were free of disease. Of the nine patients receiving adjuvant topotecan (first-line and no gross evidence of residual disease following surgery), the median progression-free interval and survival had not been reached at a median follow-up of 24 months. One of the patients receiving topotecan as second-line therapy was free of disease at >30 months of follow-up. The most common adverse events were anemia and neutropenic fever, which were experienced by six and four patients, respectively. Fifty-three percent of patients required G-CSF and/or recombinant erythropoietin support. Results of this early trial suggest that topotecan is active in uterine papillary serous carcinoma.

Currently, the role of topotecan in treating endometrial carcinomas has not been established. However, the promising results of these early trials have led to additional trials designed to further elucidate the role of topotecan. The Florida Society of Gynecologic Oncologists continues to enroll patients with advanced, persistent, or recurrent endometrial cancers into a dose-escalating phase I/II trial investigating weekly topotecan [58]. Topotecan doses up to 4.5 mg/m²/week have been well tolerated. However, caution should be used when administering topotecan in previously irradiated patients because of potential irreversible bone marrow suppression associated with radiotherapy. Updated results from this trial and results from other trials will begin to characterize the role of topotecan in the treatment of endometrial carcinomas.

**SUMMARY**

Improvements in the early detection of cervical and uterine cancers have substantially reduced the associated mortality rates over the past decades. However, the mortality rates in patients diagnosed with advanced cervical or uterine cancer have remained unchanged over the past 25 years. Treatment of early cervical and endometrial carcinomas with hysterectomy alone or with radiotherapy is associated with a high cure rate for these patients. However, patients with advanced stages of these diseases are rarely cured. Currently, patients with advanced cervical cancer are treated with radiotherapy and cisplatin; however, most cervical cancer patients will eventually relapse. Patients with advanced-stage endometrial carcinoma are often treated with a doxorubicin/cisplatin combination regimen. However, the majority of these patients also experience recurrent disease. Thus, there is a need for improved treatment options for patients with these nonovarian gynecologic malignancies. Several new cytotoxic agents have been investigated in both diseases. Of these agents, topotecan is one of the most characterized. The unique mechanism of action of topotecan and the success of this agent in the treatment of patients with relapsed ovarian cancer make it an attractive treatment option for patients with advanced cervical and endometrial carcinomas. In early reports, topotecan has demonstrated promising antitumor activity in patients with advanced or recurrent cervical cancers. In addition, preliminary data also suggest that
topotecan is active in the treatment of endometrial adenocarcinomas and uterine papillary endometrial carcinoma. Further randomized studies will be required to fully characterize the role of topotecan, as a single agent or in combination therapy, in the treatment of gynecologic malignancies other than ovarian cancer.

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