Case Studies In Recurrent Gynecologic and Lung Cancer: Chemotherapeutic Innovations

Dear Colleague:

Ovarian cancer, the fifth leading cause of cancer death among women, poses a number of treatment challenges for oncologists. Because of an absence of symptoms in the early stages of ovarian cancer, most women present with advanced disease. Despite relatively high response rates among newly diagnosed patients to a combination of surgery and platinum-containing chemotherapy, ovarian cancer inevitably recurs. In the course of relapse, most patients develop platinum resistance, requiring treatment with second-line therapies, such as topotecan, docetaxel, gemcitabine, and etoposide. These evolving treatment strategies have shown promise in extending survival in patients with recurrent ovarian cancer. Evidence suggests that alternative dosing regimens with these agents can reduce the myelosuppression associated with them without compromising efficacy.

We are pleased to offer you the first of a 12-part series of CME newsletters, Case Studies in Recurrent Gynecologic and Lung Cancer: Chemotherapeutic Innovations. These case-based newsletters, designated for .25 CME credit each, will comprise gynecologic cancers and non-small-cell lung cancer. Presentations of patient cases and discussion of relevant treatment dilemmas and options by a distinguished faculty of oncologists are designed to update you on the latest clinical trial results and their implications for clinical practice.

This newsletter, the first in a series of eight on gynecologic cancers, presents the case of a 52-year-old restaurant manager, who, after initial treatment of stage III ovarian cancer with combination chemotherapy, experiences disease recurrence within 5 months. This case examines the appropriate choice for initial treatment, and for recurrent disease, as well as the appropriate dose and schedule for second-line therapy. The discussion of this case emphasizes practical strategies for determining effective dosing sequencing, in light of recent clinical trial data.

We hope you find this series helpful and informative, and that the discussions will assist you in incorporating this information into your clinical practice.

Sincerely,

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Patient Description
Ms. G is a 52-year-old restaurant manager who initially presented to her primary care physician with complaints of progressive abdominal bloating and early satiety of 2 months’ duration. Examination showed abdominal distention, shifting dullness, and a palpable pelvic mass. A CT scan confirmed ascites, an omental cake, and pelvic mass. Her CA-125 was 1272 U/mL (normal <35 U/mL). Surgical findings included a 22-cm omental cake, 9-cm pelvic mass arising from the right ovary, and extensive peritoneal carcinomatosis. Ms. G underwent total abdominal hysterectomy, bilateral salpingooophorectomy, transverse colectomy, and optimal debulking using an ultrasonic surgical aspirator. Residual disease consisted of several peritoneal and diaphragm nodules, all less than 1 cm. Her postoperative course was uneventful, and she now presents for further treatment options. Her CA-125 is 357 U/mL, serum creatinine is 0.9 mg/dL, and complete blood cell count is normal.

Watch Your Mail for the Next Issue!

Case Studies In Recurrent Gynecologic and Lung Cancer: Chemotherapeutic Innovations

Part 2: Recurrent Fallopian Tube Carcinoma in a 67-year-old Patient: Therapeutic Choices for Second-Line Treatment

Learning Objectives
This activity is designed for oncologists and oncologic healthcare professionals who treat patients with gynecologic or lung cancer. After completing this activity, the participant should be able to:
- Compare the efficacy and safety of available regimens for treating recurrent gynecologic and lung cancers.
- Consider the risks and benefits of extending the platinum-free interval and its impact on future responses to additional treatment regimens.
- Formulate a treatment strategy that maximizes outcomes and reduces toxicity through judicious sequencing of therapies and dosing schedules when treating patients with platinum-sensitive, recurrent gynecologic or lung cancer.
- Discuss future clinical applications, including activity and toxicity profiles, of novel combinations and schedules of chemotherapies, including topoisomerase inhibitors, alone or in combination with platinum agents, in the treatment of gynecologic and lung cancer.

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Eric K. Rowinsky, MD, has received grant/research support from GlaxoSmithKline and is a consultant for GlaxoSmithKline.

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Initial Therapy

Question 1: What are the initial treatment options for this patient after the surgical intervention?

(a) Combination therapy using carboplatin and paclitaxel
(b) Single-agent therapy using carboplatin
(c) Single-agent therapy using paclitaxel
(d) Sequential doublet or triplet therapy (clinical trials)

Discussion

(a) The preferred treatment is combination therapy with paclitaxel and carboplatin for six cycles, presently considered the standard in the United States for the treatment of ovarian cancer. However, if the patient consents to enroll in a clinical trial, the Gynecologic Oncology Group (GOG) Study 182 is ideal. This large, international phase III study compares paclitaxel plus carboplatin x eight cycles with four other experimental arms that incorporate topotecan, gemcitabine, pegylated liposomal doxorubicin, paclitaxel, and carboplatin in sequential doublet or triplet therapy. Earlier clinical trials had established that the combination of cisplatin and paclitaxel was superior to cisplatin and cyclophosphamide,1 and that the more convenient combination of carboplatin and paclitaxel was similar to cisplatin and paclitaxel.2

Combination front-line therapy is the standard, but its benefits over sequential monotherapy have been challenged by two recent studies.3,4 In one, which compared cisplatin monotherapy, paclitaxel monotherapy, or combination cisplatin/paclitaxel, superior response rates and progression-free survival were observed with both cisplatin arms (monotherapy and combination therapy). However, overall survival was equivalent for both.5 Toxicity was most favorable with the combination arm compared with the monotherapy arms. In the other study, a large phase III trial, survival with carboplatin monotherapy was comparable to carboplatin/paclitaxel and cisplatin/doxorubicin/cyclophosphamide.6 Although the designs of these two studies have been challenged, the issue of combination therapy versus sequential monotherapy for ovarian cancer remains controversial. Until further evidence becomes available, combination therapy remains the standard front-line treatment for ovarian cancer.

In the initial management of Ms. G, consolidation therapy using paclitaxel, other cytotoxic agents, or biologic agents was considered. Preliminary evidence suggests that consolidation therapy delays recurrence; however, its effect on overall survival has not been established. The GOG Study 178, in which patients responsive to front-line therapy were randomized to 3 or 12 cycles of single-agent paclitaxel consolidation therapy, was terminated early due to significantly better progression-free survival with the 12-cycle arm versus the 3-cycle arm (28 and 21 months, respectively).7 Although phase III data showing improvements in overall survival are currently unavailable, discussion of consolidation chemotherapy in this clinical setting is justified. In Ms. G’s case, the recommendation is six cycles of paclitaxel and carboplatin given every 21 days, followed by observation alone.

Case Continues

Ms. G shows a complete clinical response to combination therapy, with a CA-125 of 17 U/mL and no evidence of persistent disease by physical examination or CT scan. Five months later, she presents with clinically apparent disease, a CA-125 of 247 U/mL and an enlarged abdomen. Her CT scan reveals ascites and several 1- to 2-cm peritoneal masses in the pelvis and upper abdomen. Facing recurrent disease and a poor prognosis, Ms. G asks for additional treatment options.

Secondary Therapy

Question 2: What course of therapy would you now choose for this patient with recurrent ovarian cancer?

(a) Systemic chemotherapy
(b) Hospice care
(c) Observe patient until symptomatic
(d) Secondary cytoreductive surgery

Discussion

(a) Ovarian cancer generally recurs, and managing relapsed disease is therefore critical. Systemic chemotherapy is the correct treatment now, given Ms. G’s youth and high functional status. Phase II and phase III data have conclusively demonstrated objective response rates of 15% to 30% in patients with platinum/paclitaxel-refractory ovarian cancer.8 In incurable relapsed disease, longevity and the highest quality of life are tantamount, with primary goals being symptom-free life and chemotherapy-free intervals. Although delaying chemotherapy
until symptoms arise is one option here, Ms. G would likely develop symptoms very quickly, and delaying therapy may jeopardize the achievement of another symptom-free period. Hospice care is premature at this time, since salvage chemotherapy is likely to prolong a high quality of life (QOL).

Because of the multifocal nature of this disease recurrence and, most critically, the short disease-free interval, additional surgery is not likely to improve survival at this time. Patients who have a long disease-free interval (12–24 months), and who are relatively young and healthy, experience better results from secondary cytoreduction than with chemotherapy alone.7–10 However, in patients whose disease progresses or stabilizes during primary adjuvant chemotherapy or within 6 to 12 months, secondary surgery does not appear to improve survival.1 Ms. G’s response to systemic chemotherapy will dictate her overall disease course.

**Question 3: Which chemotherapeutic agent would you now choose?**

- a. Paclitaxel
- b. Carboplatin
- c. Combination therapy with paclitaxel and carboplatin
- d. Topotecan

**Discussion**

(d) Neither paclitaxel nor carboplatin, alone or in combination, is likely to be of benefit because of the short time. No phase III data indicate that combination therapy is more effective than monotherapy in relapsed platinum-resistant disease, ie, disease that recurs less than 6 months after induction. However, interest in combination therapy in relapsed disease has surfaced following recent data from a small phase III study of paclitaxel versus cyclophosphamide/doxorubicin/cisplatin (CAP) in platinum-sensitive relapsed disease.11 Although this study demonstrated a survival benefit with the CAP combination, the results must be critically interpreted given the fact that two large phase III studies (GOG 132 and ICON 3) could not demonstrate a survival benefit with combination therapy in first-line treatment.

Topotecan is the best agent for Ms. G at this time. This novel topoisomerase I inhibitor is not cross-resistant to taxanes and to platinum analogs. Using topotecan at this stage allows Ms. G to benefit from the drug while she can best tolerate it, and reserves other chemotherapeutic agents for later use. Topotecan has shown efficacy in treating both platinum-sensitive and platinum-resistant ovarian cancer, with response rates ranging from 13% to 33%.12,13 The issue of drug sequencing has gained much attention recently. However, no conclusive data are available to suggest how to sequence, or whether sequencing has any impact on long-term survival and QOL. Many factors require consideration at the time of relapse, and a number of agents are available, notably gemcitabine, topotecan, pegylated liposomal doxorubicin, docetaxel, afltretamine, and etoposide. Without substantial evidence to direct a sequence strategy, the clinician should consider these principles:

- Avoid early use of agents with cumulative or permanent toxicities that may prohibit future agents.
- Use more toxic agents early in the sequence, when the patient can tolerate them.
- Use agents that may potentiate the activity of future agents.

Choosing an agent, like topotecan, to increase the disease-free interval is appealing, but whether this strategy increases the chances of responding to later taxane or platinum regimens is unknown. Prolonging the platinum-free interval with non–platinum-based therapy is also appealing; however, conclusive supporting data are not yet available and the concept remains controversial.14,15

**Question 4: Which topotecan dose and schedule would you select?**

- a. 0.4 mg/m² by 24 h continuous infusion x 21 days every 28 days
- b. 2.0 mg/m² x 3 days every 21 days
- c. 4.0 mg/m² IV bolus days 1, 8, and 15 every 21 days
- d. 1.25 mg/m²/day x 5 days every 21 days
- e. Other

(d) Based on current data, 1.25 mg/m²/day x 5 days every 21 days* is the most appropriate choice for Ms. G outside of a clinical trial, although a growing body of evidence supports alternative dosing strategies, such as weekly administration. The rationale for alternative topotecan dosing is presented in Table 1.17

Daily topotecan administration at the approved dose of 1.5 mg/m²/d x 5 every 3 weeks has a high rate of hematologic toxicity and suboptimal patient convenience. Lower topotecan doses (1.25 mg/m² x 5) appear to be much better tolerated by heavily pretreated patients who have had significant prior treatment with cisplatin or carboplatin-based treatment because of renal topotecan clearance and/or hematopoietic tolerance, respectively.

Therefore, investigators are exploring weekly dosing regimens. In a phase I/II study, topotecan was administered as a weekly bolus in patients with relapsed epithelial ovarian cancer (N = 32; starting dose = 1.5 mg/m²/wk, increased by 0.5 mg/m² every 3 weeks, until dose-limiting toxicity was encountered).16 Homesley reported a maximum tolerated dose of weekly topotecan of 6 mg/m² (without the use of granulocyte colony-stimulating factor support), and suggested a dosage for phase II studies of 4 mg/m² weekly bolus; an absence of dose-limiting myelotoxicity and thrombocytopenia with weekly topotecan was observed.11 In a classic three-patient-per-cohort phase I trial, Tan et al.17 demonstrated that weekly boluses of 10 mg/m² given days 1, 8, and 15 on a 28-day cycle are not associated with dose-limiting hematologic toxicity. In another study18 (N = 23; starting dose = 4.0 mg/m², decreased 0.5 mg/m² for uncomplicated grade 3/4 toxicity and decreased 1.0 mg/m² for complicated hematologic toxicity), fewer than 5% of cycles have been complicated by grade 3/4 neutropenia or thrombocytopenia, and a 32% response rate was realized in platinum-sensitive patients. Although some of these data are preliminary, the minimal toxicity (Table 2) and favorable response rates associated with weekly topotecan make this regimen very promising.

The topotecan regimen of 2.0 mg/m² daily x 3 days for 21 days has also been studied in an attempt to diminish myelotoxicity and improve patient convenience. In studies by Brown19 and Herzog,20 a topotecan regimen of 2.5 mg/m² daily for 3 days every 21 days appears to maintain activity; however, the overall response rate in GOG data in platinum-sensitive ovarian cancer (14%) was not as favorable as earlier GOG data (33%), which used the daily x 5 regimen.21 Notably, the stabilization rate with the daily x 3 regimen was similar to the GOG daily for 5 days every 21 days regimen, but the impact on survival has yet to be determined.

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*Although positive results with good tolerability have been realized using weekly topotecan dosing regimens, it should be noted that the current recommended dose of topotecan is 1.5 mg/m² by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day 1 of a 21-day course.* Therefore, it is advisable to adhere to the recommended dosing guidelines unless a patient is enrolled in a clinical trial investigating alternative dosing regimens.
Myelotoxicity was the principal toxicity seen in these studies, and its incidence appeared to be slightly less than that seen with the traditional daily x 5 regimen. However, data from these studies are somewhat discordant, showing objective response rates ranging from 8% to 38%. Although these studies showed promising antitumor effects from prolonged administration of topotecan and a favorable toxicity profile, further evidence is needed before adopting this dosing regimen.

Summary

Ovarian cancer is typically a highly chemosensitive solid tumor in the front-line setting; however, the majority of patients eventually relapse and ultimately die of chemoresistant disease. The standard paradigm of cancer therapy is to treat until progression occurs or a disease-free status is achieved. Management of recurrent disease is often dictated by a patient’s disease-free interval. Currently, the standard treatment for disease recurring more than 6 months after front-line therapy is retreatment with a platinum agent. However, using a nonplatinum agent to extend the platinum-free interval may be beneficial to the overall course of the patient’s disease. In this patient, whose cancer has recurred less than 6 months from initial therapy, several chemotherapy options are available. Topotecan would be a good choice because Ms. G will benefit from its antitumor effects and still be functional enough to tolerate the potential toxicity of topotecan. Furthermore, the use of topotecan as an early second-line agent allows for subsequent use of other salvage agents as this patient’s disease progresses. In those patients who are treated with topotecan, alternative dosing regimens such as daily x 3 and weekly bolus therapy are emerging and appear to have lower toxicity and maintain antitumor effect.

References


Table 2. Hematologic and Nonhematologic Toxicity Associated with Weekly Topotecan Dosing

<table>
<thead>
<tr>
<th>Grade 3 Toxicity</th>
<th>Morris Cases (%)</th>
<th>Homesley Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>5 (22%)</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (4%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2 (8%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Gl</td>
<td>1 (4%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

*Evaluable patients: Morris N = 23; Homesley N = 35.
CME Instructions

To receive documentation of your participation in this 12-part CME activity (for which each newsletter equals .25 hour for a total of 3 hours of CME credit), please complete the following steps:

1. Read each newsletter carefully.
2. Complete the CME Posttest included in each of the newsletters.
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Phone ________________________________________________ Fax _________________________________________________
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Please indicate your answers below.

1. The following is/are characteristic(s) of ovarian cancer:
   a. It is generally in advanced stage when diagnosed.
   b. It is chemosensitive with high response rates to first-line chemotherapy.
   c. It is associated with high relapse rates, even after successful first-line chemotherapy.
   d. All of the above

2. Available agents considered for use in patients who have relapsed include all of the following EXCEPT:
   a. Gemcitabine
   b. Trastuzumab
   c. Topotecan
   d. Docetaxel

3. The most serious and dose-limiting toxicity associated with topotecan is:
   a. Myelosuppression
   b. Hepatotoxicity
   c. Renal failure
   d. Neuropathy

4. Phase II clinical trials of topotecan have shown promising results, both in antitumor activity and mild toxicity, with the following dosing regimen(s)
   a. 1.5 mg/m²/day x 5 days every 21 days
   b. 4.0 mg/m² IV bolus once weekly every 21 days
   c. 0.4 mg/m² by 24-hour continuous infusion x 21 days every 28 days
   d. a and b
Name ……………………………………………………………………… Degrees/Credentials …………………………………………...
Address……………………………………………………………………………………………………………………………………
City ………………………………………………………………………………… State …………… ZIP ……………………………

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1. Please rate the extent to which you achieved the learning objectives:

   - Compare the efficacy and safety of available regimens for treating recurrent gynecologic and lung cancers
     - Excellent
     - Very Good
     - Good
     - Satisfactory
     - Poor

   - Consider the risks and benefits of extending the platinum-free interval and its impact on future responses to additional treatment regimens
     - Excellent
     - Very Good
     - Good
     - Satisfactory
     - Poor

   - Formulate a treatment strategy that maximizes outcomes and reduces toxicity through judicious sequencing of therapies and dosing schedules when treating patients with platinum-sensitive, recurrent gynecologic or lung cancer
     - Excellent
     - Very Good
     - Good
     - Satisfactory
     - Poor

   - Discuss future clinical applications, including activity and toxicity profiles, of novel combinations and schedules of chemotherapies, including topoisomerase inhibitors, alone or in combination with platinum agents, in the treatment of gynecologic and lung cancer
     - Excellent
     - Very Good
     - Good
     - Satisfactory
     - Poor

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6. Please rate your interest in self-directed or distance learning in the following formats:  
   a. Audioconference       ❑❑❑
   b. Videoconference       ❑❑❑
   c. Enduring materials (audiocassettes, videotapes, monographs) ❑❑❑
   d. Internet (online discussions with experts, educational activities) ❑❑❑
   e. Multimedia (online, CD-ROM) ❑❑❑

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8. Please list topics and/or experts you would find interesting and professionally relevant for future CME activities:
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   As part of our ongoing continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our CME courses on professional practice. Please indicate your willingness to participate in such a survey:
   ❑ Yes, I would be interested in participating in a follow-up survey.
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Additional comments about this activity: ..................................................................................................................................................................................................................................
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