Dear Colleague:

Fallopian tube carcinoma is the rarest cancer of the female genital tract, with a reported incidence of 0.15% to 1.8%. Women of all ages are affected, but the disease is observed most often in women who are postmenopausal and over age 50. Unfortunately, primary fallopian tube cancer is not routinely suspected, thus delaying diagnosis and treatment. Fallopian tube cancer is diagnosed and staged with surgery, analogously to ovarian cancer. The same principles of cytoreductive surgery for ovarian cancer apply to fallopian tube cancer. Because of a strong clinical similarity between fallopian tube cancer and ovarian cancer, chemotherapy management of fallopian tube cancer mirrors that of ovarian cancer. The traditional regimen for the treatment of fallopian tube cancer has been cyclophosphamide, adriamycin, and cisplatin (CAP), although combination platinum-based chemotherapy has also shown favorable results. Newer agents, such as topotecan and pegylated liposomal doxorubicin, have shown positive results and good tolerability in the treatment of ovarian cancer, with the potential for similar outcomes in the management of recurrent fallopian tube cancer.

This newsletter, the second in a series of eight on gynecologic cancers, presents the case of a 67-year-old patient with fallopian tube carcinoma, who experienced a recurrence after 4 years of remission. The discussion of this case, which highlights the similarity of this patient’s disease management to that of someone with ovarian cancer, focuses on the most appropriate chemotherapeutic choices for second-line treatment.

We are pleased to offer you *Case Studies in Recurrent Gynecologic and Lung Cancer: Chemotherapeutic Innovations*, the second of a 12-part series of CME newsletters. These case-based newsletters, designated for .25 CME credit each, will comprise gynecologic cancers and 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.

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,

Chair

Eric K. Rowinsky, MD
Director, Clinical Research
Institute for Drug Development
Cancer Therapy and Research Center
Clinical Professor of Medicine
University of Texas Health Sciences Center
San Antonio, Texas

**Patient Description**

Ms. M is a 67-year-old retired high school principal with a history of overall good health. In 1995, she was diagnosed with stage I fallopian tube carcinoma, and underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO). She responded to treatment. There was no evidence of residual disease as determined by CT scan and by a CA-125 level that remained normal for several years. In 1999, routine laboratory work revealed a CA-125 level of 650 U/mL (normal <35 U/mL). In addition, her CT scan was compatible with carcinomatosis throughout the abdomen.

**Watch Your Mail for the Next Issue of**

Case Studies in Recurrent Gynecologic and Lung Cancer: Chemotherapeutic Innovations

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.

CME Information
Projects In Knowledge is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

This 12-part newsletter is planned and produced as an independent CME activity in accordance with the ACCME Essential Areas and Policies.

Projects In Knowledge designates this educational activity for a maximum of 3 Category 1 credits toward the AMA Physician’s Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

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), complete the newsletter posttest with a passing score of 70% or higher. Full instructions for submission are included on the newsletter posttest.

Discussion

Clinical Decision Point

Question 1: Which is the best choice for the management of fallopian tube carcinoma recurring after primary surgical resection in a patient who is chemotherapy naive?

a. Radiation therapy
b. Single or combination chemotherapy using carboplatin and/or paclitaxel
c. Surgical debulking
d. Triple-agent chemotherapy

Discussion

(b) Since Ms. M has an excellent Karnofsky performance status, the choice was made to treat her recurrent cancer with a combination of carboplatin and paclitaxel.

Primary fallopian tube carcinoma is extremely rare, and represents <1% of gynecologic malignancies. Diagnosis, staging, and treatment of fallopian tube cancer are analogous to ovarian cancer. As such, agents effective in treating ovarian cancer are also favored in fallopian tube cancer, including cisplatin or carboplatin combined with paclitaxel.

In clinical trials of cisplatin-containing chemotherapy for fallopian tube cancer, response rates ranged from 29% to 92% (80%–92% in most series). In these trials, complete response rates averaged 57%, and partial response rates averaged 24%. Carboplatin and docetaxel appear to be comparable to those containing a platinum compound plus paclitaxel in the treatment of ovarian cancer, and activity has also been reported in fallopian tube cancer.

The Gynecologic Oncology Group (GOG) has included fallopian tube cancer in some trials of ovarian cancer, including trials of intraperitoneal paclitaxel. Patients whose disease recurs >6 months after initial platinum-containing therapy are considered platinum sensitive, and are therefore generally treated with single or combination chemotherapy using either carboplatin or paclitaxel.

Ms. M is relatively young. Therefore, treating her cancer aggressively with combination therapy was optimal, although there is evidence to suggest that sequential single-agent therapy may offer similar outcomes. In an assessment of survival in ovarian cancer patients receiving cisplatin or paclitaxel alone or sequentially, complete and partial response rates were significantly lower (P < .001) in patients receiving paclitaxel monotherapy than in patients receiving cisplatin alone or cisplatin/paclitaxel sequential therapy. However, overall survival was similar in all three treatment arms, with slightly lower survival among patients who received paclitaxel monotherapy compared with the other two regimens. Combination therapy had a better toxicity profile. In this study, monotherapies were discontinued more frequently than combination therapy (cisplatin because of toxicity or patient refusal, and paclitaxel because of progression). Note that these study results pertain to the treatment of ovarian cancer, not fallopion tube cancer.

Radiotherapy is the traditional adjuvant therapy for fallopian tube cancer. It requires treatment of the whole abdomen, and has been largely abandoned in ovarian and fallopion tube cancer. In this patient, radiation is not a good choice because of toxicity. There are no current cooperative group studies using whole abdominal radiation therapy in ovarian cancer.

In a patient with diffuse carcinomatosis who has had a prior TAH/BSO, surgical debulking is of limited value. Studies on ovarian cancer provide no evidence that triple chemotherapy offers any advantage over single- or double-agent regimens. However, adjunctive therapy in early ovarian cancer, and most likely in fallopion tube cancer, can increase the disease-free survival period.

Case Continues

Ms. M. was treated every 3 weeks with carboplatin and paclitaxel, for six courses. Eight weeks following treatment, her CA-125 level decreased to 125 U/mL and the CT scan revealed fewer abdominal lesions. Her Karnofsky performance status (Table 1) remained at 100.

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<thead>
<tr>
<th>Karnofsky Performance Status Scalea</th>
<th>Specific Criteria</th>
<th>Index</th>
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<tr>
<td>General Category Description</td>
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<tr>
<td>Able to carry out normal activities; no special care required</td>
<td>Normal; no evidence of disease and no physical complaints</td>
<td>80–100</td>
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<td>Unable to work; able to live at and care for most personal needs; varying amounts of assistance needed</td>
<td>Unable to carry on normal activities or to work but able to care for self</td>
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<td>Unable to care for self; requires institutional or hospital care or equivalent; disease may be rapidly progressing</td>
<td>Disabled; requires special care and assistance</td>
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**Clinical Decision Point**

**Question 2:** Which second-line therapy would you choose for a patient with good performance status whose disease stabilized on combination therapy, carboplatin, and paclitaxel?

a. Pegylated liposomal doxorubicin
b. Topotecan
c. Carboplatin
d. Radiation therapy
e. Docetaxel

**Discussion**

(a) The therapeutic ratio favors pegylated liposomal doxorubicin (PLD).

Although no data are available on treating fallopian tube cancer with PLD, several studies have evaluated its use in ovarian cancer, which is presumed to be similar. In a phase II study of ovarian cancer patients refractory to platinum- and paclitaxel-based regimens, PLD resulted in good clinical response and survival (median overall survival, 11 months), and was well tolerated. Another study compared the efficacy and safety of PLD with topotecan in patients with epithelial ovarian carcinoma following failure of first-line, platinum-based chemotherapy. Topotecan, a topoisomerase I inhibitor, is a second-line agent developed for use in disease resistant to platinum and paclitaxel therapy. The study found no significant differences in objective response rates. In a subset analysis, PLD-treated patients who were still responsive to platinum-based chemotherapy showed statistically significant increases in survival time compared with topotecan-treated patients (2.1 years versus 1.4 years, respectively; \(P = .008\)). The platinum-refractory subgroup showed a survival trend in favor of topotecan that was not statistically significant (\(P = .733\)). Therefore, topotecan treatment is also a reasonable option. The most common side effects associated with PLD in this study were palmar-plantar erythrodysesthesia and stomatitis, which, in addition to anemia and neutropenia, are the most common side effects reported in clinical trials. Hematologic toxicity (ie, grade 3/4 neutropenia) was the most common adverse event associated with topotecan in this study. No studies have evaluated the effects of PLD in fallopian tube cancer; however, because of the similarity between these cancers, there is potential for similar effects in fallopian tube cancer. Docetaxel and carboplatin would probably not be active in a patient who has already progressed on a taxane and a platinum. However, there is not complete cross-resistance between docetaxel and paclitaxel. Treatment of the whole abdominal field with radiotherapy may later compromise treatment with chemotherapy.

**Case Continues**

After treatment with four courses of PLD, Ms. M’s CA-125 level increased to 425 U/mL and her CT scan revealed an increase in the number of intra-abdominal lesions. Because Ms. M is failing PLD therapy at this point, it is appropriate to explore different treatment options.

**Clinical Decision Point**

**Question 3:** Given the patient’s disease progression after a PLD regimen, which treatment choice would now be advised?

a. Paclitaxel
b. Docetaxel
c. Carboplatin
d. Topotecan
e. Tamoxifen

**Discussion**

(d) With the potential to extend progression-free survival and improve quality of life, agents like topotecan do not exhibit cross-reactivity with platinum-based agents or paclitaxel. Topotecan’s efficacy has been investigated in a range of tumors, and it has shown good activity as second-line therapy in ovarian cancer. Phase II trials in patients with relapsed ovarian cancer showed response rates of 14% to 25% with topotecan administered at a dose of 1.5 mg/m²/day for 5 days every 21 days. Additionally, phase III studies of topotecan in ovarian cancer demonstrated good overall response rates of 13% to 20%. Although these studies were conducted in patients with ovarian cancer, topotecan would presumably have positive results in patients with fallopian tube cancer, since these two cancers are similar. There are, however, no published data to support this. 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, and intriguing results have been observed with weekly topotecan regimens. It is advisable to adhere to the recommended dosing guidelines unless a patient is enrolled in a clinical trial investigating alternative dosing regimens. Two published studies now show the safety and efficacy of weekly bolus topotecan at doses up to 4 mg/m² in ovarian cancer patients who have had multiple other regimens and wish to continue therapy. Because this once-a-week dosing schedule was well tolerated with minimal toxicity, it is now recognized that administering topotecan weekly for 3 out of 4 weeks may be better tolerated in patients who have been heavily pretreated. This allows patients to remain on treatment for three to four cycles (months) of therapy—long enough to determine response or stabilization of disease. This has been difficult to assess in the past, as topotecan has been used primarily as second- and third-line therapy in patients with advanced ovarian cancer. Another advantage is that weekly topotecan can be combined easily with other agents. In second- and third-line ovarian cancer patients, an overall response rate of 33% was observed when weekly topotecan and weekly paclitaxel were combined.

Studies have indicated that the incidence of topotecan-associated hematologic toxicity is higher in patients who have been heavily pretreated with platinum-based regimens, which can be myelotoxic, nephrotoxic, or hepatotoxic. The risk of additional toxicity can be mitigated by reducing the topotecan dose. If complicated or prolonged grade 4 anemia, thrombocytopenia, or neutropenia develops, the topotecan dose can be reduced by 0.25 mg/m²/day.

Patients with moderate renal dysfunction, determined by creatinine clearance, should be started on a lower topotecan dose of 0.75 mg/m²/day. Early studies indicated that patients with mild renal impairment did not require a dose reduction. However, a recent multicenter study that used area under the curve to determine the optimal topotecan dose concluded that patients with mild renal impairment (creatinine clearance of 40–60 mL/min) should be started on a lower dose of 1.2 mg/m²/day.

Hepatic dysfunction alone has not been associated with a higher incidence of topotecan toxicity, and dose reductions are generally not indicated. There is evidence that topotecan can be given safely with reduced myelotoxicity and more convenience using a weekly dosing regimen. A phase II study of weekly bolus topotecan is currently being performed in patients with recurrent ovarian and peritoneal cancer (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). To date, fewer than 5% of cycles have been complicated by grade 3/4 neutropenia or thrombocytopenia, and a 32% response rate has been seen in platinum-sensitive patients.

Repeat therapy with carboplatin and paclitaxel, given in combination or as monotherapy, could be used, since Ms. M’s disease did not progress when these agents were first administered. Likewise, patients with ovarian cancer later may respond to docetaxel following paclitaxel treatment, and are not at risk for progression of paclitaxel-induced neuropathy. Although the response rate has been modest, tamoxifen has also been shown to be a reasonable therapeutic option.
option in selected ovarian cancer patients, especially those with platinum-refractory disease. Since Ms. M has not received any prior hormonal therapy, tamoxifen would also be a reasonable choice for her.

Case Continues

Following weekly topotecan (4 mg/m²) treatment for 3 weeks out of every 4 for 3 months, Ms. M remained clinically stable, with a CA-125 of 125 U/mL and a performance status of 100.

Clinical Decision Point

Question 4: What course of therapy would you recommend at this time?

a. Add a second agent.

b. Continue weekly topotecan until the CA-125 rises.

c. Stop all therapy until the CA-125 rises.

d. Add hormonal therapy.

e. Switch to a new chemotherapy agent.

Discussion

At this particular juncture, it is appropriate to keep Ms. M on topotecan therapy (given weekly for 3 out of 4 weeks) until her disease progresses or until she can no longer tolerate topotecan. Although there are no data to indicate a survival benefit to continuing any chemotherapy, topotecan has been shown to alleviate symptoms, thereby improving a patient’s quality of life.

Since Ms. M was previously treated with a combination of carboptin/paclitaxel therapy for six courses, she may have low hematologic reserves, potentially increasing the risk for developing hematologic toxicity on other regimens. In clinical trials, grade 4 neutropenia has been the predominant toxicity associated with topotecan, although two dose-escalating studies reported favorable tolerability and minimal hematologic toxicity with topotecan. Prettreatment with myelosuppressive chemotherapeutic agents or radiation therapy appears to be the most important risk factor for severe topotecan-induced myelosuppression. Carboplatin, which is known to have cumulative myelotoxic effects, is associated with the most significant risk of toxicity for patients undergoing second-line therapy with topotecan. However, any anemia and fatigue Ms. M experiences can be managed with a hematopoietic growth factor. None of the other treatment alternatives would be more efficacious for this patient at this time. Depending on this patient’s performance status and her individual preferences, either tamoxifen, hormonal therapy, a minimally toxic chemotherapy regimen, or supportive care could be the next choice for treatment if further topotecan cannot be tolerated.

Summary

Although primary fallopian tube cancer is extremely rare, it resembles ovarian cancer, and is staged and managed similarly. This patient, whose fallopian tube carcinoma was originally diagnosed 4 years before recurrence, follows the clinical course and management of an ovarian cancer patient who has a multiyear interval between initial diagnosis and recurrence. Since recurrence of her disease, Ms. M has had an indolent course for the past 3 years, and has been treated with three different therapeutic regimens. She has remained relatively stable, with a steady progression of her lesions, as assessed by CT scan. She feels well enough to go dancing with friends on a regular basis. It appears that regimens that are effective and of low toxicity have afforded Ms. M a suitable quality of life.

References


**Case Studies in Recurrent Gynecologic and Lung Cancer: Chemotherapeutic Innovations**

**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.
3. Complete the Evaluation Survey included at the end of each newsletter.
4. Mail or fax each of your completed CME Posttests and Evaluations to Projects In Knowledge, One Harmon Plaza, 6th Floor, Secaucus, NJ 07094; fax: 1-201-617-7333.*

*Successful completion for 3 hours of CME credit requires a passing score of 70% or higher on each of the 12 posttests. After you have submitted each posttest, you will be issued a CME certificate for .25 credit. If your score is lower than 70% on any individual newsletter posttest, you will be notified by mail and given an opportunity to retake that test.

Name __________________________________________________________________ Degrees/Credentials _________________

Mailing Address ___________________________________________________________________________________________________

City _____________________________________________________________________ State ________ ZIP ________________

Phone ________________________________________________ Fax _________________________________________________

E-mail _____________________________________________________________________________________________________

Please indicate your answers below.

1. Fallopian tube cancer is unlike ovarian cancer and is treated with different chemotherapeutic regimens.
   A. True  B. False

2. Definitive studies have indicated that combination chemotherapy is superior to single-agent therapy for second- and third-line treatment of fallopian tube cancer.
   A. True  B. False

3. CA-125 trends can be used to assess response to treatment in most patients with fallopian tube cancer.
   A. True  B. False

4. Topotecan given weekly 3 weeks out of 4 is less myelotoxic than the 5-day topotecan regimen.
   A. True  B. False

5. Responsive and stable disease is common in fallopian tube cancer patients who have a multiyear interval between initial therapy and recurrence.
   A. True  B. False
Case Studies in Recurrent Gynecologic and Lung Cancer: Chemotherapeutic Innovations

Name _____________________________________________________ Degrees/Credentials _______________________________
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Instructions: Please complete this survey, along with the CME Posttest, and mail or fax (both sides) to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094; fax: 201-617-7333.

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

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<td>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</td>
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<td>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</td>
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2. Please rate the overall value of this enduring material:  

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   a. Audioconference
   b. Videoconference
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7. Please tell us how long it took you to complete this newsletter: ................................................................................................................................................................................................................................................................................................................

8. Please list topics and/or experts you would find interesting and professionally relevant for future CME activities:

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9. Follow-up:
   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.
   ☐ No, I’m not interested in participating in a follow-up survey.

   Additional comments about this activity: ................................................................................................................................................................................................................................................................................................................
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