Case Studies in Recurrent Gynecologic and Lung Cancer: Chemotherapeutic Innovations

Part 4 of 12: Uterine Papillary Serous Carcinoma

Dear Colleague:

Uterine papillary serous carcinoma (UPSC), a relatively rare form of endometrial cancer, is a clinically aggressive variant of endometrial adenocarcinoma, characterized by a propensity for early myometrial invasion, metastatic spread, and a poor prognosis. Histologically, its papillary architecture bears a striking resemblance to ovarian papillary serous carcinoma. Postmenopausal bleeding is the most common presenting symptom; other clinical presentations include abdominal or pelvic pain, and abdominal or pelvic mass. Surgical staging remains the single most important prognostic factor. Subsequent therapy after primary surgery depends on prognostic factors and extent of disease. Postoperative irradiation is usually implemented in patients with myometrial spread or extraterine disease, and systemic chemotherapy is suggested for the treatment of advanced disease. Although no single adjuvant modality has emerged as preeminent in the treatment of UPSC, agents used successfully in the treatment of ovarian cancer have shown efficacy in UPSC.

This newsletter presents the case of a 74-year-old patient with UPSC of the endometrium whose disease recurs with abdominal metastasis. This case identifies the similarities between UPSC and ovarian cancer, explores reasonable chemotherapy choices and dosing schedules, and discusses treatment response measures.

We are pleased to offer you Case Studies in Recurrent Gynecologic and Lung Cancer: Chemotherapeutic Innovations, the fourth 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

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Coming soon:

Part 5: The case of a 45-year-old woman with ovarian cancer illustrates the use of CA-125 level as a marker of recurrence and progression, as well as treatment response. The case also explores strategies for sequencing chemotherapy to improve overall treatment outcomes.

Defining UPSC

Question 1: What are the histologic and clinical manifestations of UPSC?

a. The serous histology of UPSC behaves in a manner similar to endometrioid carcinoma.

b. UPSC tends to metastasize throughout the peritoneal cavity in a manner similar to ovarian cancer.

c. The papillary feature of UPSC makes it behave in an indolent fashion.

d. This type of endometrial cancer spreads via lymphatics, and not transperitoneally.

Discussion

(b) Representing 1% to 10% of endometrial carcinomas, UPSC is an aggressive variant of endometrial cancer.1,2 It is a distinct histologic subtype of endometrial cancer that appears as papillary structures with fibrovascular connective tissue cores, identical to that seen in ovarian serous carcinomas.3 Postmenopausal bleeding is the most common presenting symptom; other clinical symptoms include abdominal or pelvic mass and pain.

Unlike endometrioid carcinoma, UPSC is more likely to be discovered at an advanced stage. UPSC tends to spread transperitoneally like a serous epithelial carcinoma of the ovary, and it behaves as a high-grade lesion. Metastasis may involve the lymphatics of the myometrium, cervix, broad ligament, fallopian tubes, and ovaries, extending over the peritoneal surfaces of the pelvis and abdomen. Even small lesions can be associated with early peritoneal dissemination.

UPSC is not associated with prolonged exposure to unopposed estrogen, menstrual disorders, increased perimenopausal bleeding, obesity, or nulliparity. However, there is a tendency for women diagnosed with UPSC to be elderly, not obese, and parous.4 Furthermore, mutations in the BRCA-1 tumor suppressor gene, which predisposes to breast and ovarian cancer, have been identified in a small number of women with UPSC.5,6

The current staging system of the International Federation of Gynecology and Obstetrics is based on surgical-pathologic findings.6 Long-term survival appears to be consistently higher among patients diagnosed with early stage tumors (stage I/II),8,9 but even disease confined to the uterus is associated with a high recurrence rate (50%-80%).10

The most important prognostic feature is the presence or absence of extraperitoneal disease at initial presentation and the proportion of aggressive high-grade disease.10

According to the National Comprehensive Cancer Network (NCCN) guidelines, primary treatment of UPSC includes surgical staging, total abdominal hysterectomy and bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, cytology omentectomy, peritoneal surface biopsies, and maximal tumor debulking.11 Adjuvant therapy for stage I, grade 3 cancer includes whole abdominopelvic radiation therapy with or without vaginal brachytherapy, or chemotherapy. Ms. K received pelvic radiation, in accordance with these guidelines.

There is controversy concerning the benefits of adjuvant whole abdominal radiotherapy (WART). Some data suggest increased benefit for patients at high risk,12 but others have shown that patients with locally advanced-stage UPSC are at risk of locoregional failures and distant metastases despite WART.13,14

Choosing Chemotherapy

Question 2: Is chemotherapy an appropriate option for this patient with metastatic UPSC?

a. Yes

b. No

Discussion

(a) Chemotherapy is effective for metastatic UPSC, and regimens are similar to those used for patients with ovarian cancer because of the similarities between these two diseases.1 (Specific regimens are discussed in the next section.) Published clinical trials of adjuvant chemotherapy in patients with UPSC have principally used platinum-based combination therapy15-17 and more recently have incorporated paclitaxel.18,19
Radiation therapy is generally used to palliate symptomatic metastatic disease, because many patients with UPSC present with disease throughout the peritoneal cavity, or have recurrent disease in the upper abdomen, similar to ovarian cancer. Ms. K’s bulky metastatic disease would not be expected to respond to extended-field radiation therapy because the dose of radiation that can be delivered to the upper abdomen (generally 2500–3000 cGy) is usually insufficient to eradicate macroscopic disease. A study conducted by the Gynecologic Oncology Group (GOG) compared WART with doxorubicin/cisplatin in patients with advanced endometrial cancer, including patients with UPSC, and preliminary results favored chemotherapy with regard to progression-free and overall survival. Unfortunately, a retrospective study suggests that the recent use of chemotherapy for treating patients with UPSC has not improved survival. Tay and Ward reported outcomes among 67 patients with UPSC (all treated initially by surgery) in patients treated before and after 1990, when changes were instituted. After 1990, more patients had omentectomy and complete surgical staging, chemotherapy was more widely used, all chemotherapies were platinum-based regimens, and less radiotherapy was administered. Overall survival was 43% at 3 years and 35% at 5 years, with a median survival of 31 months. There was no significant difference in survival among those managed since 1990 compared with those managed before 1990, after adjusting for stage and spread of disease.

Case Continues

Ms. K was interested in receiving chemotherapy. She understood that chemotherapy was most likely not curative and that the goal is to delay progression of her disease, prolong her life, and maintain quality of life.

Chemotherapy Options

**Question 3: Which chemotherapeutic agents should be considered for Ms. K?**

a. Doxorubicin
b. Platinum- and taxane-based chemotherapy
c. A single alkylating agent
d. Topotecan
e. Platinum chemotherapy, used only as a radiation sensitizer

(b) NCCN guidelines list a number of chemotherapy regimens for treating advanced or recurrent endometrial cancers. Responses to single-agent therapy with doxorubicin, cisplatin, carboplatin, and paclitaxel range from 21% to 36%, but no improvement in quality of life or survival has been seen. Combination therapy using doxorubicin plus either carboplatin or cisplatin, with or without cyclophosphamide has resulted in better responses, up to 81%, but the response is relatively short-lived. Other combinations are also being investigated, including cisplatin/paclitaxel and doxorubicin/cisplatin/paclitaxel.

One would expect that regimens that are active in treating ovarian serous carcinoma should have similar activity in UPSC, because the two tumors are chemosensitive and have similar behavior. However, mixed results have been reported in small studies of platinum/doxorubicin/cyclophosphamide regimens in UPSC. More encouraging results have been reported in small case series and case reports using paclitaxel, either alone or in combination with platinum agents.

Ramondetta et al reported a 77% objective response rate to paclitaxel among women with stage III or IV or recurrent UPSC, with a median time to progression of 7.3 months. A small retrospective series of UPSC patients receiving adjuvant therapy with paclitaxel plus a platinum agent found a median progression-free interval of 30 months. Objective response was also found in 8 of 9 patients with residual disease after surgery, with a median progression free interval of 13 months. Of 11 patients treated for recurrent disease, objective response occurred in 7 (64%), with a median progression-free interval of 9 months. A phase II study of paclitaxel and carboplatin reported response rates of 60% in primary UPSC patients and 50% in UPSC patients with recurrent disease.

Topotecan is not an established agent for endometrial cancer, but is being investigated with some promising results, particularly in combination regimens. A phase I/II study presented at the 2002 American Society of Clinical Oncology meeting indicates that weekly bolus intravenous topotecan (2.5–4.5 mg/m²) is active in patients with advanced, recurrent, metastatic endometrial cancer, producing partial responses in 23% (3/13). A preliminary report of an ongoing phase II study found that a 5-day regimen of topotecan (0.75 mg/m²) with cisplatin (50 mg/m²) on day 5 produced response in four of eight patients, with a 30-week progression-free interval.

Since topotecan is also used to treat relapsed ovarian cancer, it may be appropriate for patients with relapsed UPSC, just as the primary chemotherapy used for UPSC is comparable to that of epithelial ovarian cancer. A pilot study of six cycles of topotecan (1.5 mg/m²) on days 1 through 5, every 21 days in 15 patients with UPSC found a median survival of >17 months and median disease-free survival >10 months. At a median of 13 months, 92% (11/12) of those who received topotecan as first-line therapy were disease free. Thus, it appears that topotecan is active in UPSC and warrants further investigation as a single agent in combination therapy.

There has been no role for radiosensitization in the treatment of this disease by any agent, including cisplatin.

Case Continues

On June 28, 2002, Ms. K began treatment with carboplatin (AUC of 5) and paclitaxel (175 mg/m²) given intravenously every 3 weeks as an outpatient for six cycles. She started treatment with a CA-125 of 138 U/mL. Ms. K tolerated therapy well and remained active during her treatment.

The optimal chemotherapy schedule for UPSC has not been clearly established. It appears logical that dosing schedules used for the treatment of primary and recurrent ovarian cancer could also be employed in the treatment of UPSC, taking into account patient convenience and effect on quality of life.

Monitoring Response

**Question 4: How would you measure response to treatment in this patient?**

a. Serum markers
b. Improvement in quality-of-life indicators
c. Disease status in the upper abdomen, using serial scans (eg, CT scan)
d. All of the above
e. Response cannot be accurately assessed

Discussion

Ms. K was monitored with abdominal/pelvic examinations every treatment cycle, as well as measurements of CA-125, in a manner identical to the monitoring of a patient receiving this adjuvant treatment for epithelial ovarian cancer. Her quality of life during treatment was also taken into consideration.
Ms. K has measurable disease in the upper abdomen, which can be followed throughout the course of treatment with the aid of CT scans. As in ovarian cancer, the serum CA-125 level in UPSC may correlate well with clinical course, thus serving as an indicator of response to chemotherapy or disease progression. Since Ms. K exhibited elevated CA-125 levels prior to chemotherapy, CA-125 may serve as a useful serum marker in assessing her treatment response. Although not necessarily an objective measure of clinical factors, quality-of-life indicators would be valuable in assessing the patient’s overall status.

**Final Outcome**

Ms. K showed an objective, complete clinical response after three cycles of carboplatin/paclitaxel, which was followed by three more cycles. Her CA-125 levels normalized by the second chemotherapy cycle and remained normal thereafter. Following completion of the six cycles, she was clinically free of disease, with a normal CT scan. She has received ongoing monitoring as she would have for recurrent ovarian cancer.

**Summary**

Management of recurrent, metastatic papillary serous carcinoma of the endometrium parallels that of serous ovarian cancer, since these two types are similar histologically and clinically. Although clinical trials evaluating adjuvant chemotherapy in UPSC are somewhat limited, and optimal dosing schedules have yet to be determined, treatment of UPSC with agents that have shown efficacy in ovarian cancer (i.e., taxanes with or without platinum-based chemotherapy) seems logical. Indeed, this patient’s cancer showed good chemosensitivity, and she was monitored in a manner similar to ovarian cancer. Newer agents such as topotecan are being studied in the treatment of UPSC.

**References**


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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Please indicate your answers below.

1. UPSC is low-grade and has an indolent growth behavior.
   - True  ✗ False

2. UPSC is more similar to serous ovarian carcinomas than to endometrioid carcinoma.
   - True  ✗ False

3. Chemotherapy for metastatic UPSC should be essentially the same as that for metastatic ovarian cancer.
   - True  ✗ False

4. Taxanes with or without platinum-based therapy have shown encouraging results in case reports and small series of patients with UPSC.
   - True  ✗ False

5. Unlike in ovarian cancer, CA-125 does not correlate with clinical course or disease progression in UPSC.
   - True  ✗ False

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Part 4 of 12
**Case Studies in Recurrent Gynecologic and Lung Cancer:**
*Chemotherapeutic Innovations*

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   - 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

2. Please rate the overall value of this enduring material:

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   If you “Disagree” or “Strongly Disagree,” why?

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6. Please rate your interest in self-directed or distance learning in the following formats:  
   - Very Interested
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7. Please tell us how long it took you to complete this newsletter: ............................................................

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