Epithelial Ovarian Cancer

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INTRODUCTION

Ovarian cancer remains the leading cause of death among women with gynecologic malignancies and the fifth leading cause of cancer mortality in US women. According to the American Cancer Society, there will be an estimated 22,430 new cases of ovarian cancer in 2007, with approximately 15,280 deaths. This case-based review will discuss the clinical evaluation and management of patients with epithelial ovarian cancer, which comprises the majority of ovarian cancer cases.

ETIOLOGY AND RISK FACTORS

Epithelial ovarian cancer is thought to derive from malignant transformation of the ovarian surface, although the exact cell of origin is unknown. Nulliparity appears to increase the risk for developing ovarian cancer, presumably due to increased trauma and repair to the ovarian epithelium caused by uninterrupted cycles of ovulation. In contrast, oral contraceptive use, an increased number of pregnancies, and breastfeeding have all been shown to reduce ovarian cancer risk. Tubal ligation has also been correlated with a reduced risk of ovarian cancer, although the exact mechanism is unknown. Anecdotal reports have suggested a link between infertility treatment and ovarian cancer, but subsequent studies have not confirmed this correlation.

The most important risk factor for developing ovarian cancer is family history of the disease. Women with 1 affected relative have an estimated lifetime risk of 5% for developing ovarian cancer, and women with 2 affected relatives have an estimated risk of 7%, whereas the estimated risk for the US general population is 1.4% to 1.8%. In women who have at least 2 first-degree relatives diagnosed with hereditary epithelial ovarian cancer, the lifetime risk for developing ovarian cancer ranges from 25% to 50%. Overall, hereditary ovarian cancer syndromes may account for approximately 10% to 15% of all cases. Several mutations are associated with familial ovarian cancer and account for most cases. The best characterized involves germline mutation in the BRCA genes. Women carrying a BRCA1 germline mutation have an estimated lifetime risk of ovarian cancer between 16% and 62%, whereas the lifetime risk for women with a BRCA2 germline mutation is between 10% and 20%. Some studies have suggested that ovarian cancers occurring in BRCA carriers have a better prognosis, although stage and tumor histopathology appear to be similar to that of the general population. Additionally, mutations in the DNA mismatch repair genes MSH2 and MLH1 are associated with Lynch syndrome II. Carriers of these germline mutations are most likely to develop colorectal cancer or endometrial cancer but also have an elevated risk of ovarian cancer, with a lifetime risk estimated to be 9%.

CLINICAL EVALUATION

CASE PRESENTATION

A 53-year-old woman with no significant family or past medical history presents to the emergency department with significant epigastric and abdominal pain. The patient presented to her primary care physician 1 month prior with a 2-day history of lower abdominal discomfort. Physical examination was unremarkable, and she was treated for a presumed urinary tract infection. Subsequently, the patient developed significant epigastric as well as worsening lower abdominal pain. The current physical examination is unrevealing, and standard laboratory studies are normal. Computed tomography (CT) of the abdomen reveals an ill-defined soft tissue density replacing much of the omentum.

- What are the symptoms and signs of epithelial ovarian cancer?

CLINICAL FEATURES

The median age of patients at diagnosis is 60 years, although women with a hereditary cause of ovarian cancer usually develop disease earlier. Symptoms associated with ovarian cancer include abdominal discomfort, bloating, constipation, indigestion, and fatigue. A retrospective survey suggests that these symptoms may occur in up to 95% of patients prior to diagnosis, but early diagnosis remains difficult due
to their nonspecific nature. Occasionally, patients can present with acute symptoms due to ovarian rupture or torsion but this is unusual. Pelvic examination may reveal a palpable adnexal mass. Other physical findings may include evidence of ascites or a pleural effusion. Less commonly, ovarian cancer may be associated with several paraneoplastic syndromes. The sign of Leser-Trelat, a rare phenomenon characterized by a sudden eruption of pruritic seborrheic keratoses, has been reported. Other paraneoplastic syndromes associated with epithelial ovarian cancer include humorally mediated hypercalcemia of malignancy (associated with clear-cell ovarian carcinomas) and subacute cerebellar degeneration. Trélat’s syndrome, a superficial migratory thrombophlebitis, has also been associated with ovarian cancer.

- What diagnostic studies should be performed for patients with suspected ovarian cancer?

**DIAGNOSTIC STUDIES**

In women with suspected ovarian cancer, transvaginal ultrasonography is typically the most informative diagnostic test. Features associated with malignancy include presence of a complex ovarian cyst with both solid and cystic components, the presence of septations, evidence of ascites, or detectable peritoneal masses or enlarged lymph nodes. Other malignancies that may metastasize to the ovary must be considered. Signet-ring cell neoplasms, often from primary gastric carcinomas, can metastasize to the ovaries bilaterally, forming Krukenberg tumors. Other primary tumors that may have ovarian metastases include colorectal, breast, gall-bladder, and appendiceal cancers. Colonoscopy or esophagogastroduodenoscopy can be performed if a gastrointestinal malignancy is suspected. Additional imaging studies, (e.g., CT of the abdomen and pelvis) may also be informative and help guide surgery. Standard laboratory studies are often nondiagnostic. However, serum cancer antigen (CA)-125 levels should be measured in any woman with suspected ovarian cancer.

**CASE CONTINUED**

Pelvic examination of the patient reveals a small palpable right adnexal mass. Esophagogastroduodenoscopy and colonoscopy are unrevealing. The CA-125 level is measured at 5822 U/mL.

- What is the significance of the CA-125 level?

CA-125 levels have been shown to be elevated in approximately 80% of women with advanced disease, but an elevated level is not by itself sufficient to confirm the diagnosis of ovarian cancer. CA-125 levels can be elevated with other malignancies (e.g., breast and lung cancer) as well as in benign conditions (e.g., endometriosis, uterine leiomyoma, pelvic inflammatory disease). Approximately 1% of healthy women have an elevated CA-125 level and levels can fluctuate with the menstrual cycle. However, a CA-125 level that exceeds 65 U/mL in a postmenopausal woman with an abdominal or pelvic mass should raise concern for possible ovarian cancer.

- What is the next appropriate step in the evaluation and initial management of a patient with suspected ovarian cancer?

**LAPAROTOMY AND CYTOREDUCTIVE SURGERY**

For women with suspected ovarian cancer based upon initial evaluation, an exploratory laparotomy should be performed to confirm the diagnosis pathologically as well as to obtain appropriate staging data and perform optimal cytoreduction. If an ovarian malignancy is suspected preoperatively or found intraoperatively, a gynecologic oncologist should be consulted, as some studies have suggested that patients are more likely to receive optimal cytoreduction when the operation is performed by a gynecologic oncologist. Preoperative evaluation may also include an abdominopelvic CT scan to assess for sites of metastasis and aid the surgeon in planning the procedure.

Cytoreductive surgery has played an important role in the management of advanced ovarian cancer since Griffiths demonstrated that an inverse relationship existed between overall survival (OS) and residual tumor size. Bristow et al recently performed a meta-analysis that reviewed 81 cohorts of patients with stage III or IV disease from clinical trials conducted between 1989 and 1998. The results of the analysis suggested that there was an approximate 5.5% improvement in the length of OS for every 10% increase in the proportion of patients achieving maximal cytoreduction (defined as residual disease ≤ 3 cm in maximal dimension). The exact degree of debulking required to classify a cytoreductive procedure as “optimal” varies in the literature. A 2001 survey of gynecologic oncologists revealed that 12% defined optimal reduction as no residual disease, 13.7% used a 5-mm minimum threshold, 60.8% used a 1-cm threshold, and 12.6% used a 1.5- to 2-cm threshold. The National Comprehensive Cancer Network (NCCN) ovarian cancer treatment guidelines states that optimal cytoreduction has been achieved if there is no single focus of residual disease measuring more than 1 cm in maximum tumor diameter.

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**Table 1. AJCC/FIGO Staging for Ovarian Carcinoma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor limited to ovaries (one or both)</td>
</tr>
<tr>
<td>IA</td>
<td>Tumor limited to one ovary; capsule intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings$^a$</td>
</tr>
<tr>
<td>IB</td>
<td>Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>IC</td>
<td>Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>II</td>
<td>Tumor involves one or both ovaries with pelvic extension and/or implants</td>
</tr>
<tr>
<td>IIA</td>
<td>Extension and/or implants on uterus and/or tube(s). No malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>IIB</td>
<td>Extension to and/or implants on other pelvic tissues. No malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>IIC</td>
<td>Pelvic extension and/or implants (T2a or T2b) with malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>III</td>
<td>Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis</td>
</tr>
<tr>
<td>IIIA</td>
<td>Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor)</td>
</tr>
<tr>
<td>IIIB</td>
<td>Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>IIIC</td>
<td>Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastasis (excludes peritoneal metastasis)</td>
</tr>
</tbody>
</table>

$^a$The presence of non-malignant ascites is not classified. The presence of ascites does not affect staging unless malignant cells are present.

**STAGING**

Surgery plays a critical role in assessing disease stage. Typically, patients undergo total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Any free fluid encountered as well as washings of the peritoneal cavity are collected and sent for cytologic evaluation. Biopsy specimens are taken from the peritoneal surfaces (including the diaphragmatic surfaces); samples may also be taken from the para-aortic and pelvic lymph nodes. Staging is performed using the American Joint Committee on Cancer and International Federation of Gynecologic Oncologists (FIGO) joint staging system (Table 1).

**MANAGEMENT**

**CASE CONTINUED**

Based upon the clinical findings, the patient undergoes exploratory laparotomy. Intraoperatively, diffuse infiltration of the omentum is noted, with an overall tumor size of approximately 25 cm. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy are performed. At the conclusion of surgery, no residual disease can be visualized. Pathology from the collected specimens reveals papillary serous carcinoma of the ovary, involving both ovaries and the omentum. Peritoneal washings are positive for malignant cells. Given these findings, the patient’s disease is staged as IIC.

- What are the treatment options for early-stage ovarian cancer?

Disease stage is an important factor in determining prognosis and selecting treatment for ovarian carcinoma. Early-stage (stage I or II) disease is associated with a significantly better prognosis, with 5-year survival ranging from approximately 65% to more than 90%. In contrast, 5-year survival for stage III and stage IV disease is estimated to be just under 50% and less than 20%, respectively (Table 2). However, there is a significant risk of recurrence even for patients diagnosed with early-stage disease, and most patients should receive adjuvant chemotherapy following surgical resection.

**EARLY-STAGE DISEASE**

**Observation**

The NCCN guidelines currently recommend that patients with grade 1 stage IA or IB disease undergo observation only. Patients with grade 2 stage IA or IB disease may also undergo observation.

**Adjuvant Systemic Chemotherapy**

Retrospective studies have suggested a beneficial effect of platinum-based adjuvant therapy for high-risk early-stage disease, and several reviews have also advocated this approach. Two phase III trials have demonstrated benefit using platinum-based regimens for adjuvant chemotherapy. The ACTION trial enrolled 448 women with high-risk, early-stage disease (FIGO stages IA–IB, grade 2–3, all stage IC and IIA disease, and all stages I–IIB with a clear-cell component). Following cytoreductive surgery, patients were randomized to either observation or treatment with between 4 and 6 cycles of platinum-based therapy. After a median follow-up of 5.5 years, there was a statistically significant improvement
in recurrence-free survival in the arm receiving adjuvant treatment (hazard ratio [HR], 0.65; \( P = 0.02 \)). Despite a trend favoring the treatment arm, there was no statistically significant difference in OS (HR, 0.69; \( P = 0.10 \)). However, a subset of patients in whom optimal debulking was not achieved also demonstrated a statistically significant improvement in both OS and recurrence-free survival with adjuvant chemotherapy. The ICON1 trial\(^1\) enrolled 477 women with early-stage disease patients regardless of tumor grade. Patients were treated with 6 cycles of a platinum-containing regimen. After a median follow-up of 51 months, a statistically significant improvement in both OS (HR, 0.66; \( P = 0.03 \)) and recurrence-free survival (HR, 0.45; \( P = 0.03 \)) was observed. A combined analysis of these 2 largest international studies suggested a significant benefit in 5-year OS in patients with higher-risk early-stage disease who are treated with adjuvant therapy (74\% versus 82\%, respectively).\(^2\) At this time, the NCCN guidelines recommend that patients with stage IC disease of any grade to all categories of stage II disease undergo adjuvant chemotherapy using a combination platinum/taxane regimen.\(^3\) These guidelines also state that this option can be considered for patients with grade 2 stage IA or IB disease.

Additional studies concerning adjuvant chemotherapy in early-stage disease have addressed the question of how many cycles of platinum-based therapy should be administered. The Gynecologic Oncology Group (GOG) conducted a randomized phase III trial that enrolled 427 patients who received either 3 or 6 cycles of adjuvant carboplatin and paclitaxel.\(^4\) These results indicated a trend towards a lowered recurrence risk with 6 cycles of treatment (HR, 0.761; \( P = 0.18 \)). No difference in OS was observed. Adjuvant radiation therapy has also been investigated, but few randomized trials are available and its usage in adjuvant therapy in ovarian cancer is less commonly practiced.\(^2\)

- **What are the treatment options for advanced-stage ovarian cancer?**

## ADVANCED-STAGE DISEASE

### Intraperitoneal Chemotherapy

Most patients with ovarian cancer will have advanced (stage III or IV) disease at the time of diagnosis. Until recently, intravenous (IV) chemotherapy with a platinum- and taxane-based regimen was considered the standard of care for advanced-stage disease.\(^2\) Three US phase III clinical trials have assessed the efficacy of intraperitoneal (IP) administration of chemotherapeutic agents to patient with optimally debulked stage III ovarian cancer, based on the theory that regional delivery of cytotoxic drugs directly into the peritoneal cavity would result in higher local concentrations than can be safely reached with systemic IV chemotherapy alone. Alberts et al\(^5\) randomized 654 patients with optimally debulked disease (defined as no residual disease > 2 cm) to receive either IV cyclophosphamide and cisplatin or IV cyclophosphamide and IP cisplatin. An OS benefit was observed in the IV/IP arm, with a median survival of 49 months as compared with 41 months in the IV arm (\( P = 0.02 \)). However, the benefit of IP cisplatin was questioned because paclitaxel was not given as part of either regimen. Markman et al\(^6\) randomized 523 patients with optimally debulked disease (defined as no residual disease > 1 cm) to a regimen of IV cisplatin and paclitaxel or a regimen of IV carboplatin, followed by IP cisplatin and paclitaxel. A statistically significant longer progression-free survival (PFS) was associated with the use of IP therapy (27.9 mo) as compared with IV therapy (22.2 mo; \( P = 0.01 \)). Although the OS in the IP arm was longer than in the IV arm (63.2 versus 52.2 mo), this difference did not achieve statistical significance. Furthermore, the IP regimen resulted in significant patient toxicities. Critics also argued that patients in the IP arm received an increased dose of chemotherapy due to the addition of IV carboplatin, and the overall benefit of IP chemotherapy in this setting was felt to still be unclear. In the GOG 172 trial,\(^7\) 415 patients with optimally debulked ovarian cancer (defined as no residual disease > 1 cm) were randomized to receive either IV paclitaxel on day 1, followed by IV cisplatin on day 2; or IV paclitaxel on day 1, IP cisplatin on day 2, and IP paclitaxel (60 mg/m\(^2\)) on day 8. The OS was 65.6 months in the IV/IP arm versus 49.7 months in

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**Table 2. Survival by FIGO Stage**

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th>1-Year Survival (%)</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>632</td>
<td>98.4</td>
<td>89.6</td>
</tr>
<tr>
<td>Ib</td>
<td>69</td>
<td>100</td>
<td>86.1</td>
</tr>
<tr>
<td>Ic</td>
<td>663</td>
<td>96.3</td>
<td>83.4</td>
</tr>
<tr>
<td>Ila</td>
<td>72</td>
<td>93</td>
<td>70.7</td>
</tr>
<tr>
<td>Ilb</td>
<td>93</td>
<td>93.4</td>
<td>65.5</td>
</tr>
<tr>
<td>llc</td>
<td>241</td>
<td>93.6</td>
<td>71.4</td>
</tr>
<tr>
<td>llad</td>
<td>128</td>
<td>88.1</td>
<td>46.7</td>
</tr>
<tr>
<td>llb</td>
<td>271</td>
<td>85.7</td>
<td>41.5</td>
</tr>
<tr>
<td>llc</td>
<td>2030</td>
<td>84.8</td>
<td>32.5</td>
</tr>
<tr>
<td>IV</td>
<td>626</td>
<td>72.4</td>
<td>18.6</td>
</tr>
</tbody>
</table>


FIGO = International Federation of Gynecologic Oncologists.
the IV arm (P = 0.03). This survival benefit was observed despite only a 42% completion rate of all 6 cycles of IP-based chemotherapy, with most patients transitioning to IV platinum/taxane-based chemotherapy to complete the full 6 cycles. Based upon this study, the National Cancer Institute announced that women with optimally debulked stage III ovarian cancer should be counseled about the clinical benefit associated with a combined regimen of IV and IP chemotherapy.57

Despite the outcomes of the these phase III trials, controversy remains over the role of IP chemotherapy as first-line treatment for optimally debulked advanced ovarian cancer. An editorial written after the publication of GOG 172 argued that IP chemotherapy in ovarian cancer should remain experimental, claiming that the statistical evidence for OS in the trial remained borderline and citing the significant toxicity of IP chemotherapy.58 However, a recent meta-analysis of all trials comparing IP and IV chemotherapy demonstrated a survival benefit in favor of the IP regimens.59 Based upon the evidence currently available and the survival benefit observed with IP chemotherapy, IP chemotherapy should be considered for patients with optimally debulked stage III disease.60 Although toxicities do exist with IP chemotherapy, progress has also been made with supportive care in oncology, which includes improved antiemetics and use of growth factor. Currently, clinical trials are enrolling patients to assess the efficacy of other agents administered intraperitoneally (eg, carboplatin) as well as to evaluate the side effects associated with IP chemotherapy.

**Intravenous Chemotherapy**

For patients who have suboptimally debulked disease (residual cancer > 1 cm), are poor candidates for IP therapy, and/or decline IP treatment, IV chemotherapy remains the treatment of choice. In 1996, McGuire et al60 established the superiority of combined platinum and paclitaxel for systemic treatment of advanced ovarian cancer. In this study, 410 patients with suboptimally debulked (residual disease > 1 cm) stage III or IV disease were randomized to receive either IV cisplatin and cyclophosphamide or IV cisplatin and paclitaxel. Response rates were significantly better in the cisplatin/paclitaxel arm (73% versus 60%; P = 0.01), and OS was significantly longer in the cisplatin/paclitaxel arm (38 versus 24 mo; P < 0.001). A second randomized phase III study has confirmed these results.61 Several randomized trials have subsequently demonstrated that carboplatin can be substituted for cisplatin with equal efficacy.62–64 Myelosuppression occurred more frequently in patients treated with carboplatin, whereas neurotoxicity, ototoxicity, and nephrotoxicity occurred more frequently with cisplatin. Overall, carboplatin is less toxic than cisplatin. Based on these results, an IV carboplatin-based regimen including paclitaxel was considered to be the standard of care for systemic chemotherapy for advanced ovarian cancer prior to the publication of GOG 172.64 The SCOTROC study65 has suggested that an alternative regimen of docetaxel and carboplatin appears to be similar to that of paclitaxel and carboplatin in terms of survival. Combination docetaxel and carboplatin caused significantly more grade 3/4 myelosuppression (94% versus 84%; P < 0.001) but less grade 2 or higher neurotoxicity (11% versus 30%; P < 0.001) than combination paclitaxel and carboplatin.

As new cytotoxic agents have become available, the benefit of adding additional drugs to the carboplatin/paclitaxel regimen is being tested. A recent international 5-arm randomized controlled trial accruing over 4000 patients was presented at the American Society of Clinical Oncology annual meeting in 2006. At this time, no statistical difference in PFS has been demonstrated among the following IV regimens: standard carboplatin and paclitaxel; carboplatin, paclitaxel, and gemcitabine; carboplatin, paclitaxel, and pegylated liposomal doxorubicin (PLD); carboplatin and topotecan; and carboplatin and gemcitabine.66

- **Is there a role for neoadjuvant chemotherapy in patients with unresectable tumors?**

**Neoadjuvant Chemotherapy and Secondary Surgical Cytoreduction**

For patients who are unable to undergo debulking surgery because of the morbidity and possible mortality of the surgery or because an attempt at debulking has been made but failed, neoadjuvant chemotherapy can be considered for disease palliation and cytoreduction that may allow for possible future surgery. In 1 study, patients with suboptimally debulked ovarian cancer were randomized to receive either 6 cycles of chemotherapy with cisplatin and cyclophosphamide alone or 3 cycles of initial chemotherapy with cisplatin and cyclophosphamide, followed by interval debulking surgery and an additional 3 cycles of chemotherapy.67 Survival was improved by 6 months in patients who received interval debulking surgery (26 versus 20 mo; P = 0.012). However, GOG performed a similar study in which all surgeries were performed by gynecologic oncology surgeons. No improvements in either OS or disease-free survival among patients randomized to interval cytoreduction or to no surgery were observed.66 Currently, there are no definitive data that clearly demonstrate a survival benefit to this approach.
CASE CONTINUED

The patient is treated with 6 cycles of combined IP/IV chemotherapy with cisplatin and paclitaxel per the GOG 172 protocol. Postoperatively, the CA-125 level is 132 U/mL. After the completion of chemotherapy, the CA-125 level is 7 U/mL.

- Is there a role for continued maintenance chemotherapy?

MAINTENANCE CHEMOTHERAPY

Maintenance chemotherapy has been studied as a way to possibly delay disease recurrence and prolong OS in patients who achieve remission following primary treatment. In a phase III trial, 277 patients with advanced ovarian cancer who had achieved clinical remission following first-line chemotherapy were randomized to receive maintenance therapy with either 3 or 12 cycles of IV paclitaxel given once monthly.\(^{49}\) Results demonstrated longer PFS in patients receiving 3 cycle of single-agent paclitaxel (28 mo) as compared with patients receiving 12 cycles (21 mo; \(P = 0.0035\)), but there were no differences in OS. GOG is currently actively enrolling patients to a study randomizing women in clinical remission to 3 possible treatments: (1) placebo; (2) paclitaxel once monthly for 12 months; or (3) paclitaxel poliglumex, a novel formulation of paclitaxel, once monthly for 12 months.\(^{70}\) The results of this study will help further define the benefits, if any, of maintenance chemotherapy.

- How should the patient be monitored for disease recurrence?

SURVEILLANCE

For patients who achieve complete remission following adjuvant chemotherapy, surveillance typically occurs every 3 months and consists of history, physical examination (including a pelvic examination), and monitoring of CA-125 levels. One study that examined the correlation between CA-125 levels and disease progression found that CA-125 levels are elevated in 73% of patients at the time of progression, with elevation of CA-125 levels occurring before clinical progression in 63% of all patients.\(^{71}\) In patients who had elevated CA-125 levels before clinical progression, the median lag time to progression was 4.5 months (range, 0.5–29.5 mo). The Gynaecologic Cancer Intergroup (GCIG) has proposed a set of criteria, based upon the CA-125 level in conjunction with standard RECIST (Response Evaluation Criteria in Solid Tumors) criteria, to evaluate clinical response and progression in clinical trials conducted by its participating groups.\(^{72}\) Specifically, the GCIG/RECIST criteria for disease response is a 50% reduction in CA-125 levels that is maintained for 28 days. The GCIG/RECIST criteria for disease progression are dependent on the patient’s CA-125 level prior to treatment. For patients with an initially elevated CA-125 level that normalized following treatment or for patients who initially had a normal CA-125 level, progression is defined as a CA-125 level 2 times greater than the upper limit of normal on 2 occasions separated by at least 1 week. For patients with an initially elevated CA-125 that did not normalize following treatment, progression is defined as a CA-125 2 times greater than the nadir following treatment. In patients with suspected recurrence, a CT scan should also be considered to assess for the presence of visible disease. However, the sensitivity of CT in some studies has been shown to be as low as 40%.\(^{73}\)

CASE CONTINUED

The patient continues with surveillance visits conducted every 3 months. Approximately 15 months after initially completing chemotherapy, the CA-125 level is measured at 93 U/mL. The result of a repeat CA-125 assay performed 1 week later is 108 U/mL. On physical examination, no abnormalities are noted, and the patient is asymptomatic.

- How should the patient’s recurrence be managed?

RECURRENT DISEASE

The optimal timing of initiation of salvage therapy for recurrent ovarian cancer remains somewhat unclear. Because monitoring CA-125 levels closely is a part of routine surveillance in the United States, disease recurrence is often diagnosed at a time when the patient is still asymptomatic. Since the goal of chemotherapy in recurrent disease is palliative, some experts have proposed that treatment can be deferred until the patient becomes symptomatic.\(^{2}\) An alternative perspective argues that small volume disease may respond better to early treatment and that treatment should be initiated at the time of recurrence, regardless of the bulk of cancer. Currently, there are no data to support the superiority of either approach. Two trials (GOG 198 and Medical Research Council OV05/EORTC 55955) are currently investigating whether there is increased benefit with initiating treatment at the time of asymptomatic recurrence.

Predicting Response Rate

The treatment-free interval (TFI) following completion of initial therapy is one of the most important predictors of outcome and response to further treatment. A retrospective analysis of 72 patients initially treated with a platinum-based regimen demonstrated that response
rates to repeat platinum-based therapy was dependent on the TFI, with response rates of 27% at a TFI of 5 to 12 months, 33% at 13 to 24 months, and 59% at greater than 24 months.\cite{74} Patients who had a TFI of greater than 24 months and had not received additional treatment had a 77% response rate and a 32% surgical complete response rate.\cite{74} Given the importance of the TFI in predicting response, the GOG stratifies patients with recurrent disease in 1 of 3 categories: (1) platinum-resistant disease, defined as a TFI of less than 6 months following platinum-based therapy; (2) platinum-refractory disease, defined as progression of cancer during platinum-based therapy; and (3) platinum-sensitive disease, defined as a TFI of greater than 6 months after a platinum-based regimen. It is important to note that the TFI typically shortens with each subsequent treatment with platinum,\cite{75} eventually evolving into platinum-resistant disease with decreased overall response rates to chemotherapy, even in patients with initially platinum-sensitive disease at recurrence.

- What are the treatment options for recurrent platinum-sensitive disease?

**Platinum-Sensitive Disease**

**Single-agent therapy.** The US Food and Drug Administration (FDA) has approved the use of cisplatin and carboplatin for single-agent treatment of recurrent ovarian cancer. Response rate to these agents as single therapy in platinum-sensitive disease is up to 50%,\cite{76,77} and the degree of response depends on the length of the platinum-free interval (TFI) and whether the patient is primarily platinum-sensitive. Even for patients who have developed platinum-resistant disease, it is possible to have some reversal of the platinum resistance if the PFI is greater than 12 months.\cite{78} Cisplatin and carboplatin appear to have equivalent response rates in the recurrent setting, but their toxicity profiles differ. Nonplatinum single agents have also been studied in the setting of platinum-sensitive disease. Single-agent paclitaxel, topotecan, and PLD have all demonstrated some efficacy in the setting of recurrent platinum-sensitive disease, with response rates between 20% and 30% in phase III trials.\cite{79,80}

Some have theorized that lengthening the PFI by using nonplatinum single-agent therapies may benefit patients with recurrent disease.\cite{81} Currently, there are no data comparing initial platinum therapy and use of nonplatinum agents to prolong the PFI. In trials assessing nonplatinum single-agent therapies, the response rates in platinum-resistant disease are approximately 10% to 15% lower than in patients with platinum-sensitive disease.\cite{79,80} Suggesting that the underlying biology of the cancer dictates its response to therapy and that prolonging the PFI alone may not alter the clinical outcome. In selected patients with recurrent platinum-sensitive disease, a choice may be made to avoid initial platinum therapy due to concerns for toxicity or patient preference. In these situations, possible options for nonplatinum-based therapy include PLD,\cite{83} topotecan,\cite{84} or paclitaxel,\cite{85} but the range of choices is broad and no specific agent is superior. Therefore, choice of therapy in this situation should be based upon ease of route of administration and avoidance of prior toxicities.

**Combination therapy.** Several randomized phase III clinical trials and a randomized phase II clinical trials have been conducted to address the question of whether platinum-based combination therapy is superior to single-agent therapy in recurrent platinum-sensitive disease. The results of 2 phase III trials were pooled and reported together as ICON4/AGO.\cite{86} In this combined study of these 2 parallel-run trials, 802 patients with platinum-sensitive recurrent ovarian cancer were enrolled between 1996 and 2002. Eligible patients were required to previously have received a platinum-based regimen at the time of initial diagnosis. The 2 trials differed in terms of the TFI: the TFI needed to be greater than 12 months for patients to be considered eligible in the ICON4 trial and greater than 6 months in the AGO trial. Patients were randomized to receive either single-agent platinum or platinum with paclitaxel. Overall, response rates were 66% in the platinum plus paclitaxel group and 54% in the platinum group ($P = 0.06$). However, survival data favored the combination platinum/paclitaxel group, with a statistically significant HR of 0.82, translating into a superior median survival (29 versus 24 mo). GEICO\cite{87} conducted a similar phase II trial that randomized 81 patients to treatment with carboplatin or carboplatin plus paclitaxel and yielded similar results, with a response rate of 75.6% in the carboplatin/paclitaxel arm versus 50% in the carboplatin alone arm. In another randomized phase III trial, GCIG\cite{88} compared combination gemcitabine and carboplatin therapy with carboplatin alone in platinum-sensitive recurrent disease. Interim analysis of the data revealed increased response rates with the combination gemcitabine/carboplatin therapy (47.2% versus 30.9%; $P = 0.0016$). The HR for median OS was 0.96, and the HR for PFS was 0.72, with a median PFS of 8.6 months in the combined therapy arm versus 5.8 months in the carboplatin alone arm. Based upon these findings, the FDA recently approved gemcitabine for use in combination with carboplatin for platinum-sensitive recurrence.

Despite the results of the ICON4/AGO, GEICO, and GCIG trials, controversy still remains regarding the role
of platinum-based combination therapy in the setting of platinum-sensitive recurrent disease. Criticisms of the trials include the relatively low number (40%) of patients in ICON4 who had received a taxane during their initial therapy. However, 87.2% of the patients received a taxane as part of their initial therapy in the GEICO trial. In addition, these trials do not address the possible role of sequential therapy in comparison with combined therapy. Combination regimens do result in higher response rates and will likely benefit the symptomatic patient more rapidly, but they also carry a higher rate of toxicity. In the ICON4/AGO and GEICO trials, grade 2 to 4 neurologic toxicity of the combined platinum and paclitaxel regimen was approximately 20%. In the GCIG study, there was a 78.3% incidence of grade 3 or 4 hematologic toxicity with the combined carboplatin and gemcitabine regimen.

**Intrapерitoneal chemotherapy for platinum-sensitive recurrent disease.** In addition to IV-based chemotherapy, IP-based chemotherapy can also be considered for selected patients with highly platinum-sensitive disease. Studies of IP therapy in the recurrent setting have shown that response rates are low in patients with bulky disease, therefore, IP chemotherapy should only be considered in selected patients who have very platinum-sensitive cancer, who are motivated to undergo IP chemotherapy, have no evidence of extraabdominal disease, and have interval surgery following recurrence resulting in optimal debulking (≤ 1 cm residual cancer). A more complete discussion of IP therapy for recurrent ovarian cancer is beyond the scope of this review.

**Case Continued**

The patient receives 6 cycles of IV carboplatin and paclitaxel. After completing chemotherapy, the CA-125 level is measured at 17 U/mL. At a follow-up visit 3 months later, the CA-125 level has risen to 87 U/mL. A repeat level returns at 83 U/mL. The patient does not report any new symptoms.

- **What are the treatment options for platinum-resistant disease?**

**Platinum-Resistant Disease**

Given the short TFI before evidence of progression, the case patient has developed platinum-resistant disease. Patients with platinum-resistant cancer or platinum-refractory disease carry a poor prognosis. Phase II data suggest response rates of approximately 20% or less for single-agent therapies, whereas randomized phase III trials involving patients with platinum-resistant disease report response rates of only 6% to 13% with a median time to progression between 2 and 3 months with single-agent therapy. Overall, there are few randomized data to provide guidance for therapy in the setting of platinum-resistant disease. In general, single-agent therapy is used for the treatment of platinum-resistant disease due to the increased toxicities associated with combination therapy and the lack of data supporting increased benefit with the use of more than 1 agent. Drugs active in this setting include but are not limited to paclitaxel, docetaxel, PLD, topotecan, oral etoposide, gemcitabine, vinorelbine, ifosfamide, and tamoxifen or other anti-estrogen therapies including aromatase inhibitors. No one drug, however, appears to be superior. Finally, agents such as bevacizumab and other therapy directed against vascular endothelial growth factors are being investigated to determine their efficacy in treating recurrent ovarian cancer. Three of the agents used to treat platinum-resistant disease are discussed in the following section.

**Taxanes.** Before paclitaxel was used as frontline therapy for ovarian cancer, its activity was first characterized in patients with platinum-refractory ovarian cancer who had initially been treated with platinum-based therapy. Standard first-line therapy for ovarian cancer has incorporated taxanes since 1996. Paclitaxel can also be considered for second-line therapy in patients who have recurrent or platinum-resistant disease and have not previously received taxanes. Additional phase II studies of paclitaxel in patients with recurrent disease have demonstrated response rates between 20% and 33%, and dosing can be performed in a once weekly or once every 3 weeks fashion. Docetaxel has also been investigated in the recurrent setting, with observed response rates of 10% to 20% in platinum- and paclitaxel-resistant disease.

**Pegylated liposomal doxorubicin.** Phase II studies evaluating PLD in the setting of platinum-resistant ovarian cancer have demonstrated a response rate ranging from 16.9% to 25.7%, with a median time to progression of 4.5 to 5.7 months. The most significant toxicity associated with PLD is the development of grade 3 or 4 hand-foot syndrome, which was seen in between 20% and 28% of the patients in these studies. Two retrospective analyses and a phase II trial have suggested that using a reduced dosages of PLD (40 mg/m² given once every 28 days) is equally effective and has decreased toxicity.

Two phase III trials have studied PLD in comparison...
with other single nonplatinum agents in the setting of recurrent ovarian cancer, one comparing PLD with paclitaxel and the other comparing PLD with topotecan. In the trial comparing PLD with paclitaxel, 121 taxane-naive patients with disease progression or recurrence following platinum-based therapy were enrolled and randomized to either PLD or paclitaxel treatment. Response rates between the 2 arms were statistically equivalent, with a response rate of 17.8% for the PLD arm and 22.4% for the paclitaxel arm. Median PFS was 21.7 weeks in the PLD arm and 22.4 weeks in the paclitaxel arm. The OS did not differ significantly at 45.7 weeks in the PLD arm and 56.1 weeks in the paclitaxel arm. In a phase III study involving patients with both platinum-sensitive and platinum-resistant disease, OS with longer follow-up favored PLD versus topotecan (HR, 1.216; P = 0.05), but there was no statistically significant difference in OS for patients with platinum-resistant disease. Bone marrow suppression and dose-adjustments were more frequent in the topotecan arm.

Topotecan has been studied as a 5-day infusion administered parenterally in phase II clinical trials in recurrent ovarian cancer, with observed response rates ranging between 14% and 27%, depending on the status of platinum resistance. A large European phase II study found response rates to be 5.9%, 17.8%, and 26.7% in cisplatin-refractory, cisplatin-resistant, and cisplatin-sensitive disease, respectively. Toxicity associated with topotecan is primarily hematologic, with grade 3 or 4 toxicity occurring in up to 95% of patients. Further studies have compared dosing regimens, and there are reports that a lower dose has similar response rates and decreased toxicity, as does weekly dosing.

Phase III studies comparing topotecan to PLD (discussed earlier) and paclitaxel in the setting of recurrent disease have also been performed. In the phase III trial comparing topotecan with paclitaxel in the setting of recurrent disease following prior platinum-based therapy, overall response rates of 20.5% and 13.2% were observed in the topotecan and paclitaxel arms (P = 0.138), respectively. For patients with platinum-resistant disease, response rates of 13.3% and 6.7% were observed in the topotecan and paclitaxel arms (P = 0.303), respectively. The median time to progression favored topotecan at 23 weeks versus paclitaxel at 14 weeks (P = 0.002).

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